DEPARTMENT OF THE TREASURY
ALCOHOL AND TOBACCO TAX AND TRADE BUREAU
WASHINGTON, D.C. 20005

May 3, 2017

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Dear Mr. Emord,

By letter dated April 12, 2016, as counsel for Bellion Spirits, LLC, and Chigurupati Technologies (collectively "the petitioners"), you submitted a petition to the Alcohol and Tobacco Tax and Trade Bureau (TTB). The petition requests that TTB "declare, via rulemaking or through the exercise of enforcement discretion, that the use of the Petitioners' proposed health-related statements concerning the hepatoprotective and DNA-protective effects of NTX® [a proprietary blend of three ingredients] in the labeling and advertising of wines, distilled spirits, and malt beverages is permissible." By letter dated November 1, 2016, you submitted a "Supplement" to the petition, which included five new exhibits.

After careful consideration of the petition and the materials submitted with that petition, and after consultation with the U.S. Food and Drug Administration (FDA) on the issue of whether the scientific data you submitted substantiates the proposed health-related statements, TTB has determined that the proposed claims about alcohol beverages infused with NTX® are explicit and implicit specific health claims that are not supported by credible evidence, and thus are not "truthful and adequately substantiated by scientific or medical evidence" as required by the TTB labeling and advertising regulations.[1] Furthermore, because the claims are not substantiated, the proposed labeling and advertising statements "create a misleading impression" that consumption of alcohol beverages infused with NTX® will protect consumers from certain serious health risks associated with both moderate and heavy levels of alcohol consumption, and thus they violate TTB's regulations prohibiting the use of misleading statements in general, and misleading health-related statements in particular.[2]

TTB also reviewed the proposed disclaimer set forth in the petition. TTB has determined that the proposed disclaimer does not in any way address the limitations of the evidence cited in support of the proposed health claims and makes implicit health claims of its own, which are also misleading.

[1] See 27 CFR 5.42(b)(8)(ii)(B)(2); 4.39(h)(2)(ii)(B); and 7.29(e)(2)(ii)(B) (use of specific health claims on distilled spirits, wine, and malt beverage labels) and 5.65(d)(2)(ii); 4.64(i)(2)(ii); and 7.54(e)(2)(ii) (use of specific health claims in advertising of distilled spirits, wine and malt beverages).
[2] See 27 CFR 5.42(a)(1) and (b)(8)(ii)(A); 4.39(a)(1) and (h)(2)(i); and 7.29(a)(1) and (e)(2)(i) (labeling of distilled spirits, wine, and malt beverages) and 27 CFR 5.65(a)(1) and (d)(2)(i); 4.64(a)(1) and (i)(2)(i); and 7.54(a)(1) and (e)(2)(i) (advertising of distilled spirits, wine, and malt beverages).

Accordingly, the claims, including when viewed with the proposed disclaimer, do not comply with TTB regulations regarding the use of health-related statements or specific health claims in the labeling or advertising of wine, distilled spirits, or malt beverages.

For the reasons set forth more fully in this letter, TTB is denying your request to initiate rulemaking on the claims, or to issue a ruling that would authorize the use of such statements on labels or in advertisements. It is TTB's position that the use of the claims set forth in the petition, including when viewed with the proposed disclaimer, on labels or in advertisements for distilled spirits, wines, or malt beverages would violate the Federal Alcohol Administration Act (FAA Act) and its implementing regulations by making specific health claims that are not adequately substantiated, and by misleading consumers as to the serious health consequences of both moderate and heavy levels of consumption of alcohol beverages containing NTX®.

TTB's response begins with an overview of the petition and subsequent correspondence with the petitioners (including the receipt of the supplement to the petition) and discusses the nature of the petitioners' requests. Next, this response provides a review of the applicable law and regulations and discusses the health risks associated with alcohol beverage consumption, which are relevant to the consideration of any health claims proposed in connection with such consumption. This response then turns to the eight claims and the disclaimer proposed in the petition. After discussing the proper classification of each of the proposed claims under TTB regulations, the response then describes how TTB consulted with FDA so that FDA could provide its evaluation of the scientific evidence submitted by the petitioners and the results of that consultation. Finally, this response sets forth TTB's determination as to whether any of the proposed claims are permissible specific health claims or health-related statements under TTB regulations and addresses the remaining legal arguments advanced by the petitioners.

I. Petition

TTB views your petition as a request that TTB issue a ruling on whether use of the labeling and advertising statements set forth in the petition would violate TTB regulations, or, in the alternative, that TTB initiate rulemaking to allow the use of such statements on labels and in advertisements. *See* 27 CFR 70.471 (allowing any person to request a ruling regarding matters under the FAA Act) and 27 CFR 70.701(c) (which provides that "[i]nterested persons may petition for the issuance, amendment, or repeal of a rule").

Jonathan W. Emord, Esq.

A. Petitioners

The petition states that Bellion Spirits, LLC, "is the independent bottler and distributor of Bellion brand Vodka" and that its principal place of business is in Secaucus, New Jersey.[3] Petition, pp. 3–4. The petition (p. 4) further states as follows:

> Bellion Spirits was founded to pioneer innovation in the alcohol beverage industry, through the introduction of functional alcoholic beverages, which generally retain the customary characteristics of alcoholic beverages, while reducing or mitigating the unwanted negative effects, like damage to the liver, genetic injuries, and oxidative stress. Bellion's scientific and commercial goals focus on the education of consumers concerning the detrimental effects of alcohol consumption, along with the advantages of functional beverages or spirits that aid consumers in making smarter, safer, and healthier choices. Bellion's objectives include the distribution of products and technologies that help to educate consumers about the chemical interactions of alcohol in the body (both positive and negative). Bellion has coined the phrase "Functional Spirits" as a description of the benefits or protective properties conveyed through its technology, as described more fully below in this petition.

The petition (pp. 4–5) states that Bellion Spirits purchases NTX®, an ingredient in "Bellion Vodka," from Chigurupati Technologies Private Ltd. (Chigurupati Technologies), which is "solely a Research & Development institution founded with the objective to 'aid in the evolution of mankind.'" According to the petition, Chigurupati Technologies' principal place of business is in India. The petition (pp. 4–5) states that:

> Chigurupati Technologies Private Ltd. developed and owns a proprietary blend of three generally recognized as safe ingredients combined through a proprietary process and sold under the name "NTX." These three ingredients are Glycyrrhizin Acid, D-Mannitol, and Potassium Sorbate. "NTX" is thus an ingredient in Bellion Vodka that Bellion purchases from Chigurupati Technologies.

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[3] Distillers and bottlers of beverage distilled spirits are required to obtain a permit from TTB under the FAA Act. *See* 27 U.S.C. 203(b). TTB's public records on FAA Act basic permits reflect that Bellion Spirits, LLC has two permits as a wholesaler and one permit as an importer of alcohol beverages. See https://www.ttb.gov/foia/xls/frl-alcohol-wholesalers-ut-to-wy.htm; https://www.ttb.gov/foia/xls/frl-alcohol-wholesalers-mi-to-nh.htm; and https://www.ttb.gov/foia/xls/frl-alcohol-importers-ut-to-wy.htm. However, TTB's public records on FAA Act basic permits do not reflect any evidence that Bellion Spirits, LLC has a permit as a distiller or bottler of distilled spirits. See https://www.ttb.gov/foia/xls/frl-spirits-producers-and-bottlers.htm. The websites were all accessed on May 2, 2017. The approved certificates of label approval for "Bellion Vodka Infused with Natural Flavors" show that "Bellion Spirits" is used as a trade name for the bottler of the product, Frank-Lin Distillers Products, Ltd.

The petition states that in 2015, TTB approved two certificates of label approval for "Bellion Vodka" labels that referenced NTX®, one of which has now expired. (Petition, pp. 6–7 and n. 6).[4]

B. Health Claims Relating to NTX®

The petition (p. 5) further claims as follows:

> Studies commissioned by Chigurupati Technologies reveal that "NTX," when infused into liquor, yields a protective effect on the human liver during alcohol consumption, lessening the adverse effect of alcohol on the liver. Heretofore that information has not appeared on the label, in the labeling, or in the advertising for alcohol containing products sold in the United States. NTX® also adds flavor and smoothness to the vodka drink. Bellion Vodka has not promoted the use of NTX for health purposes, but seeks to convey the liver and DNA protective effects of alcohol containing NTX® through this instant petition.

According to the petition, "NTX® is a proprietary blend of glycyrrhizin, mannitol, and potassium sorbate." Petition, p. 1. The petition claims that "when NTX® is infused into alcoholic beverages, it renders them safer, i.e., less toxic, than counterparts that do not contain NTX®. NTX® reduces the adverse effects of alcohol on the liver and on DNA. Thus, NTX® lessens certain deleterious effects caused from consumption of alcohol." *Id*.

In light of these purported effects, the petition (p. 7) requests that "TTB rule that alcoholic spirit beverages that contain NTX® may bear one or more of the following health-related statements in its labeling, advertising, or promotional speech:" [For ease of reference, we are assigning numbers to the claims, in the order in which they were set out in the petition.]

1. NTX® provides antioxidant and anti-inflammatory support;
2. NTX® helps protect against, i.e., reduces, alcohol-induced oxidative damage to the liver;
3. NTX® helps maintain normal liver enzyme production and function;

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[4] TTB notes that a search of TTB's Public COLA Registry *(available at* https://www.ttbonline.gov/colasonline/publicSearchColasBasic.do) reveals that there are currently two approved labels for such products. One label, (TTB ID 15091001000076), which was referred to in the petition, was approved on April 7, 2015. A second label (TTB ID 16109001000457) was approved on July 12, 2016, after the submission of the petition. Both products are designated as "Vodka Infused with Natural Flavors" and include the following statement on the label: "For over 600 years, vodka has been made the same way. No longer. Infused with NTX® [a proprietary blend of glycyrrhizin, mannitol, and potassium sorbate], Bellion® changes vodka forever." The labels also state: "We made it smart. Please drink it responsibly." Finally, the labels state: "Vodka Evolved – Infused with Natural Flavors – Created with NTX."

