KING & SPALDING LLP

King & Spalding LLP
1700 Pennsylvania Avenue, N.W.
Washington, DC 20006-4706
Main: 202-737-0500
Fax: 202-626-3737

Sheldon T. Bradshaw
Partner
202-626-9225
sbradshaw@kslaw.com

January 16, 2018

Via Electronic Submission to www.regulations.gov

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA-2017-P-5082

CHROMADEX INC.'S SUPPLEMENTAL CITIZEN PETITION

Petitioner ChromaDex, Inc. ("ChromaDex") submits this supplement to the Citizen Petition ChromaDex filed on August 18, 2017 (FDA-2017-P-5082) to request that the Commissioner of Food and Drugs take the following actions: (1) state in a public guidance or similar announcement that the guidelines published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ("ICH") addressing residual solvents in drugs do not apply to dietary supplements; (2) issue an order pursuant to Section 413(b) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act" or "Act") [21 U.S.C. § 350b(b)] that nicotinamide riboside chloride is not reasonably expected to be safe if it contains new impurities such as toluene or any other Class 1 or Class 2 drug solvents that were not included in the toxicology studies conducted to establish the safety of nicotinamide riboside chloride for its intended use; and (3) finalize the 2016 U.S. Food and Drug Administration ("FDA") draft guidance on New Dietary Ingredient Notifications ("NDINs")[1] and clarify that FDA will prioritize enforcement of the NDIN requirement established in Section 413(a)(2) of the FD&C Act [21 U.S.C. § 350b(a)(2)] in circumstances where a dietary supplement manufacturer has taken the necessary steps to comply with the notification requirement, but other manufacturers continue to distribute products containing the same New Dietary Ingredient without complying with that law.

I. Background

The Citizen Petition ChromaDex submitted on August 18, 2017 notified FDA that a dietary supplement manufactured by Elysium Health, Inc. ("Elysium") sold under the name

[1] *See* FDA, Draft Guidance for Industry, *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* (Aug. 2016).

"Basis" is adulterated pursuant to Section 402(a) and (f) of the FD&C Act [21 U.S.C. § 342(a) and (f)] because it contains the toxic industrial solvent, toluene. The Citizen Petition also notified FDA that Basis is adulterated pursuant to Section 402(f)(1)(B) of the Act [21 U.S.C. § 342(f)(1)(B)] because it contains a New Dietary Ingredient, nicotinamide riboside chloride ("NR"), for which Elysium has not filed an NDIN.

On September 22, 2017, Elysium filed a comment in response to ChromaDex's Citizen Petition. In its comment, Elysium did not deny that it failed to file an NDIN for NR. Elysium did not attempt to justify its violation of the FD&C Act or assure FDA that it is planning to comply with the Act. Moreover, Elysium did not deny that Basis contains toluene in measurable levels, as shown in the laboratory report filed with FDA, nor did Elysium promise to remove toluene from its product. Instead, Elysium suggested that the presence of toluene in dietary supplements is acceptable due to guidelines that do not apply to dietary supplements. The guidelines cited by Elysium, issued by the ICH, outline prohibitions relating to the presence of residual solvents in drug manufacturing.[2] FDA's Center for Drug Evaluation and Research ("CDER") and its Center for Biologics Evaluation and Research ("CBER") adopted those guidelines for drug and biologics manufacturing. FDA's Center for Food Safety and Applied Nutrition ("CFSAN"), however, has never applied those guidelines to dietary supplements.[3]

Elysium's response is alarming because it appears that Elysium (1) is willfully disregarding the NDIN requirement established in Section 413(a)(2) of the FD&C Act [21 U.S.C. § 350b(a)(2)]; and (2) is not making any attempt to remove toluene from its product.

II. Supplemental Requests

As a result of Elysium's response to the original Citizen Petition,[4] ChromaDex is filing this Supplemental Citizen Petition to make the following requests:

---

[2] *See* FDA, Guidance for Industry, *Q3C Impurities: Residual Solvents* (Dec. 1997).

