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January 25, 2018

Via Electronic Submission
Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: FDA-2017-P-5082—Comment on ChromaDex, Inc.'s Supplemental Citizen Petition dated January 16, 2018

Skadden, Arps, Slate, Meagher & Flom LLP, on behalf of Elysium Health, Inc. ("Elysium") hereby responds to the supplemental citizen petition (the "Supplemental Petition") filed by ChromaDex, Inc. ("ChromaDex") on January 16, 2018. The Supplemental Petition provides factually incorrect information regarding Elysium's dietary supplement product, Basis, and Elysium briefly responds in order to provide FDA with additional and corrective information, as described below.

Toluene Has Been Removed from Elysium's Basis

ChromaDex's Supplemental Petition alleges that Elysium's Basis contains toluene, and appears to base its assertion on testing conducted by ChromaDex in its laboratories sometime prior to its August 2017 citizen petition filing. Had ChromaDex re-tested Basis before filing its Supplemental Petition, it would have discovered that **the toluene has been removed from Basis so that it currently is at or below non-detect levels** for numerous forms of testing. Although Elysium believes that the ICH Guidelines establish the safety of toluene at the minimal levels previously found in Basis,[1] Elysium elected to eliminate the presence of toluene from Basis as part of its continuing efforts to ensure superior product quality.

[1] ICH Guidelines allow for nearly one hundred times the levels of toluene purportedly found in Basis in pharmaceutical products. ChromaDex claims in the Supplemental Petition that FDA's

The NR in Elysium's Basis Has Never Contained Toluene

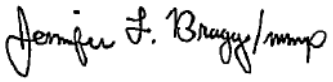
ChromaDex's Supplemental Petition also claims that Elysium is "distributing NR that has been contaminated with toluene" and on that basis asks FDA to issue an order stating that NR is not reasonably expected to be safe if it contains "new" impurities like toluene. ChromaDex's statement that Elysium distributes NR "contaminated" with toluene, apparently a conclusion drawn from ChromaDex's testing of Basis prior to submission of its citizen petition in August 2017, is false. Basis is a combination product containing both NR and pterostilbene, and **the NR incorporated within Basis has never contained any level of toluene**.

The NR in Elysium's Basis Is Generally Recognized as Safe

Finally, ChromaDex's Supplemental Petition suggests that Elysium ignores the NDIN requirement and that its product therefore contains a new dietary ingredient that has not been demonstrated to be safe.[2] This assertion is unsupported and incorrect. In reality, **the NR within Basis enjoys "Generally Recognized As Safe" status, which is supported by extensive safety and toxicological testing**. Elysium is in the process of conducting further testing in support of an NDIN and anticipates making that submission promptly upon its completion.

Elysium is available to provide further information regarding any of the issues described above.

Sincerely,



Jennifer L. Bragg

Center for Food Safety and Applied Nutrition ("CFSAN") has "never applied those guidelines to dietary supplements." This is false. CFSAN regularly accepts applications from dietary supplement manufacturers that make reference to the ICH Guidelines to establish the safety of residual solvent levels in dietary supplements. This is evident from ChromaDex's own submissions to CFSAN: Both its NDIN and Notice of GRAS Status for its nicotinamide riboside chloride ("NR") reference the ICH Guidelines with respect to the residual solvent levels in its product. *See* Appendix A (excerpt of publicly-available New Dietary Ingredient Notification for Niagen submitted on August 20, 2015); Appendix B (excerpt of publicly-available Generally Recognized as Safe (GRAS) Determination for Niagen, submitted on March 8, 2016).

[2] ChromaDex includes this allegation as the basis for its request that FDA finalize August 2016 draft guidance describing the circumstances under which a dietary supplement manufacturer must submit an NDIN. Elysium presumes this request encompasses the section of that guidance making clear that a dietary manufacturer must submit an NDIN for products containing a new dietary ingredient at a higher single-serving dose than that described in a previous NDIN for the same ingredient—a requirement that ChromaDex flouted in offering its TruNiagen product for sale to consumers without submitting an NDIN.