4. NTX® supports normal liver defenses and regenerative mechanisms;
5. NTX® reduces the risk of alcohol-induced liver diseases, including fibrosis and cirrhosis;
6. NTX® helps maintain normal liver functions;
7. NTX® helps protect DNA from alcohol-induced damage; and
8. NTX® reduces alcohol-induced DNA damage.

In conjunction with the proposed statements, the petition (p. 8) also sets forth the following disclaimer that would be included in labeling, advertising, or promotional claims:

> NTX® does not protect against all health risks associated with moderate and heavy levels of alcohol consumption, including, but not limited to, motor vehicle accidents, high blood pressure, stroke, cancer, birth defects, psychological problems, and alcohol dependency. Do not consume alcohol if: you are younger than the legal drinking age; you are pregnant or may become pregnant; you are taking medicine that can interact with alcohol; you have a medical condition for which alcohol is contraindicated; you plan to drive; or you cannot restrict your drinking to moderate levels. If you consume alcohol, only consume it in moderation. "Moderation" means up to one drink per day for women and up to two drinks per day for men.

II. Correspondence

A. Correspondence Regarding the Original Petition

By letter dated May 26, 2016, TTB acknowledged receipt of your petition, and advised you that TTB interpreted your petition as a request that TTB issue a ruling on whether use of the labeling and advertising statements set forth in the petition would violate TTB regulations, or, in the alternative, that TTB initiate rulemaking to allow the use of such statements on labels and in advertisements. *See* 27 CFR 70.471 (allowing any person to request a ruling regarding matters under the FAA Act) and 27 CFR 70.701(c) (which provides that "[i]nterested persons may petition for the issuance, amendment, or repeal of a rule"). Accordingly, your petition was referred to TTB's Regulations and Rulings Division for review.

The letter also advised you that, based on the specific provisions of the TTB health claims regulations in 27 CFR 5.42(b)(8)(ii)(B)(1), 4.39(h)(2)(ii)(A) and 7.29(e)(2)(ii)(A), TTB had forwarded the petition, including the exhibits, to FDA, so that TTB could consult with FDA officials as set forth in those regulations. TTB also advised you that TTB would provide you with an update on the status of the review of the petition by July 12, 2016.

By letter dated July 12, 2016, TTB advised you that TTB was actively reviewing your petition and the attached exhibits. TTB stated that it would provide you with an update on the status of our review no later than October 10, 2016. By letter dated October 7, 2016, TTB advised you that it would issue a decision on the petition no later than November 10, 2016.

B. Supplement Dated November 1, 2016

By letter dated November 1, 2016, you submitted a "Supplement" to the April 12, 2016, petition. The supplement included five exhibits, described in the letter as constituting "additional and compelling evidence, including a peer-reviewed article and two new human clinical studies, confirming the hepatoprotective and DNA protective effects of NTX®."

The letter also stated as follows:

> Your letter dated October 7, 2016 promised a decision by November 10, 2016. We expect that decision to encompass the supplemental exhibits attached hereto because they are relevant and supportive of Bellion's pending petition and, as such, should be included within the administrative record. *See Larita-Martinez v. I.N.S.*, 220 F.3d 1092, 1095 (9th Cir. 2000) (due process requires that the agency "review all relevant evidence"). Supplementing the record with timely and relevant information is necessary to ensure a full and complete record for decision at the administrative level.

C. TTB Response to Supplement

By letter dated November 10, 2016, TTB advised you that TTB was in the process of consulting with FDA about the evidence submitted with the supplement. TTB advised that it would provide you with a status update on its review of the newly submitted materials no later than December 9, 2016.

By letter dated December 9, 2016, TTB advised you that it anticipated that it would be able to provide you with a response to the petition within 90 days from the date of that letter. As you requested, we stated that this response would include our review of all materials submitted in support of the petition, including the additional materials that you submitted on November 1, 2016.

By letter dated March 20, 2017, TTB advised you that it was finalizing its review of the petition, including the supplement and the attached exhibits, and it anticipated providing you with a decision on the petition no later than April 7, 2017.

III. Applicable Law and Regulations

A. Federal Alcohol Administration Act (FAA Act)

The FAA Act generally requires bottlers of distilled spirits, wine, and malt beverages, and importers of bottled distilled spirits, wine, and malt beverages, to obtain a certificate of label approval (COLA) from TTB prior to introducing their products in interstate or foreign commerce. *See* 27 U.S.C. 205(e). The FAA Act also makes it unlawful for industry members to introduce or receive such products in interstate or foreign commerce unless the alcohol beverages are bottled and labeled in conformity with regulations issued by the Secretary with regard to the labeling of wine, distilled spirits, and malt beverages.[5] *See* 27 U.S.C. 205(e). Furthermore, it is unlawful for industry members to publish or disseminate advertisements of distilled spirits, wine, or malt beverages in (or calculated to induce sales in) interstate or foreign commerce, or by mail, unless the advertisements conform to the advertising regulations issued by the Secretary. *See* 27 U.S.C. 205(f).

The FAA Act specifically authorizes the issuance of labeling and advertising regulations that will prevent deception of the consumer, provide the consumer with adequate information as to the identity and quality of the product, and prohibit false or misleading statements. *See* 27 U.S.C. 205(e) and (f). Additionally, the law provides authority to prohibit, irrespective of falsity, labeling or advertising statements relating to age, manufacturing processes, analyses, guarantees, and scientific or irrelevant matters that the Secretary of the Treasury finds are likely to mislead the consumer. *Id.*

B. FAA Act Regulations that Prohibit Misleading Labeling and Advertising Statements

With regard to distilled spirits,[6] the implementing regulations at 27 CFR 5.42(a)(1) prohibit the use of labeling statements that are “false or untrue in any particular, or that, irrespective of falsity, directly, or by ambiguity, omission, or inference, or by the addition of irrelevant, scientific or technical matter, tend[] to create a misleading impression.” The wine and malt beverage labeling regulations contain identical language. *See* 27 CFR 4.39(a)(1) and 7.29(a)(1), respectively. Furthermore, the advertising regulations

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[5] TTB administers the FAA Act pursuant to section 1111(d) of the Homeland Security Act of 2002, codified at 6 U.S.C. 531(d). The Secretary of the Treasury has delegated various authorities to the TTB Administrator to perform the functions and duties in the administration and enforcement of these provisions through Treasury Department Order 120–01 (dated December 10, 2013, superseding Treasury Order 120–01 (Revised), "Alcohol and Tobacco Tax and Trade Bureau," dated January 24, 2003).

[6] Because the only approved labels for alcohol beverage products containing NTX® are for distilled spirits products, our analysis focuses on the distilled spirits regulations. Because the petition also asks for approval for wines and malt beverages, we briefly discuss those regulations as well. As set forth in this response, the regulations pertaining to distilled spirits, wine, and malt beverages are substantively identical with regard to the use of misleading claims in general, and health-related statements (including specific health claims) in particular, on labels and in advertisements, respectively.

for distilled spirits, wine, and malt beverages, respectively, include the same general prohibition. *See* 27 CFR 5.65(a)(1); 4.64(a)(1); and 7.54(a)(1).

C. TTB Regulations on Health-Related Statements

1. *Implementation of TTB's FAA Act regulations on health-related statements*

In addition to TTB's general prohibition on misleading labeling and advertising statements, TTB's regulations specifically address health-related statements, as well as a narrower subset of such statements—specific health claims. Those regulations were issued in 2003,[7] as a result of notice-and-comment rulemaking that included two public hearings and that was initiated by TTB's predecessor agency, the Bureau of Alcohol, Tobacco and Firearms (ATF). The preamble to the final rule explains the history of health claims regulations relating to alcohol beverage labeling and advertising by noting that up until that date, TTB regulations prohibited claims regarding "curative or therapeutic effects if the representation is untrue in any particular or tends to create a misleading impression. This standard originated more than 60 years ago with the initial labeling and advertising regulations issued under the FAA Act." 68 FR at 10076. The preamble further noted that "TTB and its predecessor agencies have historically taken a very strict view of the regulatory prohibition on false or misleading curative or therapeutic claims about alcohol beverages. This strict interpretation is based on the view that 'distilled spirits, wines and malt beverages are, in reality, alcoholic beverages and not medicines of any sort, * * *.' FA-129, dated January 5, 1938." *Id.*

The final rule also noted the role played by various other Federal agencies, including FDA, in the health claim issue. Among other things, the preamble noted that "ATF always utilized, as TTB does now, the scientific and public health expertise of FDA in approving ingredients in alcohol beverages, requiring label disclosure of certain substances, and identifying adulterated alcohol beverages that are deemed mislabeled." 68 FR at 10078. The final rule also noted that "[b]ecause TTB is not an expert on public health issues, we (and our predecessors) have generally deferred to the findings of the Department of Health and Human Services, including NIAAA [the National Institute on Alcohol Abuse and Alcoholism], FDA, CSAP [the Center for Substance Abuse Prevention], and the Surgeon General, on issues related to the effects on health of alcohol consumption." 68 FR at 10084.

2. *Requirements of regulations on health-related statements*

The TTB regulations at 27 CFR 5.42(b)(8)(i)(A) define the term "health-related statement," in pertinent part, to mean:

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[7] T.D. TTB-1, Health Claims and Other Health-Related Statements in the Labeling and Advertising of Alcohol Beverages, 68 FR 10076 (2003).

> [A]ny statement related to health (other than the warning statement required by § 16.21 of this chapter) and includes statements of a curative or therapeutic nature that, expressly or by implication, suggest a relationship between the consumption of alcohol, distilled spirits, or any substance found within the distilled spirits, and health benefits or effects on health. The term includes both specific health claims and general references to alleged health benefits or effects on health associated with the consumption of alcohol, distilled spirits, or any substance found within the distilled spirits, as well as health-related directional statements. The term also includes statements and claims that imply that a physical or psychological sensation results from consuming the distilled spirits, as well as statements and claims of nutritional value (e.g., statements of vitamin content).

The rules for "health-related statements" provide as follows:

> In general, labels may not contain any health-related statement that is untrue in any particular or tends to create a misleading impression as to the effects on health of alcohol consumption. TTB will evaluate such statements on a case-by-case basis and may require as part of the health-related statement a disclaimer or some other qualifying statement to dispel any misleading impression conveyed by the health-related statement.

See 27 CFR 5.42(b)(8)(ii)(A).