[3] Elysium also argued in its comment that ChromaDex intentionally misled FDA about this issue, citing the fact that ChromaDex has produced certificates of analysis ("CoAs") for certain raw materials that reference the ICH guidelines and disclose the presence of toluene. Elysium's argument is completely baseless. ChromaDex performs exhaustive testing on its raw materials, which it produces for both drug manufacturers and dietary supplement manufacturers. ChromaDex does not provide different CoAs for the raw materials supplied to the manufacturers of drugs (to which the ICH guidelines pertain) as opposed to the manufacturers of dietary supplements. Unlike Elysium, ChromaDex works diligently to disclose the contents of its products to all purchasers. Thus, the fact that ChromaDex openly disclosed the presence of toluene in a bulk raw material sold to manufacturers is not at all comparable to Elysium's purposeful cover-up of toluene in a product marketed to consumers for direct human consumption. Notably, Elysium does not assert that ChromaDex's NR contains toluene, because it does not.

[4] For the sake of clarification, ChromaDex's original Citizen Petition was intended (1) to bring these issues to FDA's attention so that FDA can consider an appropriate response and (2) to request a determination that Elysium's product containing toluene is adulterated under the FD&C Act. Given FDA's response to prior Citizen Petitions seeking its discretionary action, ChromaDex reasonably believes that FDA welcomes and considers Petitions providing information about adulterated products, even if the Petitions ultimately are denied. *See, e.g.*, FDA Response to Wood, Herron & Evans (Feb. 28, 2017), *available at* https://www.regulations.gov/document?D=FDA-2016-P-3195-0004; FDA Response to Fluoride Action Network (Nov. 29, 2016), *available at* https://www.regulations.gov/document?D=FDA-2016-P-1288-0020; FDA Response to King & Spalding (July 19, 2010), *available at* https://www.regulations.gov/document?D=FDA-2002-P-0381-0004; FDA Response to The Pharmaceutical Security Institute, Inc. (Mar. 2, 2012), *available at* https://www.regulations.gov/document?D=FDA-

A. ChromaDex Requests That FDA State in a Public Guidance or Similar Announcement That the ICH Guidelines for Residual Solvents in Drugs Do Not Apply to Dietary Supplements and That the Safe Use of Solvents in Manufacturing Is Determined Through the NDIN Process.

Elysium's response to ChromaDex's original Citizen Petition suggests that the presence of toluene in dietary supplements is acceptable because "FDA adopted the ICH guidelines establishing acceptable amounts of toluene and other residual solvents *in pharmaceuticals*."[5]

As noted above, however, CFSAN has never established tolerance levels for toluene in dietary supplements. CFSAN's position is justified. Drugs are regulated in a fundamentally different way than dietary supplements and other foods. Drugs generally are subject to premarket approval requirements, which enable FDA to strictly regulate the drug manufacturing process. By contrast, dietary supplements and other foods are not subject to the same premarket approval requirements. Establishing tolerance levels for toxic solvents in dietary supplements would effectively authorize the use of such toxic solvents, unaccompanied by the tighter regulatory structure and oversight applicable to drug manufacturing.

The guidance published by CDER and CBER addressing the presence of residual solvents in drugs and biologics demonstrates why there should be no tolerance level for such solvents in dietary supplements. The guidance notes: "Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements."[6]

The guidance places solvents into three classes: (1) solvents to be avoided (i.e., known human carcinogens, strongly suspected human carcinogens, and environmental hazards); (2) solvents to be limited (i.e., nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity, and solvents suspected of other significant but reversible toxicities); and (3) solvents with low toxic potential. CDER and CBER have emphasized that Class 2 solvents "should be limited in pharmaceutical products because of their inherent toxicity."[7] CDER and CBER listed toluene as a Class 2 solvent.[8]

Even though CFSAN has never adopted the ICH guidelines for dietary supplements, it appears that Elysium is willing to ignore that fact and incorporate a Class 2 solvent in its Basis product—notwithstanding the solvent's "inherent toxicity"—without providing the substantiation of safety that is required for NDIs. It is difficult to know how widespread the use of such solvents is in dietary supplements, but it could be extensive. As a result, ChromaDex requests that FDA issue an explicit statement (whether in a guidance or other public document) declaring that the ICH guidelines do not apply to dietary supplements. Elysium's response to the Citizen Petition has highlighted the need for FDA to make an industry-wide clarification on this issue.