APPENDIX A

Spherix
CHROMADEX CONSULTING

August 20, 2015

Fred Hines, DVM
Consumer Safety Officer
FDA/CFSAN/HFS-810
Division of Dietary Supplement Programs
New Dietary Ingredient Review Team
Harvey Wiley Building
5100 Paint Branch Parkway
College Park, MD 20740

RECEIVED
AUG 24 2015
BY: FAH for FDA
NDI 882 ORIGINAL

Dear Dr. Hines:

In accordance with the Federal Food, Drug, and Cosmetic Act, Section 413(d), 21 U.S.C. 350b(d), enclosed please find one original and one copy of the New Dietary Ingredient Notification for Niagen (Nicotinamide Riboside Chloride), as well as the accompanying references and appendices. This NDI notification has been prepared by Spherix Consulting, Inc. on behalf of its parent company, ChromaDex, Inc.

Should you have any questions or concerns, please contact me at 301-897-0611 or clairek@chromadex.com.

Sincerely,

Claire L. Kruger, Ph.D., D.A.B.T.
President

Enclosures:

One original and one copy of the New Dietary Ingredient Notification for Niagen (Nicotinamide Riboside Chloride)

One original and one copy of all references used in the New Dietary Ingredient Notification for Niagen (Nicotinamide Riboside Chloride)

One original and one copy of all appendices used in the New Dietary Ingredient Notification for Niagen (Nicotinamide Riboside Chloride)

11900 Parklawn Drive, Suite 200
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Tel.: (301) 897-0613; Fax: (301) 897-2567
www.spherixconsulting.com

NEW DIETARY INGREDIENT NOTIFICATION FOR NIAGEN (NICOTINAMIDE RIBOSIDE CHLORIDE)

Prepared for:

ChromaDex, Inc.
10005 Muirlands Boulevard., Suite G
Irvine, CA 92618

Prepared by:

Spherix Consulting, Inc.
11900 Parklawn Drive, Suite 200
Rockville, MD 20852

August 20, 2015

I. EXECUTIVE SUMMARY

A. NAME AND ADDRESS OF NOTIFIER

ChromaDex, Inc.
10005 Muirlands Boulevard, Suite G
Irvine, CA 92618

Contact:
Troy Rhonemus, Chief Operating Officer
Tel: +1.949.600.9734
Fax: +1.949.356.1634
TroyR@chromadex.com

B. IDENTITY OF NEW DIETARY INGREDIENT

The ingredient that is the subject of this notification is Niagen™, a New Dietary Ingredient, not marketed prior to October 15, 1994. Niagen is identical to Nicotinamide Riboside (NR), a form of vitamin B_3 (Erdman et al. 2012) that is found naturally in small quantities in milk and is synthetically manufactured using a patented method. DSHEA defines a dietary supplement as "a product, other than tobacco, intended to supplement the diet that contains at least one or more of the following ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, or a dietary substance for use to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, or extract or combination of any of the previously mentioned ingredients."[1]

[1] Statutory language in FDCA Section 411, added by the Proxmire Amendments in 1976, is intended to bar FDA from imposing maximum limits on the potency of "any synthetic or natural vitamin or mineral" and from classifying "any natural or synthetic vitamin or mineral" as a drug solely because it exceeds the level of potency which FDA determines is nutritionally rational or useful. These amendments document that by 1976, Congress was well aware that vitamins and minerals were marketed in both natural and synthetic forms. Once Congress had established in the Proxmire Amendments that vitamins and minerals should be treated the same way by FDA regardless of whether they are naturally or synthetically derived, it did not need to specify this fact again in DSHEA, after those amendments had been effective for nearly twenty years. And just as Congress was aware, by the time of the Proxmire Amendments, that vitamins and minerals were marketed in both natural and synthetic forms, it is also presumed to have been aware that synthetic botanical constituents had been in the food supply for many decades by the time DSHEA was enacted. Accordingly, where Section 201(ff)(1)(A)-(D) identifies vitamins, minerals, botanicals, and amino acids as dietary ingredients, Congress intended to include both the naturally and synthetically derived forms. This language makes clear that Congress did not view the terms "vitamin" and "mineral," standing alone, as inherently meaning the natural form of these dietary ingredients; otherwise, there would have been no need in the Proxmire Amendments to specify natural as well as synthetic vitamins and minerals (CRN 2012).