3. Regulations on specific health claims

TTB regulations in 27 CFR 5.42(b)(8)(i)(B) define a specific health claim as follows:

> [A] type of health-related statement that, expressly or by implication, characterizes the relationship of the distilled spirits, alcohol, or any substance found within the distilled spirits, to a disease or health-related condition. Implied specific health claims include statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between distilled spirits, alcohol, or any substance found within the distilled spirits, and a disease or health-related condition.

Specific health claims are prohibited on distilled spirits labels unless they meet the conditions set forth in the regulations. Among other things, the regulations provide that TTB will consult with FDA, as needed, on the use of a specific health claim on labels. If FDA determines that the use of a labeling claim is a drug claim that is not in compliance with the requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA), TTB will

not approve the use of that specific health claim on a distilled spirits label. *See* 27 CFR 5.42(b)(8)(ii)(B)(1).

The conditions for approving specific health claims on distilled spirits labels are as follows:

> TTB will approve the use of a specific health claim on a distilled spirits label only if the claim is truthful and adequately substantiated by scientific or medical evidence; sufficiently detailed and qualified with respect to the categories of individuals to whom the claim applies; adequately discloses the health risks associated with both moderate and heavier levels of alcohol consumption; and outlines the categories of individuals for whom any levels of alcohol consumption may cause health risks. This information must appear as part of the specific health claim.

27 CFR 5.42(b)(8)(ii)(B)(2).

4. Wine, malt beverage, and advertising regulations

The regulations with regard to the use of health-related statements and specific health claims on the labels of wine and malt beverages include the same language as the distilled spirits regulations with regard to the definitions and the standards for the use of such labeling statements. *See* 27 CFR 4.39(h) and 7.29(e).

The advertising regulations similarly prohibit the use of health-related statements, including specific health claims, that are untrue in any particular or that tend to create a misleading impression. *See* 27 CFR 4.64(i) (advertising of wines); 27 CFR 5.65(d) (advertising of distilled spirits); and 27 CFR 7.54(e) (advertising of malt beverages). The advertising regulations with regard to specific health claims have substantially the same criteria as the labeling regulations on specific health claims, including the requirement that the claims must be truthful and adequately substantiated by scientific or medical evidence.[8]

D. Alcoholic Beverage Labeling Act of 1988 (ABLA)

Finally, we note that the Alcoholic Beverage Labeling Act of 1988 (ABLA) requires a health warning statement on alcoholic beverage containers. 27 U.S.C. 213 et seq. The ABLA contains the following declaration of policy and purpose:

> The Congress finds that the American public should be informed about the health hazards that may result from the consumption or abuse of alcoholic

[8] One difference is that because advertisements, unlike labels, are not subject to prior approval requirements, the advertising regulations do not include references to prior approval of advertising claims by TTB.

> beverages, and has determined that it would be beneficial to provide a clear, nonconfusing reminder of such hazards, and that there is a need for national uniformity in such reminders in order to avoid the promulgation of incorrect or misleading information and to minimize burdens on interstate commerce.

27 U.S.C. 213. As a result of this concern, the ABLA requires that any alcoholic beverage container held for sale or distribution in the United States must bear the following statement on the label:

> **GOVERNMENT WARNING:** (1) According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects. (2) Consumption of alcoholic beverages impairs your ability to drive a car or operate machinery, and may cause health problems.

27 U.S.C. 215(a). *See also* 27 CFR 16.20 and 16.21.

It is clear that one of the purposes of the ABLA was to avoid confusing the American public about the health hazards associated with the consumption of alcoholic beverages. In order to effectuate this goal, Congress prescribed specific language that must appear on the labels of alcoholic beverage containers. As TTB pointed out in the preamble to its 2003 final rule on the use of health claims, the health warning statement itself is not a disclaimer that may be relied upon by industry members who wish to use health claims on labels, because "[t]he use of health claims or other health-related statements without qualification or disclosure of adverse effects to 'balance' the mandatory warning statement not only undermines the intent of the ABLA; it also tends to confuse consumers about the very real health risks associated with alcohol consumption." *See* T.D. TTB-1, 68 FR 10076, 10100 (2003).

IV. Health Risks Associated with Alcohol Consumption

A. Health Risks Recognized by TTB in its 2003 Final Rule

The health risks associated with alcohol consumption and abuse are significant. TTB and its predecessor agency, ATF, discussed those health risks in the rulemaking that led to the issuance of the health claim regulations in 2003. In T.D. TTB-1, 68 FR 10076, 10084 (2003), TTB summarized these risks as follows:

> The evidence presented by the medical experts, as well as the studies presented with some of the comments, indicate that there are differences of opinion as to how the relative risks and benefits of alcohol consumption should be weighed. The evidence reflects a broad consensus that heavy levels of alcohol consumption pose serious health risks. The record also

reflects that there is a broad consensus that certain categories of people should not consume any alcohol. With regard to those individuals for whom alcohol consumption is not contraindicated, there was some difference among the experts as to how to weigh the relative risks and benefits of moderate consumption, with some experts stressing the protection against cardiovascular disease, and other experts stressing the increased risk of injury and certain cancers.

Because TTB is not an expert on public health issues, we (and our predecessors) have generally deferred to the findings of the Department of Health and Human Services, including NIAAA, FDA, CSAP, and the Surgeon General, on issues related to the effects on health of alcohol consumption. In the case at hand, TTB finds that the evidence in the rulemaking record supports the findings of NIAAA's 1999 "Alcohol Alert" and the 2000 Dietary Guidelines published by USDA [the U.S. Department of Agriculture] and HHS. The main points of these findings can be summarized as follows:

- Alcohol beverages are harmful when consumed in excess, and some people should not drink at all. Excess alcohol alters judgment and can lead to dependency and many other serious problems. Heavy levels of alcohol consumption cause social and psychological problems, cirrhosis of the liver, inflammation of the pancreas, and damage to the brain and heart.
- Taking more than one drink per day for women or two drinks per day for men can raise the risk for motor vehicle accidents, other injuries, high blood pressure, stroke, violence, suicide, and certain types of cancer. Even one drink per day can slightly raise the risk of breast cancer.
- Alcohol consumption during pregnancy increases the risk of birth defects.
- Certain individuals should not drink any alcohol; for these individuals, even moderate levels of alcohol consumption may cause health risks. Included in this category are children and adolescents; individuals of any age who cannot restrict their drinking to moderate levels; women who may become pregnant or who are pregnant; individuals who plan to drive, operate machinery, or take part in other activities that require attention, skill, or coordination; and individuals taking prescription or over-the-counter medications that can interact with alcohol.
- Moderate levels of alcohol consumption are associated with a reduced risk of coronary artery disease for certain individuals, but causation has not been conclusively established.
- To the extent that moderate consumption is linked to a lowered risk for coronary heart disease, the link appears mainly among men over 45

and women over age 55. Moderate consumption provides little, if any, health benefit for younger people.

- The effects on health of alcohol consumption vary from individual to individual, depending on the individual's health profile and history, as well as the levels of consumption. Risk of alcohol abuse increases when drinking starts at an early age. Some studies suggest that older people may become more sensitive to the effects of alcohol as they age.

Based on the above, it is TTB's conclusion that the medical data still supports ATF's longstanding (and now our) position that notwithstanding the data linking moderate alcohol consumption to a reduced risk of heart disease in some individuals, there are significant health risks associated with all levels of alcohol consumption. The medical data submitted by the commenters, as well as the testimony presented by experts at the public hearings, suggest that there is a link between moderate alcohol consumption and a reduced risk of heart disease in certain individuals; however, causation has not been conclusively established. The risk/benefit ratio varies with the individual's own health profile and the level of consumption. For example, moderate alcohol consumption confers few, if any, benefits on people at low risk for heart disease. The evidence also establishes that there are serious risks associated with higher levels of alcohol consumption, and that even moderate consumption poses health risks for certain individuals. Finally, there are certain categories of individuals for whom any level of alcohol consumption is not recommended.

B. Current Evidence Regarding Health Risks Associated with Alcohol Consumption

The health risks associated with alcohol consumption and alcohol abuse remain clear. According to *Alcohol Facts and Statistics,* a publication of the NIAAA, an estimated 88,000 people in the United States die from alcohol-related causes annually, "making alcohol the fourth leading preventable cause of death in the United States."[9] In 2010, alcohol misuse cost the United States $249 billion. Three-quarters of the cost of alcohol misuse is related to binge drinking.[10]

The 2015 National Survey on Drug Use and Health states that 15.1 million adults ages 18 and older had "Alcohol Use Disorder" or "AUD."[11] According to *Alcohol Facts and*

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[9] *See* National Institute on Alcohol Abuse and Alcoholism, *Alcohol Facts and Statistics,* http://pubs.niaaa.nih.gov/publications/AlcoholFacts&Stats/AlcoholFacts&Stats.htm (Updated January 2017).
[10] *Id.*
[11] *Id.*

Statistics, "AUD is a medical condition that doctors diagnose when a patient's drinking causes distress or harm" and includes both alcohol abuse and alcohol dependence. Furthermore, "NIAAA defines binge drinking as a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08g/dl. This typically occurs after 4 drinks for women and 5 drinks for men – in about 2 hours."[12]

One risk related to alcohol consumption is liver disease. As noted in the petition, the harmful effects of alcohol abuse on the human liver are well established. According to *Alcohol Facts and Statistics*, in 2013, of the 72,559 liver disease deaths among individuals aged 12 and older, 45.8 percent involved alcohol. Among all cirrhosis deaths in 2011, 47.9 percent were alcohol-related. The proportion of alcohol-related cirrhosis was highest (76.5 percent) among decedents aged 25-34, followed by decedents aged 35-44, at 70.0 percent.[13] Drinking alcohol also increases the risk of cancers of the mouth, esophagus, pharynx, larynx, liver and breast.[14]