2011-P-0881-0004.

[5] *See* Elysium, Comment on ChromaDex Citizen Petition (Sep. 22, 2017) (emphasis added).

[6] FDA, Guidance for Industry, *Q3C Impurities: Residual Solvents* (Dec. 1997), at 2.

[7] FDA, Guidance for Industry, *Q3C Tables and List* (June 2017), at 6.

[8] *See id.* at 7.

B. ChromaDex Requests That FDA Issue an Order Pursuant to Section 413(b) of the FD&C Act [21 U.S.C. § 350b(b)] Stating That Nicotinamide Riboside Chloride Is Not "Reasonably Expected To Be Safe" If It Contains New Impurities, Such as Toluene, That Have Not Been Reviewed Under the NDIN Process.

The FD&C Act provides that "[a]ny person may file with the Secretary a petition proposing the issuance of an order prescribing the conditions under which a new dietary ingredient under its intended conditions of use will reasonably be expected to be safe."[9]

ChromaDex's NDIN for NR (NDI 882) outlines the manufacturing process for the product. The notification makes it clear that ChromaDex's NR does not utilize any toluene. Moreover, the notification fully disclosed the Class 2 solvents used in the manufacturing process (i.e., methanol and acetonitrile), which were tested for toxicological safety. As a result, FDA reviewed that information as part of the NDIN process. Similarly, the generally recognized as safe ("GRAS") notice submitted by ChromaDex supporting the use of NR as an ingredient in vitamin waters, protein shakes, nutrition bars, gum, and chews, also clarifies that every drug solvent utilized in the manufacturing process was reviewed by qualified experts.

Given that Elysium apparently plans to continue distributing NR that has been contaminated with toluene, ChromaDex requests that FDA issue an order pursuant to Section 413(b) of the FD&C Act [21 U.S.C. § 350b(b)] stating that NR is only "reasonably expected to be safe" if it does not contain toluene or any other drug solvents that have not been reviewed by FDA as a part of the NDIN process.

C. ChromaDex Requests That FDA Finalize Its NDIN Guidance and Clarify Its Enforcement Policy With Respect to Dietary Supplement Manufacturers That Include a New Dietary Ingredient in Their Products Without Complying With Section 413(a) of the FD&C Act [21 U.S.C. § 350b(a)].

ChromaDex is concerned that FDA is not prioritizing enforcement of the NDIN requirement established in Section 413(a) of the FD&C Act [21 U.S.C. § 350b(a)]. As noted above, ChromaDex's Citizen Petition highlighted the fact that Elysium is distributing its NR product, Basis, without having submitted the required NDIN. In its comment, Elysium did not try to justify its failure to file the required notification (which it cannot), nor did it promise to rectify the problem by submitting the required notification in the future. Elysium did not bother to address this issue in its comment at all.

Elysium's willingness to ignore this issue (along with its exposure to potential civil and criminal sanctions) should be a wake-up call for FDA. If FDA does not prioritize enforcement in this area, then the NDIN requirement will become a dead letter in the law.[10] The failure to

---

[9] FD&C Act § 413(b); 21 U.S.C. § 350b(b).

[10] *See* Jennifer Grebow, *When in Doubt, Submit a NDI Notification, Urge NPA Webcast Speakers, Nutritional Outlook* (Aug. 18, 2016) (quoting FDA official as saying: "The NDI notification process is very important to the FDA. The notification process is FDA's only premarket opportunity to review products, to review the formulation and the safety of products, and we take that seriously.").

enforce the requirement only serves to punish legitimate dietary supplement manufacturers who undertake the burden, time, and expense of preparing the required notification, including responding to any issues raised by FDA.[11] As a result, if FDA chooses not to enforce the notification requirement, then compliance will erode even further.