E. CLINICAL STUDY (STUDY NUMBER 14NBHC; APPENDIX H)

1. Summary

The pharmacokinetics and safety of single administration of three dosages of Niagen was studied in healthy human subjects in a randomized, double-blind three-arm crossover trial. Results indicate that Niagen is metabolized similarly to nicotinamide in healthy humans and can be utilized as a form of Vitamin B_3. No clinically adverse effects on hematology, clinical chemistry, urinalysis or liver or kidney function parameters were noted.

2. Test article Used in Study 14NBHC

The test article used in the clinical trial came from preliminary batch lot #13201, produced using manufacturing conditions slightly different from those described in the manufacturing section (batch analysis data in Table 15). Between preliminary batch Lot #13201 and subsequent commercial batches, the washing steps of the production process were further modified and optimized. Mainly, the changes involved altering the rinse procedures such as replacing the acetone slurry in the first step; reversing addition of solvents, introducing an extended methanol water slurry; a reduced acetone water slurry and updated drying condition in the second the second step of the process. This led to an overall improvement in the levels of solvent residues remaining in the final ingredient product. The batch used in the clinical study had slightly higher lead residue than specifications for commercial product allow however, all other specifications were met. This did not compromise the use of this batch for testing purposes because it represents a worst case from the perspective of lead contamination. Commercial batches all comply with specifications.

Table 15. Specifications and Batch Analysis for Niagen Batch # 13202

Parameter	Specifications	Method	Batch 13201
Color	White to light brown	Visual	Off-white
Form	Powder	Visual	Powder
Purity	95 – 102 (wt%) by HPLC	99.1-CD-3.0-000591	99.9 (wt%)
Identification	Conforms to structure by NMR	99.1-CD-1.0-000122	Conforms to structure
Water Content	NMT 1%	99.1-CD-6.0-000094	0.25%
Residual Solvents			
Acetone	<5000 ppm*	99.1-CD-7.0-000115	4818
Methanol	<3000 ppm*	99.1-CD-7.0-000115	378
Acetonitrile	<410 ppm*	99.1-CD-7.0-000115	ND
Methyl *t*-Butyl Ether	<5000 ppm*	99.1-CD-7.0-000115	ND****
Reaction By-products			
Methyl acetate	<5000 ppm*	99.1-CD-7.0-000115	ND
Acetamide	<27 ppm**	99.1-CD-1.0-000616	ND

Table 15. Specifications and Batch Analysis for Niagen Batch # 13202			
Parameter	**Specifications**	**Method**	**Batch 13201**
Acetic Acid	<5000 ppm*	99.1-CD-7.0-000115	87
Microbiological Limits			
Total Plate Count	≤1,000 CFU/g	USP <2023(h)>	<1000 CFU/g
Yeast and Mold	≤1000 CFU/g	USP <2023(h)>	<1000 CFU/g
E.coli	Absent/10g	USP <2023(h)>	Absent/ 10g
Heavy Metals			
Arsenic	≤1 ppm	AOAC 993.14	<0.5 ppm
Mercury	≤ 1 ppm	AOAC 993.14	<0.1 ppm
Cadmium	≤ 1 ppm	AOAC 993.14	<0.25 ppm
Lead	≤ 0.5 ppm	AOAC 993.14	0.054 ppm

ND- Not Detected
BLOQ- Below Limit of Quantitation
**Final Specifications on Residual Solvents by ICH Q3C*
***Based on California Proposition 65.(NSRL 10 µg/day)*

3. Study Design

The clinical study is a randomized, double-blind, single-dose, three-arm crossover, 24 hr pharmacokinetic study. Twelve healthy participants (6 males and 6 females) were enrolled in the study and randomized to a three treatment sequence after screening and passing eligibility criteria, with all 12 subjects receiving each dose (100mg, 300mg and 1000mg) of Niagen on separate study days with a 7 day wash-out period in between study days. This study was conducted in subjects of any ethnicity. The period from screening to study completion was approximately six weeks.

Standardized meals devoid of whey protein, milk and dairy products were provided. Breakfast were provided after the 1 h sampling, lunch after the 4h sampling and supper between the 6h and 12h sampling. Subjects were counseled to refrain from consuming vitamins, nutritional yeast, milk and other whey proteins, energy drinks and dairy products between the 12h and 24h sampling. Adverse events including vasodilation (flushing), were assessed at each study visit.