According to the NIAAA publication *Beyond Hangovers – Understanding Alcohol's Impact on Your Health,*[15] "[m]ore than 2 million Americans suffer from liver disease caused by alcohol. In general, liver disease strikes people who drink heavily over many years." Furthermore, "[s]tatistics show that about one in five heavy drinkers will develop alcoholic hepatitis, while one in four will develop cirrhosis." The most critical lifestyle change for people with alcoholic liver disease, according to this NIAAA publication, "is abstinence from alcohol. Quitting drinking will help prevent further injury to your liver." *Id.* Similarly, a publication of the Centers for Disease Control and Prevention, *Fact Sheets – Moderate Drinking,* provides that "[f]or some conditions, such as certain types of cancer (e.g., breast cancer) and liver disease, there is no known safe level of alcohol consumption." [Footnotes omitted.][16]

Another risk related to alcohol abuse is brain damage. In an Alcohol Alert publication entitled "Alcohol's Damaging Effects on the Brain," dated October 2004, the NIAAA summarizes these effects as follows:

> Clearly, alcohol affects the brain. Some of these impairments are detectable after only one or two drinks and quickly resolve when drinking

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[12] *Id.*
[13] *Id.*
[14] *Id.*
[15] *See* National Institute on Alcohol Abuse and Alcoholism, *Beyond Hangovers – Understanding Alcohol's Impact on Your Health,* http://pubs.niaaa.nih.gov/publications/Hangovers/beyondHangovers.htm (September 2010).
[16] See https://www.cdc.gov/alcohol/fact-sheets/moderate-drinking.htm. This publication also notes that "[a]lthough past studies have indicated that moderate alcohol consumption has protective health benefits (e.g., reducing risk of heart disease), recent studies show this may not be true. While some studies have found improved health outcomes among moderate drinkers, it's impossible to conclude whether these improved outcomes are due to moderate alcohol consumption or other differences in behaviors or genetics between people who drink moderately and people who don't." [Footnotes omitted.]

> stops. On the other hand, a person who drinks heavily over a long period of time may have brain deficits that persist well after he or she achieves sobriety.[17]

The 2015-2020 *Dietary Guidelines for Americans*[18] defines moderate consumption as up to one drink per day for women and up to two drinks per day for men, and provides the following information with regard to alcohol consumption:

> Excessive alcohol consumption—which includes binge drinking (4 or more drinks for women and 5 or more drinks for men within about 2 hours); heavy drinking (8 or more drinks a week for women and 15 or more drinks a week for men); and any drinking by pregnant women or those under 21 years of age—has no benefits. Excessive drinking is responsible for 88,000 deaths in the United States each year, including 1 in 10 deaths among working age adults (age 20-64 years). In 2006, the estimated economic cost to the United States of excessive drinking was $224 billion. Binge drinking accounts for over half of the deaths and three-fourths of the economic costs due to excessive drinking. [Footnotes omitted.]

V. Overview of TTB's Evaluation of the Eight Proposed Claims

TTB evaluated the eight proposed claims in the petition against TTB's distilled spirits labeling regulations. Those regulations, as outlined above, establish three regulatory standards that can apply to claims of the sort that the petitioners wish to make. First, and most broadly, all statements on a distilled spirits label are subject to TTB's prohibition on statements that are "false or untrue in any particular, or that, irrespective of falsity, directly, or by ambiguity, omission, or inference, or by the addition of irrelevant, scientific or technical matter, tend[] to create a misleading impression." *See* 27 CFR 5.42(a)(1). Second, any statement that is "health-related" must not be "untrue in any particular or tend[] to create a misleading impression as to the effects on health of alcohol consumption." *See* 27 CFR 5.42(b)(8)(ii)(A). And third, any health-related statement that is also a "specific health claim" must, among other requirements, be "truthful and adequately substantiated by scientific or medical evidence." *See* 27 CFR 5.42(b)(8)(ii)(B)(2).

In light of that regulatory framework, TTB first had to make a determination as to the nature of the claims in the petition. As explained below, TTB has concluded that all eight of the proposed claims are health-related statements that are also specific health claims. Accordingly, the eight petition claims must satisfy each of the three labeling regulations just discussed.

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[17] *See* https://pubs.niaaa.nih.gov/publications/aa63/aa63.htm.

[18] *See* 2015-2020 Dietary Guidelines for Americans, https://health.gov/dietaryguidelines/2015/resources/2015-2020_Dietary_Guidelines.pdf.

The most detailed of those requirements is the third—the threshold requirement that any specific health claim be "truthful and adequately substantiated by scientific or medical evidence." *See* 27 CFR 5.42(b)(8)(ii)(B)(2). TTB therefore begins its discussion of the petition claims by assessing whether each claim meets this standard. To aid in that evaluation, TTB has consulted with FDA and has drawn on that agency's substantial expertise in assessing scientific studies.

After reviewing FDA's evaluation of the scientific evidence, TTB has determined that none of the eight claims is supported by credible scientific or medical evidence. It is TTB's judgment that, *at a minimum,* in order to be "adequately substantiated" within the meaning of the TTB regulations on specific health claims, the claims must be supported by credible scientific or medical evidence.[19] Additionally, TTB has determined that the eight proposed claims also fail to comply with the broader regulations on health-related statements and label statements more generally because they tend to create a misleading impression as to the effects on health of alcohol consumption. Finally, the misleading nature of the claims is not cured by—and, in fact, is compounded by—the disclaimer that the petitioners proposed in conjunction with the eight claims.

VI. Classification of the Eight Proposed Claims

A. Classification of the Eight Claims as Health-Related Statements

As an initial matter, TTB has determined that all eight of the claims proposed in the petition fall under the definition of a "health-related statement" under TTB regulations. As noted above, the term "health-related statement" includes both specific health claims and general references to alleged health benefits or effects on health associated with the consumption of alcohol, distilled spirits [or wine or malt beverages], or any substance found within the alcohol beverage. The term includes claims of nutritional value. *See* 27 CFR 5.42(b)(8)(i)(A).

In the context of this petition, the eight claims all address a substance found within the distilled spirits product ("Bellion Vodka infused with natural flavors"): NTX®.[20] The claims all relate to the alleged protective effects on health of NTX®. Accordingly, because each claim suggests a relationship between the consumption of NTX® and health benefits or effects on health, the claims all qualify as health-related statements.

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[19] Courts have recognized that agencies may require companies to substantiate health claims used to promote their products. *See, e.g., POM Wonderful, LLC v. FTC*, 777 F.3d 478, 501 (D.C. Cir. 2015), *cert. denied,* 136 S. Ct. 1839 (2016) ("In finding petitioners liable for deceptive ads, the Commission determined that petitioners' efficacy and establishment claims were misleading because they were unsubstantiated by [randomized and controlled human clinical trials]. We have upheld that approach in this opinion."). In this case, it is unnecessary to more precisely quantify the level of evidence required to "adequately substantiate" the eight claims, because the evidence used to support the claims does not even meet the "credible" evidence standard established by courts and used by the FDA to evaluate qualified health claims.

[20] Again, this letter focuses on the distilled spirits product for which Frank-Lin Distillers Products, Ltd. has obtained two certificates of label approval, but we note that the same analysis would apply to wines and malt beverages.

B. Classification of the Eight Claims as Specific Health Claims

TTB has also determined that each claim from the petition is a "specific health claim" under TTB regulations. As previously noted, a specific health claim is defined as a health-related statement that "expressly or by implication, characterizes the relationship of the distilled spirits, alcohol, or any substance found within the distilled spirits, to a disease or health-related condition." TTB's regulations provide additional details about when a statement qualifies as a specific health claim "by implication," noting that "[i]mplied specific health claims include statements, symbols, vignettes, or other forms of communication that suggest, within the context in which they are presented, that a relationship exists between distilled spirits, alcohol, or any substance found within the distilled spirits, and a disease or health-related condition." *See* 27 CFR 5.42(b)(8)(i)(B).

At a minimum, the phrase "disease or health-related condition" includes damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension). Accordingly, a "disease or health-related condition" includes alcohol-induced liver disease or damage; alcohol-induced brain disease or damage; alcohol-induced DNA damage; or any other alcohol-induced damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning.[21]

1. *The two claims that explicitly mention liver disease and liver damage are specific health claims.*

Two of the claims from the petition ("NTX® reduces the risk of alcohol-induced liver diseases, including fibrosis and cirrhosis" and "NTX® helps protect against, i.e., reduces, alcohol-induced oxidative damage to the liver") explicitly claim that consumption of NTX® in an alcohol beverage will reduce the risk of alcohol-induced liver diseases and liver damage, respectively. As set forth above, an alcohol-induced liver disease (such as fibrosis or cirrhosis) and alcohol-induced oxidative damage to the liver each qualify as a "disease or health-related condition," as that term is used in TTB's regulations. These claims are therefore specific health claims.

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[21] TTB notes that this interpretation of "disease or health-related condition" is similar to the definition of that phrase in the FDA's regulations, though those regulations contain some exclusions for nutrient-related diseases that are not relevant here. Compare FDA regulations at 21 CFR 101.14(a)(5), which define the term "*Disease or health-related condition"* to mean "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are not included in this definition (claims pertaining to such diseases are thereby not subject to § 101.14 or § 101.70)." TTB's interpretation of "disease or health-related condition" may not always be consistent with the FDA's, however, because of the differences in the two agencies' statutory authority and the nature of the products the agencies regulate. For instance, TTB notes that while some of the petition's claims refer to "normal" liver defenses and functions, there is no exemption in the TTB regulations for "structure/function" claims. It is TTB's position that such claims should be evaluated on a case-by-case basis under TTB's regulations, in the context in which they are presented, to determine if they are specific health claims or health-related statements.

2. *The three claims that address liver defenses and function are specific health claims.*

Three other claims ("NTX® helps maintain normal liver enzyme production and function"; "NTX® supports normal liver defenses and regenerative mechanisms"; and "NTX® helps maintain normal liver functions") claim that NTX® will help protect the liver without specifically referencing alcohol-induced liver disease or damage.