FDA has adjusted its enforcement priorities in similar situations. For instance, in Compliance Policy Guide 440.100, entitled, "Marketing Unapproved Drugs," FDA emphasized that when a company obtains approval of a new drug application ("NDA") for a product that other companies, for historical reasons, have been marketing without an approved NDA, FDA will to take enforcement action against the remaining unapproved drugs.[12] FDA explained that "[w]e want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective."[13]

ChromaDex requests that FDA issue a similar Compliance Policy Guide, or other public announcement, emphasizing that the agency will prioritize enforcement of the NDIN requirement in cases where a manufacturer has taken the necessary steps to comply with the requirement, but other manufacturers either start or continue to distribute products containing the same New Dietary Ingredient without complying with the law. After all, FDA should want to encourage voluntary compliance with the NDIN requirement because such voluntary compliance benefits the public health by increasing the assurance that dietary supplements contain only safe ingredients.

Elysium may not claim ChromaDex's NDIN for its product. FDA has already stated in a Draft Guidance on NDINs that *each* manufacturer of a New Dietary Ingredient must comply with the notification requirement.[14] FDA explained that the FD&C Act is not designed to allow New Dietary Ingredients to be distributed *en mass* by various manufacturers under the cover of a single notification filed by one manufacturer.[15] In fact, this situation demonstrates precisely why

---

[11] While FDA has issued Warning Letters to companies that have not submitted an NDIN, *see, e.g.*, FDA, Warning Letter to NutraClipse, Inc. (Mar. 31, 2016), such warnings have not been systemic, given the number of supplements on the market that contain New Dietary Ingredients.

[12] *See* FDA, Compliance Policy Guide, Sec. 440.100, *Marketing New Drugs Without Approved NDAs or ANDAs* (Sep. 19, 2011).

[13] *Id.* at 7.

[14] *See* FDA, Draft Guidance for Industry, *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues* (Aug. 2016), at 31. The Draft Guidance notes that

> in situations where the NDI manufacturer or distributor has not submitted a notification, the statute deems a dietary supplement that contains the NDI to be adulterated unless the manufacturer or distributor of "the" dietary supplement (that particular dietary supplement), not "a" dietary supplement (some other dietary supplement containing the NDI) has submitted a notification. Accordingly, if the NDI manufacturer or distributor has not submitted a notification covering the conditions of the NDI's use, each manufacturer or distributor of a supplement containing the NDI must submit an NDI notification 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" (21 U.S.C. 350b(a)(2)).

Id.

[15] *See id.*

a separate notification is needed. ChromaDex's NDIN for NR highlighted substantial manufacturing controls that preclude the use of toxic solvents like toluene. Elysium's NR product, however, is contaminated with toluene. The fact that one manufacturer has submitted a NDIN does not demonstrate that the same or similar New Dietary Ingredient manufactured by a different company "will reasonably be expected to be safe."[16]

Clarifying that each dietary supplement manufacturer must comply with the NDIN requirement in a draft guidance document is not enough. FDA should finalize the guidance and support it with appropriate enforcement priorities. ChromaDex is requesting that FDA finalize the guidance and issue a public announcement that it will prioritize enforcement in situations where one company has complied with the NDIN requirement with respect to a specific New Dietary Ingredient and others have not.

III. Conclusion

The use of toxic solvents in dietary supplements and other foods raises important public health issues. FDA's enforcement policy with respect to the NDIN requirement also has a significant impact on the public health. ChromaDex respectfully requests that FDA give serious consideration to the issues raised in its Citizen Petition and in this Supplemental Citizen Petition.

Sincerely,

Sheldon T. Bradshaw
Counsel to ChromaDex, Inc.

cc: Frank L. Jaksch, Jr.
Rob Fried
Troy Rhonemus
ChromaDex, Inc.

[16] FD&C Act § 413(a)(2); 21 U.S.C. 350b(a)(2).