Fasting blood sample was collected for hematology parameters (hemoglobin, hematocrit, WBC, RBC, MCV, MCH, MCHC, RDW, platelets, neutrophils, lymphocytes, monocytes), clinical chemistries (electrolytes, AST, ALT, GGT and bilirubin) as well as for measuring Niagen and Niagen metabolite levels at 24hours post dose time point. Urine samples from 12-24hours interval were also collected. Vitals were taken for 24 hours post dose time point.

APPENDIX B

GR

ORIGINAL SUBMISSION

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ORIGINAL

Spherix
CHROMADEX CONSULTING

GRN 000635

March 8, 2016

Office of Food Additive Safety
HFS-255
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

To Whom It May Concern:

Enclosed please find three copies of the dossier entitled "Generally Recognized as Safe (GRAS) Determination for Niagen™ (Nicotinamide Riboside Chloride)" and the GRAS Expert Panel Consensus Statement. This GRAS determination has been prepared by Spherix Consulting, Inc., on behalf of its parent company, ChromaDex, Inc.

The data and information that serve as the basis for this GRAS determination is available for review and copying at reasonable times at the office of Claire L. Kruger, Ph.D., D.A.B.T., President, Spherix Consulting, Inc., 11900 Parklawn Drive, Suite 200, Rockville, MD 20852, Telephone: 301-897-0611; Facsimile: 301-897-2567; Email: clairek@chromadex.com, or will be sent to FDA upon request.

Should you have any questions or concerns, please contact me at the number listed above.

Sincerely,
(b) (6)

Claire L, Kruger, Ph.D., D.A.B.T.
President

Enclosures:

Three copies of the GRAS Panel Consensus Statement for the above-referenced GRAS Notification

Three copies of the dossier entitled "Generally Recognized as Safe (GRAS) Determination for Niagen™ (Nicotinamide Riboside Chloride)"

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Rockville, MD 20852
Tel.: (301) 897-0613; Fax: (301) 897-2567
www.spherixconsulting.com

Generally Recognized as Safe (GRAS) Determination for Niagen™ (Nicotinamide Riboside Chloride)

Prepared for:

ChromaDex, Inc.
10005 Muirlands Boulevard., Suite G
Irvine, CA 92618

Prepared by:

Spherix Consulting, Inc.
11900 Parklawn Drive, Suite 200
Rockville, MD 20852

December 21, 2015

I. EXECUTIVE SUMMARY

A. NAME AND ADDRESS OF SPONSOR

ChromaDex, Inc.
10005 Muirlands Boulevard, Suite G
Irvine, CA 92618

Contact:
Troy Rhonemus, Chief Operating Officer
Tel: 949-600-9734
Fax: 949-356-1634
TroyR@chromadex.com

B. COMMON AND USUAL NAME OF GRAS SUBSTANCE

The substance of this Generally Recognized As Safe (GRAS) determination is Nicotinamide Riboside Chloride (NR), a form of vitamin B_3. NR is a single chemical moiety containing nicotinamide and ribose (Chi and Sauve, 2013). NR is sold by ChromaDex under the name Niagen™.

C. INTENDED USE

ChromaDex, Inc. proposes to add Niagen to selected foods and beverages to provide a source of vitamin B_3 (vitamin waters, protein shakes, nutrition bars, gum and chews). The intended maximum use level is 0.027% by weight and will be in powdered beverages designed to be reconstituted with water or milk. The intended maximum use level in all other foods will be 0.0057% by weight.

D. BASIS FOR GRAS DETERMINATION

This GRAS determination for the use of Niagen as an ingredient in vitamin waters, protein shakes, nutrition bars, gum and chews, is based upon scientific procedures as described under 21 CFR §170.30(b). The intake of Niagen from the intended uses specified above has been shown to be safe and GRAS, using scientific procedures, under the Federal Food, Drug, and Cosmetic Act (FFDCA), Section 201(s). To demonstrate that Niagen is safe, and GRAS, under the intended conditions of use, the safety of the intake of this product has been determined to be GRAS by demonstrating that the safety of this level of intake is generally recognized by experts

2. Raw Materials and Chemicals

Certificates of Analysis (CoAs) for D-ribofuranose tetraacetate and nicotinamide document appropriate specifications; specifications for nicotinamide comply with USP 2015.