The petition makes it clear, however, that the claims at issue generally relate to the broad proposition that "when NTX® is infused into alcoholic beverages, it renders them safer, i.e., less toxic, than counterparts that do not contain NTX®. NTX® reduces the adverse effects of alcohol on the liver and on DNA. Thus, NTX® lessens certain deleterious effects caused from consumption of alcohol." Petition, p. 1. Moreover, the petition explicitly links the three claims about liver defenses and liver function to a claim that consumption of alcohol beverages infused with NTX® protects the liver from the toxic effects of alcohol consumption. For instance, the petition links the concept of maintaining normal liver function—a benefit touted in two of the previously mentioned claims—to the alleged "ability of NTX® to preclude alcohol toxicity." Petition, p. 25. And the petition also expressly links the claim that NTX® supports the liver's regenerative mechanisms—the third of the previously mentioned claims—to "reduc[ing] the risk of liver diseases like fibrosis and cirrhosis." *Id*. Thus, even though the claims themselves do not explicitly mention liver disease, they are clearly conveying a message about protecting the liver from the damage caused by alcohol consumption. For that reason alone, these three claims are specific health claims.

There is additional context, however, that provides an independent basis for concluding that the three claims about liver defenses and liver function are specific health claims. First, the petitioners do not propose to make these claims in a vacuum, but rather to feature them on a label, or in an advertisement, for an alcohol beverage. As previously noted, more than 2 million Americans suffer from liver disease caused by alcohol,[22] and in 2013, 45.8 percent of all liver-disease deaths among individuals 12 and older involved alcohol.[23] In other words, the petitioners seek to make claims about liver health on a product that has been widely linked to liver disease. The clear implication of such claims is that consuming alcohol with NTX® can help maintain a healthy liver *and therefore prevent or mitigate* the deleterious effects of alcohol on the liver.

Second, and relatedly, the disclaimer proposed by the petitioners, which would be appended to each of the eight claims (including the three concerning liver defenses and functions), implies that NTX® protects consumers from liver damage and liver disease. The disclaimer notes, in relevant part, that "NTX® does not protect against *all* health

[22] *Beyond Hangovers – Understanding Alcohol's Impact on Your Health, supra.*
[23] *Alcohol Facts and Statistics, supra.*

risks associated with moderate and heavy levels of alcohol consumption. . . ." Petition, p. 8 (emphasis added). The clear implication from this language, however, is that each of the claims are supposed to signal that NTX® *does* protect against *some* health risks associated with "moderate and heavy levels of alcohol consumption." *Id.* The disclaimer then proceeds to list some of the health risks that NTX® does not protect against—namely, "motor vehicle accidents, high blood pressure, stroke, cancer, birth defects, psychological problems, and alcohol dependency." *Id.* Conspicuously absent from that list of alcohol-induced health risks are liver disease and liver damage. By omitting these well-known risks from its list, the disclaimer leaves a clear impression that the three claims about liver health are in fact claims that consumption of NTX® in an alcohol beverage will protect consumers from liver disease and liver damage.

In sum, the three claims about liver defenses and liver function imply that consumption of an alcohol beverage product infused with NTX® will reduce the damage to the liver that is otherwise caused by alcohol consumption. This is particularly true when the claims are considered together with arguments made in the petition, the context in which those claims would appear, and the omission from the proposed disclaimer of any mention of liver disease. Thus, it is TTB's conclusion that these claims are specific health claims.

3. *The three claims regarding antioxidant support and DNA damage are specific health claims.*

Like the previous three claims, the remaining three claims ("NTX® provides antioxidant and anti-inflammatory support;" "NTX® helps protect DNA from alcohol-induced damage;" and "NTX® reduces alcohol-induced DNA damage") suggest a relationship between drinking alcohol beverages infused with NTX® and reducing the risk of damage to the liver and, for two of the claims, to the brain.

The first claim ("NTX® provides antioxidant and anti-inflammatory support") clearly implies that this ingredient, when infused in alcohol beverages, will reduce the risk of liver damage and liver disease caused by alcohol consumption. According to the petition, the "health-related statements regarding the antioxidant, anti-inflammatory effects of NTX® that serve to protect *the liver* against oxidative damage have been thoroughly substantiated." Petition, p. 23 (emphasis added). In other words, the first claim advances the contention that NTX® protects the liver from alcohol's harmful effects. Given the context in which it is presented, and for all the reasons outlined in the previous subsection, this claim implies that the antioxidant and anti-inflammatory support provided by NTX® will protect the liver from alcohol-induced damage. The first proposed claim from the petition is therefore a specific health claim.

The seventh and eighth claims from the petition state that NTX® will protect from, and reduce, respectively, alcohol-induced DNA damage. The petition states that "[a]side from [Alcoholic Liver Disease], recent research is demonstrating that alcohol abuse

causes the dual-harms of accumulated DNA damage and alcohol-induced dysfunction to DNA repair, which coalesce into the well-known negative effects of alcohol on the brain, i.e. brain damage." Petition, pp. 19–20. Furthermore, the petition states that "[e]xcess alcohol consumption generally contributes to the production of oxidative damage to DNA and the epigenome… Epigenetic changes, even slight alterations, may affect gene expression and could ultimately result in liver disorders." Petition, p. 27 [citations omitted]. The petition claims that "NTX and its major components have been shown to reduce DNA damage from DNA single and double strand breaks induced by alcohol and other ROS [reactive oxygen species] generating systems in the liver." *Id.*

Accordingly, Claims 7 and 8 imply that consuming an alcohol beverage infused with NTX® will provide a reduction of risk from alcohol-induced damage to the liver and the brain. The previous subsection explains why claims about alcohol-induced liver damage are specific health claims. The same logic also applies to claims about alcohol-induced brain damage. Specifically, the link between alcohol and brain damage is well documented.[24] And like liver damage, brain damage is conspicuously absent from the list of alcohol-induced health risks included in the petitioners' proposed disclaimer. *See* Petition, p. 8. Omitting brain damage from that list reinforces the link that the petition draws—namely, that consumption of NTX® in an alcohol beverage will protect consumers from brain damage by reducing and protecting against alcohol-induced DNA damage.

In sum, Claims 7 and 8, when read in the relevant context, *i.e.*, on a label or in an advertisement for an alcohol beverage that contains NTX®, and when considered together with arguments made in the petition as well as the proposed disclaimer, implicitly claim that consuming an alcohol beverage infused with NTX® will provide a reduction of risk from well-known alcohol-induced diseases and health-related conditions, including liver disease and brain damage. Accordingly, these claims are specific health claims.

C. The Eight Claims Relate to Both Moderate and Heavy Levels of Alcohol Consumption

Before evaluating the eight proposed claims from the petition under TTB's existing regulatory framework, it is important to note one significant way in which the claims go beyond the kinds of health-related statements and specific health claims that were the focus of the 2003 rulemaking. That rulemaking was initiated, in part, in response to a petition regarding the use of a potential claim regarding an association between *moderate* alcohol consumption and alleged health benefits. The rulemaking did not contemplate health-related statements and specific health claims associated with *heavy* levels of alcohol consumption, whose serious health risks were not in dispute.

[24] See *Alcohol Alert* publication entitled "Alcohol's Damaging Effects on the Brain," dated October 2004.

As explained above, though, all eight proposed claims from the petition address—either explicitly or by implication—alleged protection from alcohol-induced liver disease, liver damage, or brain damage. As explained below, these are diseases and health-related conditions that are generally associated with levels of alcohol consumption that exceed moderate consumption.

The petition (p. 19) appears to address this implication of the proposed claims (in the context of liver disease) by suggesting that even moderate drinkers are at risk for alcoholic liver disease ("ALD"):

> While it is axiomatic in the ALD context that the more heavily one consumes alcohol – and the greater frequency of drinking – the more likely one is to develop cirrhosis, it should be noted that alcohol tolerance varies from person to person, and for some people one drink a day is sufficient to leave permanent scars on the liver. Thus hepatoprotective effects that limit liver injury are cumulative and likely to benefit moderate drinkers over their adulthood. [Citation omitted.]

However, according to the NIAAA publication *Beyond Hangovers – Understanding Alcohol's Impact on Your Health,*[25] "[m]ore than 2 million Americans suffer from liver disease caused by alcohol. In general, liver disease strikes people who drink heavily over many years." Furthermore, as mentioned earlier, "[s]tatistics show that about one in five heavy drinkers will develop alcoholic hepatitis, while one in four will develop cirrhosis." The most critical lifestyle change for people with alcoholic liver disease, according to this NIAAA publication, "is abstinence from alcohol. Quitting drinking will help prevent further injury to your liver." *Id.*

The message presented by this Government publication is clear – in general, alcoholic liver disease is associated with heavy levels of consumption, and the recommended course of action for such people is to quit drinking altogether.

At bottom, even if *some* moderate drinkers may be at risk for liver damage, the claims made by the petitioners apply to those who are generally understood to be at risk for alcoholic liver disease (and brain damage) – people who consume heavy levels of alcohol.

Furthermore, as noted above, the disclaimer provides that "NTX® does not protect against all health risks associated with moderate *and heavy* levels of alcohol consumption." Petition, p. 8. This language reinforces the conclusion that the claims seek to convey that NTX® *does* protect against some health risks associated with "moderate *and heavy* levels of alcohol consumption." *Id.* (emphasis added).

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[25] See National Institute on Alcohol Abuse and Alcoholism, *Beyond Hangovers – Understanding Alcohol's Impact on Your Health,* http://pubs.niaaa.nih.gov/publications/Hangovers/beyondHangovers.htm (September 2010).

Taken as a whole, the petition, the eight proposed claims, and the proposed disclaimer are advancing the hypothesis that adding NTX® to an alcohol beverage will reduce some of the serious health risks associated with *both moderate and heavy* levels of alcohol consumption. For the reasons outlined later in this petition response, the petitioners have failed to adequately support this hypothesis because they have failed to adequately substantiate any of their eight proposed claims. But even if the petitioners' hypothesis *were* adequately substantiated by medical and scientific evidence, the fact that the eight proposed claims encompass heavy levels of alcohol consumption would pose serious questions as to how the petitioners' message could be conveyed in a non-misleading fashion. In particular, TTB would need to ensure that the petitioners were not falsely leading consumers to believe that heavy levels of alcohol consumption are in fact safe, as long as the alcohol is infused with NTX®. The risk of misleading consumers would be particularly acute, given the clearly recognized risks of excessive alcohol consumption to the people engaging in such activity,[26] as well as the risks to individuals other than the consumer, such as motorists who are the victims of drunk drivers.