3. Processing Aids

Specifications are set for the final product to comply with appropriate controls on residual solvents and other processing aids for food. The processing aids used in the production of Niagen are listed below:

a. Solvents

Acetone: Approved as a secondary direct food additive under 21 CFR § 173.210 and is a Class 3 solvent [2] for pharmaceutical products with permitted daily exposure of 50 mg/day and a concentration limit of 5000 ppm (ICH Q3C (R5) 2011; MAPP 2014).

A residual amount of acetone in finished product of ≤ 3000 ppm is determined to be GRAS in GRN 491 for rooster comb extract. The calculated EDIs for rooster comb and Niagen are similar, therefore the limit of ≤ 3000 ppm determined in GRAS Notification 491 serves as precedent for a specification of ≤ 3000 ppm for acetone for Niagen.

Methyl t-butyl ether: Categorized as a Class 3 Solvent for Pharmaceutical products with permitted daily exposure of 50 mg/day and a concentration limit of 5000 ppm (ICH Q3C (R5) 2011; MAPP 2014). The solvent is safe for use as a processing aid for Niagen under the conditions that the specification for residue is not detected at the LOD (4ppm).

Acetonitrile: A residual amount of acetonitrile in finished product of ≤ 40 ppm is determined to be GRAS in GRN 202 for the use of polyoxyethanyl-alpha-tocopheryl sebacate (PTS) as a solubilizer for the dietary ingredient coenzyme Q10. The specification for residue is not detected at the LOD (6 ppm).

Methanol: A residual amount of methanol in finished product of ≤ 740 ppm is determined to be GRAS based on the methanol specification of 200 ppm in GRNs 448, 329, 323, 304, 303, 275, 253 for steviol glycosides. GRN 275 may be used for calculation purposes to

[2] Solvents in Class 3 may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5,000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice (GMP).

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3. Impurities, Residuals, and Contaminants of Concern

Potential contaminants of Niagen include microbial contamination, heavy metals, residual solvents, processing aids and by-products. The specifications set for Niagen control these impurities to assure acceptable final product. Batch data for three different lots document control of final product to meet these specifications. Specifications and batch data are presented in Table 2.

a. Potential Reaction By-Products

Methyl acetate: It is a potential byproduct in the manufacture of Nicotinamide Riboside Chloride, but undetected in the final product. It is used as an extraction solvent in the production of some foods. In EU directive 88/344/EEC the European Union established a limit when used in the production of sugar from molasses of 1 mg/kg in the sugar. A limit of 20 mg/kg is permitted when used in decaffeination of coffee and tea. It is classified as a Class 3 Solvent for Pharmaceutical products with permitted daily exposure of 50 mg/day and a concentration limit of 5000 ppm (ICH Q3C (R5) 2011; MAPP 2014). A specification for Niagen is set at below the LOD/BLOQ (limit of detection/below limit of quantitation; 5/15 ppm).

Acetamide: Acetamide is a byproduct that could be formed during the preparation of the Nicotinamide Riboside Chloride as a result of the deacetylation step with ammonium hydroxide (Step 2). Acetamide is undetectable in the final product; it is removed based on its high solubility in solvents (alcohol, water) used to wash the product (Maryadele et al., 2006; Yalkowsky et al., 1992). The preparation and processing of Nicotinamide Riboside Chloride (Step 2 product) involves removing the volatiles under vacuum. Subsequently, the slurry is rinsed with large volumes of methyl-t-butyl ether, methanol, methanol/water and acetone /water. The use of these large volumes of organic solvents such as methanol, acetone and also volumes of water is expected to remove any residual acetamide that could remain in the product. The solubility in alcohol is high at about 0.5g/mL. Solubility in water is extremely high at >2g/mL at 25°C (Maryadele et al., 2006; Yalkowsky et al., 1992). A specification for Niagen is set at below the LOD/BLOQ (limit of detection/below limit of quantitation; 10/25 ppm)

Acetic Acid: Approved as a direct food substance affirmed as GRAS under 21 CFR §184.1005 at levels not to exceed current good manufacturing practice. A specification for Niagen is set at ≤ 5000 ppm.