Thus, if the petitioners' hypothesis were adequately substantiated, TTB would want to proceed carefully before approving any claims that encompass heavy levels of alcohol consumption. First, TTB would have to evaluate the claims under the remaining conditions set forth in the specific health claim regulations. Second, TTB would consider whether it would be appropriate to engage in notice-and-comment rulemaking to solicit comments on this issue from consumers, the alcohol beverage industry, the public health community, and Federal and State agencies that deal with the public health problems posed by alcohol abuse.

As previously noted, however, these additional steps would only be necessary if TTB were to find that any of the eight proposed specific health claims are adequately substantiated. For the reasons that follow, TTB has determined that none of the proposed claims are supported by credible evidence, and therefore none satisfies the requirement of adequate substantiation.

VII. Overview of TTB's Consultation with FDA

To aid in its assessment of the eight proposed specific health claims, TTB consulted with FDA. In doing so, TTB relied on FDA's expertise in assessing the kind of articles and studies submitted in support of the petition and the supplement.

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[26] As previously noted, the 2015-2020 Dietary Guidelines for Americans provide that "Excessive alcohol consumption—which includes binge drinking (4 or more drinks for women and 5 or more drinks for men within about 2 hours); heavy drinking (8 or more drinks a week for women and 15 or more drinks a week for men); and any drinking by pregnant women or those under 21 years of age—has no benefits. Excessive drinking is responsible for 88,000 deaths in the United States each year, including 1 in 10 deaths among working age adults (age 20-64 years). In 2006, the estimated economic cost to the United States of excessive drinking was $224 billion. Binge drinking accounts for over half of the deaths and three-fourths of the economic costs due to excessive drinking."

At the outset, TTB notes that the petition raises several objections to the possibility of a consultation with FDA. *See* Petition, pp. 12–13. TTB regulations provide, however, that "TTB will consult with [FDA], as needed, on the use of a specific health claim on a distilled spirits label." *See* 27 CFR 5.42(b)(8)(ii)(B)(1). Those regulations also provide that "[i]f FDA determines that the use of such a labeling claim is a drug claim that is not in compliance with the requirements of the Federal Food, Drug, and Cosmetic Act, TTB will not approve the use of that specific health claim on a distilled spirits label." *Id.*

Even if this express authority did not exist, TTB notes that it could still consult with FDA, particularly given FDA's expertise in evaluating scientific and medical evidence, as well as the long-established track record of FDA providing advice to TTB regarding scientific and public health issues. As reflected below, TTB did not delegate any of its decision-making authority to FDA, and the memoranda FDA provided make clear that FDA did not recommend any decision with regard to the ultimate issue of whether to approve the eight claims in the petition.

A. Scope of the Consultation

By letter dated April 26, 2016, TTB transmitted the petition, including the exhibits, to FDA. TTB initially asked FDA for a determination on whether the use of any of the eight claims from the petition would violate the provisions of the FFDCA with regard to drug claims, pursuant to TTB regulations. *See* 27 CFR 5.42(b)(8)(ii)(B)(1), 4.39(h)(2)(ii)(A), and 7.29(e)(2)(ii)(A). TTB also requested a scientific consultation regarding the evidence purported to support the proposed claims. Specifically, TTB asked FDA to analyze the scientific data submitted in the exhibits to the petition.

After further discussion, TTB determined it was not necessary for FDA to make a determination as to whether the use of the claims in question were drug claims that would violate the FFDCA. Rather, because the threshold question presented by this petition is whether the eight proposed claims are truthful and adequately substantiated by scientific or medical evidence, TTB requested a consultation from FDA on the scientific and medical evidence submitted by the petitioners.

By letter dated November 10, 2016, TTB transmitted the November 1, 2016, Supplement to FDA for review.[27] TTB requested that "FDA provide a scientific consultation on the newly submitted materials, in the same manner that FDA provided a scientific consultation on the materials submitted with the original petition on this matter.

[27] Before TTB transmitted the supplement to FDA, FDA provided its assessment of the studies submitted with the original petition. In a memorandum dated November 4, 2016, FDA concluded that the studies reviewed by FDA provided "no evidence" for seven of the eight proposed claims. For part of the first claim – that NTX® provides antioxidant support – the memorandum stated that two studies (collectively using 24 subjects) measured the effect of NTX® on GSH activity, a measure of antioxidant support. In these two studies, a statistically significant increase was seen at some but not all time points after administration of NTX® when compared to the control.

Specifically, we ask for FDA's views on whether the scientific data submitted in the petition, including the exhibits in the Petition Supplement, adequately substantiate the proposed claims set forth in the petition."

TTB's letter to FDA again clarified that TTB was not seeking a consultation on the issue of whether the claims were drug claims under the FFDCA, noting that TTB would "let FDA know if TTB determines that it is appropriate to request such a consultation after FDA has provided a consultation on whether the petition, as supplemented by the newly submitted exhibits, substantiates the proposed health-related statements."

By memorandum dated March 22, 2017, the FDA provided its analysis of the studies submitted in the petition and the supplement. That analysis is attached to this letter. *See* Attachment, which consists of a memorandum entitled "Scientific consultation, Bellion scientific literature and studies (including supplement)" (referred to as the "FDA Cover Memorandum"); and a memorandum from Paula R. Trumbo, Ph.D., Leader, Nutrition Science Review Team, Nutrition Programs Staff, Office of Nutrition and Food Labeling, Center for Food Safety and Applied Nutrition (CFSAN) (referred to as "the CFSAN Memorandum").

The FDA Cover Memorandum (p. 1) confirms the nature of TTB's consultation with FDA. It explains that the CFSAN Memorandum "analyzes the scientific literature and studies that Bellion submitted to TTB, including the newly submitted supplement." The Cover Memorandum also clarifies that the CFSAN Memorandum "does not address the question of whether or not TTB should authorize the statements that Bellion proposed in their petition." *Id.*

The CFSAN Memorandum has two attachments. Attachment 1 is a memorandum from the Center for Drug Evaluation, Division of Gastroenterology and Inborn Errors Products, "Medical Officer Consult Reply and Responses to Questions" (referred to as "the CDER Memorandum"). Attachment 2 is entitled "Categorization of Articles" and consists of a breakdown of the 112 articles submitted in support of the petition and the primary reasons provided by CFSAN for not evaluating 106 of those articles (reasons that are discussed in greater depth below).

As explained in the CFSAN Memorandum (p. 1), CFSAN consulted with CDER so that CDER could analyze several studies that "evaluated NTX in humans, including the applicability of the various endpoints measured in th[o]se studies." Specifically, the CDER Memorandum addresses the question of whether certain enzymes and metabolites measured in the studies can be considered "surrogates of liver disease risk" and whether any of the endpoints measured in the studies (both the original studies and the studies submitted with the petition supplement) "are appropriate for measuring risk of alcohol-induced liver disease, oxidation, inflammation, liver function, and/or DNA damage." CDER Memorandum, p. 3.

As explained in the CDER Memorandum, CDER viewed its role as providing "technical consultation, based on CDER's experience and expertise in analyzing scientific materials and based on this Division's particular expertise regarding liver function." CDER Memorandum, p. 26. Additionally, the CDER Memorandum clarifies that it "does not address the question of whether or not TTB should, under the applicable regulations, authorize the specific statements that Bellion Spirits proposed in their petition." *Id*.

B. TTB Reliance on FDA Criteria for Determining When Scientific Conclusions Can Be Drawn from an Article or Study

When FDA evaluates the evidence offered in support of health claims, it uses criteria set forth in FDA's *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final,* January 2009, as well as criteria set forth in other FDA rulemaking and guidance documents, to determine whether it is possible to draw scientific conclusions from that evidence. The January 2009 FDA guidance document provides criteria with regard to the evaluation of studies to determine whether scientific conclusions should be drawn from them about the substance that is the subject of a health claim and the relationship between consumption of the substance and reducing the risk of a disease.[28]

The criteria articulated in FDA's guidance and regulations are relevant in determining whether a specific health claim is "truthful and adequately substantiated by scientific or medical evidence," within the meaning of the applicable TTB regulations, because those criteria provide a systematic and science-based approach to assess whether the evidence in support of a specific health claim actually substantiates it. Accordingly, TTB is relying on the FDA criteria—including the relevant parts of the 2009 Guidance and other FDA rulemaking and guidance documents—that pertain to whether scientific conclusions may be drawn from certain categories of evidence.

TTB's reliance on the FDA criteria on this particular issue does not mean that TTB is adopting FDA's overall regulatory standards for approval of health claims. TTB noted in its final rule on the use of health claims in the labeling and advertising of alcohol beverages that TTB's regulations on this issue differ from FDA regulations on this matter. *See* T.D. TTB-1, 68 FR 10076, 10098 ("Because of the differences in statutory authority, as well as the differences in the products regulated under these two statutes, TTB's regulatory scheme for health claim labeling will differ from FDA's regulatory scheme.") Moreover, TTB is enforcing its own regulations, not those of FDA, with regard to the evaluation of whether the proposed claims comply with TTB regulatory standards. TTB recognizes, however, that FDA has expertise in reviewing scientific studies regarding proposed health claims and has established criteria that are useful for

[28] *See Alliance for Natural Health v. Sebelius*, 786 F. Supp. 2d 1, 16 (D.D.C. 2011) (reviewing the January 2009 FDA guidance document and finding the framework consistent with applicable First Amendment precedent).

determining whether scientific conclusions can be drawn from certain kinds of evidence. Having explained our reliance on FDA's criteria, TTB turns now to the FDA's application of its criteria to the articles and studies offered in support of the petition and the supplement.

C. FDA's Evaluation of the Articles and Studies Submitted in Support of the Petition and the Supplement

1. Consistent with FDA criteria, scientific conclusions relevant to the proposed claims could not be drawn from 106 of the 112 articles and studies submitted by the petitioners because they did not meet threshold criteria for consideration.

The petitioners submitted 108 articles and studies with the original petition. *See* Petition, Exhibit 5.[29] An additional four articles and studies were submitted with the supplement, for a total of 112 articles or studies. See Supplement, Exhibits A – D. FDA reviewed all 112 of those articles and studies, and it concluded that scientific conclusions relevant to the proposed claims could not be drawn from 106 of them. The basis for that decision is explained as follows in the CFSAN Memorandum:

> Of the 112 articles submitted, FDA would normally eliminate from its further evaluation 106 of the articles for one or more reasons. As explained in more detail in the footnotes below, these reasons include:
>
> 1) The studies did not evaluate NTX *per se*, but rather individual components of NTX (glycyrrhizin or mannitol),[CFSAN4]
>
> 2) the studies were conducted in animals or *in vitro,*[CFSAN5]

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[29] The petition states that Exhibit 5 includes "more than 100 studies" that "substantiate the health claims" requested by the petition. These articles and studies are set out in Attachment 2. The petitioners also submitted two reports as separate exhibits, the Stohs report (Exhibit 1) and the Preuss report (Exhibit 3). These reports were not included in Attachment 2 because they summarized and interpreted the other articles and studies submitted with the petition.

[CFSAN4] When the substance of a health claim represents more than one food component, FDA only considers studies in which all of the components are evaluated together (*see, e.g.*, "Proposed Rule: Health Claims; Calcium and Osteoporosis, and Calcium, Vitamin D, and Osteoporosis," 72 FR 497, 503 (January 5, 2007)). Here, the substance is NTX, which is a blend of glycyrrhizin, mannitol and potassium sorbate. Therefore, evidence on NTX *per se* is needed to draw scientific conclusions about its role in the 8 proposed claims. It is also worth noting that the petition states that glycyrrhizin and mannitol work *synergistically* to protect the liver from the harmful health effects of alcohol.

[CFSAN5] *See* Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances. Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease in humans. These studies therefore do not provide information

3) the articles were not on the findings of studies, but rather book chapters, review articles, government and WHO documents or patents,[CFSAN6]

4) the studies were published in a foreign language,[CFSAN7]

5) the studies were conducted in individuals who already had liver disease (e.g., hepatitis),[CFSAN8]

6) the study measured endpoints other than those that are the subject of the proposed claims (e.g., pancreatitis, renal failure),[CFSAN9] and/or

7) the studies did not evaluate NTX or individual components of NTX.[CFSAN10]

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from which scientific conclusions can be drawn regarding a relationship between the substance and disease or health-related condition in humans.

[CFSAN6] *See* Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm. Reports that discuss a number of different studies, such as review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. Such articles do not provide sufficient information on individual studies to substantiate a statement about the relationship between a substance and a disease or health-related condition.

[CFSAN7] If any part of the material submitted is in a foreign language, FDA regulations require that it shall be accompanied by an accurate and complete English translation (21 CFR 101.70(a)). Although that regulation need not govern this technical consultation, the fact remains that we are unable to evaluate data provided in articles published in a foreign language unless an accurate and complete English translation is provided.

[CFSAN8] *See* Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm. Health claims involve reducing the risk of a disease in people who do not have the disease that is the subject of the claim. FDA considers evidence from studies with subjects who have the disease that is the subject of the claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease, based on the presence of factors that are identified in section III-D of the 2009 guidance. These factors were not present in any of the submitted studies that involved subjects with liver disease.

[CFSAN9] *See* Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm. An important threshold question that FDA asks when evaluating studies is, "Have the studies appropriately specified and measured the specific disease or health-related condition that is the subject of the claim?" Studies should identify a specific measurable disease or health-related condition by either measuring incidence, associated mortality, or validated surrogate endpoints that predict risk of a specific disease.

[CFSAN10] *See* Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm. FDA considers the publicly available data and written information pertaining to the relationship between a substance and disease. An important threshold question that FDA asks when evaluating studies is "Have the studies specified and measured the substance that is the subject of the claim?"

CFSAN Memorandum, pp. 2–3. Attachment 2 to the CFSAN Memorandum, "Categorization of Articles," identifies the "primary reasons" why scientific conclusions could not be drawn from 106 of the 112 articles and studies. As is apparent from this breakdown, there were many articles and studies to which multiple reasons applied.

With regard to the first reason for eliminating studies from consideration ("The studies did not evaluate NTX *per se*, but rather individual components of NTX (glycyrrhizin or mannitol)"), out of an abundance of caution, TTB asked FDA to review studies that included only a single ingredient of NTX®, if those studies were not otherwise excluded by FDA's criteria. As reflected in the CFSAN Memorandum, the only study that fell under this category was England et al. (1986).[30] Accordingly, the CFSAN Memorandum "included the [England] study in the evaluation (even though, under FDA policy described above, CFSAN would not normally consider it)." CFSAN Memorandum, p. 4.

To be clear, TTB does not believe that valid scientific conclusions can be drawn from studies regarding an individual component of NTX® rather than from NTX® *per se*. As previously noted, TTB is relying on FDA's criteria related to this issue. And in any event, TTB notes that the petition claims that the two primary ingredients in NTX®, glycyrrhizin and mannitol, "work synergistically to protect the liver from the harmful health effects of alcohol." Petition, p. 23. Instead, as part of its evaluation of the entire record, TTB simply wanted to know whether there were potentially relevant studies that related to single ingredients of NTX®.

FDA concluded as follows with regard to the England study:

> While this study showed a significant reduction in hydrogen peroxide with mannitol administration (which was apparently done intravenously), this study evaluated the effect of CPB [cardio pulmonary bypass], not alcohol, on the production of cytoxic oxidative radicals. Therefore, scientific conclusions cannot be drawn about whether mannitol, especially when consumed orally, plays a role in alcohol induced radical formation.

CFSAN Memorandum, p. 10.

FDA also noted that the England study did not provide any findings that CFSAN considered would be "potentially relevant to the proposed claims" and therefore "the England study provides no evidence to support the … eight claims." *See* CFSAN Memorandum, p. 10. [31]

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[30] England MD, Cavarocchi NC, O'Brien JF et al. Influence of antioxidants (mannitol and allopurinol) on oxygen free radical generation during and after cardiopulmonary bypass. *Circulation* 1986;74:SIII134-137.

[31] See also CDER Memorandum (p. 24), which noted that: "Again, as we do not know the dose of mannitol in this study and the dose in the NTX product and as the route of administration is different, interpretation of this data in

TTB concurs with FDA's findings that the England study is not potentially relevant to the proposed claims. Accordingly, TTB finds that the study should be excluded on the grounds that it does not involve NTX® *per se*, as well as the more detailed reasons provided by FDA for why the study is not relevant to the claims set forth in the petition.

In addition, one of the criteria that FDA used in rejecting 106 of the 112 articles and studies warrants a brief additional discussion in light of an argument raised in the petition. Specifically, the petitioners argue that TTB must consider animal and *in vitro* studies for the following reasons:

> TTB must in conformity with First Amendment standards consider all scientific evidence supportive of the requested claims. The TTB must acknowledge that human clinical testing in areas concerning alcohol exposure carries significant health and liability risks that render repeat (or expansive) testing impractical, costly, and perhaps unethical (e.g., long-term studies). The universe of scientific data is therefore limited by those practical considerations. Animal and in vitro models must be considered where supportive of the mechanism of action, or where such studies explain the biophysical or biochemical responses. Animal and in vitro models are often essential to develop or prove causal connections between the test components and a statistically significant effect later observed in human models.

Petition, p. 28.

The petitioners have not provided a sufficient reason for TTB to consider animal and *in vitro* studies as providing scientific information from which conclusions can be drawn about the claims. Rather, the relevant criteria in FDA's Guidance are appropriate here. As set forth in the FDA Guidance, FDA uses "animal and *in vitro* studies as background information regarding mechanisms that might be involved in any relationship between the substance and disease. The physiology of animals is different from that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances." [Citation omitted.] Therefore, the FDA Guidance provides that "Animal and *in vitro* studies can be used to generate hypotheses, or to explore a mechanism of action of a specific food component through controlled animal diets; however, these studies do not provide information from which scientific conclusions can be drawn regarding a relationship between the substance and disease in humans."

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relation to the proposed route of administration and indication is impossible. We do not find these results pertinent to the question of efficacy and safety of NTX."

TTB disagrees that the existence of a limited "universe of scientific data" to support the proposed claims means that TTB is required to accept evidence from which scientific conclusions may not be drawn regarding a relationship between a substance and disease in humans. *See POM Wonderful, LLC v. FTC*, 777 F.3d 478, 505 (D.C. Cir. 2015), *cert. denied*, 136 S. Ct. 1839 (2016) (in which the D.C. Court of Appeals upheld an order by the Federal Trade Commission to the extent that it required at least one randomized and controlled human clinical trial in order to adequately substantiate use of a disease-related statement in advertisements relating to pomegranate-based products). As previously noted, the public health stakes regarding alcohol beverages are very high. *See* n. 26, *supra*. TTB also notes that since making this argument in the original petition, the petitioners have supplemented the record with studies involving additional human clinical trials involving NTX®.

In sum, in reliance on FDA's criteria—including its position on animal and *in vitro* studies—TTB determined that 106 of the articles and studies submitted by the petitioners do not allow scientific conclusions to be drawn about the claims. Because TTB is relying on FDA's criteria, those articles cannot provide the basis for finding that the petition's specific health claims are adequately substantiated by scientific or medical evidence. Accordingly, TTB turns to FDA's assessment of the remaining six articles and studies.

2. FDA eliminated one of the remaining six studies from consideration because of the lack of underlying information necessary for evaluation.

FDA determined that scientific conclusions may not be drawn from the first Pandit study (Study on the Evaluation of Hepatoprotective and Anti-Oxidant Effect of Processed Glycyrrhiza glabara Fortified Ethanol (NTX) in Alcoholics Subjects).[32] As explained in the CFSAN Memorandum (p. 3), FDA did not include this study in its evaluation based on its determination that it provided no information other than the study's findings:

> The report did not include information on the study, such as study subjects (e.g., health status) and study design (e.g., provision of the control and test (NTX products), dose of NTX provided, appropriateness of control group). Because this information is necessary to conduct a proper evaluation of the results, this study was not included in the CFSAN evaluation.

In light of FDA's determination that scientific conclusions cannot be drawn from the first Pandit study,[33] TTB concluded that this study cannot provide scientific or medical

[32] TTB notes that the first Pandit study has the same title as the second Pandit study, but they appear to be different studies. To avoid confusion, TTB will refer to this study as the "first" Pandit study.

[33] *See also* CDER Memorandum, p. 17, which notes that limited information is provided about the Pandit study, in particular noting the lack of data about the study design, dose of alcohol, or demographics, and stating that "[f]urther

evidence that would adequately substantiate the proposed claims within the meaning of the TTB regulations.

3. FDA concluded that four studies involving NTX® and human subjects merited further consideration.

After applying its criteria as reflected above, FDA determined that there were five articles provided by the petitioners left to review. Two of those articles, however, were "the findings of the same study with one being a published version of the other.[CFSAN12] [CFSAN] reviewed both articles and determined that they present the same findings of the study. Therefore, [CFSAN's] review represents the findings of both the unpublished and published study." CFSAN Memorandum, p. 4. In other words, FDA determined there were a total of four separate studies that merited further consideration as they relate to the eight proposed claims in the petition. Those four studies were:

1. Chigurupati[CFSAN13,]--Evaluation of Reactive Oxygen Species (ROS)

2. Udani[CFSAN14,CFSAN15]--Hepatoprotective Effects of a Proprietary Product during Alcohol Consumption

3. Pandit[CFSAN16] –Study on the Evaluation of Hepatoprotective and Anti-Oxidant Effect of Processed Glycyrrhiza glabara Fortified Ethanol (NTX) in Alcoholics Subjects. [34]

4. Nobel[CFSAN17] –NTX Protective Effects from Alcohol Induced ROS and Genotoxicity.

Of these four studies, only one was published and peer-reviewed. One was unpublished, but not designated as confidential, and the remaining studies, including the

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interpretation of the data is hindered by the lack of a protocol and information on study design and population as well as the lack of information on statistical methods."

[CFSAN12] I) Udani J. Hepatoprotective Effects of a Proprietary Product During Alcohol Consumption. Unpublished. 2) Chigurupati H, Auddy B, Biyani M, Stochs SJ. Hepatoprotective effects of a proprietary glycyrrhizin product during alcohol consumption: A randomized, double-blind, placebo-controlled, crossover study. Phytotherapy Research. 2016.

[CFSAN13] Chigurupati. Evaluation of reactive oxygen species (ROS) from blood at different time intervals after oral consumption of two different alcohol formulations: A comparative, double blind, crossover, pilot clinical trial. Unpublished.

[CFSAN14] Udani J. Hepatoprotective Effects of a Proprietary Product During Alcohol Consumption. Unpublished.

[CFSAN15] Chigurupati H, Auddy B, Biyani M, Stochs SJ. Hepatoprotective effects of a proprietary glycyrrhizin product during alcohol consumption: A randomized, double-blind, placebo-controlled, crossover study. Phytotherapy Research. 2016.

[CFSAN16] Pandit. Study on the Evaluation of Hepatoprotective and Anti-Oxidant Effect of processed Glycyrrhiza glabara fortified Ethanol (NTX) in Alcoholics Subjects. Unpublished.

[34] TTB notes that the above-referenced Pandit study appears to be separate from the study referred to as the "first Pandit study." To avoid confusion, this study will be referred to as "the Pandit study."

[CFSAN17] Nobel. NTX Protective Effects from Alcohol Induced ROS and Genotoxicity. Unpublished.

unpublished Udani study, were designated by the petitioners as confidential proprietary data. As noted in the CFSAN Memorandum, FDA's regulations provide that FDA looks at "the totality of *publicly available* scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles)" in determining whether to promulgate regulations authorizing a health claim. *See* 21 CFR 101.14(c) (emphasis added). Accordingly, studies marked as confidential "would not be considered publicly available evidence if pertinent information is redacted." CFSAN Memorandum, p. 10 (footnote omitted.) Nonetheless, FDA evaluated the studies that the petitioners submitted that were marked as "confidential." The results of that evaluation are reflected below.

TTB notes, however, that the petitioners' designation of several studies as confidential business information clearly imposes limits on TTB's ability to seek meaningful comment from the public, including the scientific and medical communities, on the data submitted.

VIII. Evaluation of the Four Remaining Studies and Assessment of the Eight Proposed Claims

A. Issues Raised by FDA's Overall Assessment of the Four Studies

For the reasons explained above, the four studies that FDA evaluated are the only materials before TTB that merited further consideration as they relate to the eight proposed claims, in order to determine if the claims are adequately substantiated by scientific or medical evidence, as required by TTB's regulations. The FDA's review established two important points. First, the FDA review noted that none of the studies includes information about the dosage of NTX® consumed by the study subjects, which would be necessary for TTB to evaluate whether the studies adequately substantiate the proposed claims. This shortcoming makes it impossible to draw any valid scientific conclusions regarding the health effects of consumption of alcohol beverages containing NTX® in the quantities in which such an ingredient would be allowed in alcohol beverages.

Second, the CDER and CFSAN Memoranda conclude that the studies measured biomarkers that were not valid surrogates for long-term risk of liver disease. Accordingly, it is TTB's determination that the studies do not present credible evidence that supports the eight proposed claims, and thus the claims have not been adequately substantiated as required by the TTB regulations.

1. Lack of dosage information in the studies

Certain important information is missing from all four of the studies FDA evaluated. While the studies provide information about the quantity of alcohol consumed by the

study subjects, there is no specific information provided about the dosage of NTX® (or its component ingredients) consumed by the study subjects.

For instance, the published Chigurupati study refers to quantities as follows:

> The study product (NTX®) was a proprietary blend of glycyrrhizin (licorice) and D-mannitol with and potassium sorbate as a product stabilizer. The study product was provided by Chigurupati Technologies Private Limited, Hyderabad, India, and was Good Manufacturing Practice (GMP) certified. Based on the U.S. Patent (9,149,491 B1), the product contains glycyrrhizin preferably in the range of 0.1 – 0.3% and D-mannitol preferably in the range of 1.0 – 2.5%.

Exhibit 1 to the original petition, the Stohs report, also addresses the safety of NTX® by referring to the amounts set forth in the patent, noting as follows:

> The patent for NTX® notes that glycyrrhizin is used at a concentration of 0.05-0.3 % while mannitol is used in the range of 0.5-3.0 %. For someone consuming 60 ml of an alcoholic beverage (4 shots) containing NTX, they would consume 30-180 mg of glycyrrhizin and 300 mg-1.80 grams of mannitol, amounts that are clearly within the safety ranges for both ingredients. [Footnote omitted.]

See Petition, Exhibit 1, p. 35.

As FDA determined, however, none of the four studies that evaluated NTX in humans (Chigurupati, Udani/Chigurupati (2016), Pandit, and Nobel) "provided information on the amount of NTX consumed by the study subjects." CFSAN Memorandum, p. 10. Accordingly, FDA found, "it is not possible to determine if the findings observed in the four NTX studies are relevant to the amount of NTX that is consumed in the commercially available alcohol products." *Id.*[35]

The lack of dosage information was also noted in the CDER Memorandum (p. 25), which discussed the dosage issue as follows:

> In addition, the amount of alcohol given to subjects was variable across the studies, and the results from different studies are also not consistent. It was not clear what amount of the active ingredients were present in the

[35] Notwithstanding the lack of dosage information in these four studies, the CFSAN Memorandum explained that, "in the interest of providing as much information as possible," the memorandum offered "observations about how the findings of these four studies might relate to the eight claims that Bellion has proposed to TTB." CFSAN Memorandum, p. 10.

> NTX given to patients in these trials, and if it is the same as the to-be-marketed formulation.
>
> 2. *The risk biomarkers measured in the studies are not considered surrogate endpoints for liver disease.*

As part of its consultation with CDER, CFSAN forwarded the six studies[36] relating to human clinical trials involving NTX and the England study. *See* CDER Memorandum, p. 4.

After reviewing the studies, CDER concluded as follows:

> With these studies, the sponsor has failed to provide conclusive evidence that: 1) short-term reductions in ROS or dROS; 2) short-term increases in glutathione; and/or 3) differences in elevations in transaminases observed in NTX treated subjects relative to controls are "hepatoprotective," as claimed. Specifically, the sponsor did not submit any convincing information that there is a quantitative link between the small changes in the biomarkers measured in the above-described studies and a reduction in risk of alcohol-induced liver disease, including long-term progression to liver fibrosis and cirrhosis. The potential benefit of an "additive" such as NTX when used repeatedly over time remains theoretical at this point, and the submitted studies are considered hypothesis generating and require confirmation that they actually do prevent induction of liver disease by alcohol.

CDER Memorandum, pp. 24–25. With regard to the issue of whether the surrogate endpoints in the studies were valid, the CDER Memorandum (p. 25) concluded as follows:

> None of the biomarkers evaluated in the NTX studies has been validated as surrogate endpoints for liver disease and, as already mentioned, the sponsor has not submitted adequate scientific justification to support that the short-term changes in these biomarkers will predict changes of risk for disease progression over time.

The CFSAN Memorandum (p. 5) similarly stated that "[n]one of the risk biomarkers measured by Chigurupati, Udani/Chigurupati (2016), Pandit, Nobel or England are considered surrogate endpoints of liver disease." However, for the sake of completeness, the CFSAN Memorandum analyzed all of the risk

[36] As explained above, two of those articles presented the findings of the same study, with one being a published version of the other.

biomarkers that were measured by Chigurupati, Udani/Chigurupati (2016), Pandit, Nobel, and England, regardless of whether they are surrogate endpoints of liver disease. *Id.* The CFSAN Memorandum thus assessed the evidence with regard to each of the eight claims set out in the petition. This assessment is set forth below.

B. TTB's Assessment of the Eight Proposed Specific Health Claims in Light of the Evidence

FDA's assessment of the evidence from the studies leads TTB to conclude that there is no credible evidence to support these proposed claims. Because there is no credible evidence to support the proposed claims, none of the eight claims is adequately substantiated; therefore, the claims cannot be approved as specific health claims. Similarly, TTB also concludes that, in light of the lack of evidence in support of the eight claims, the eight claims would create a misleading impression as to the effects on health of consumption of alcohol beverages infused with NTX®. Accordingly, even if the claims were considered only health-related statements, instead of also falling into the narrower category of specific health claims, TTB would not approve any of the claims. This is true even if the claims are read alongside the petitioners' proposed disclaimer.

1. Neither the petition nor the studies provide dosage information.

As previously discussed, the CFSAN and CDER memoranda state that the studies that were evaluated do not specify the quantity of NTX®, or the quantities of the individual components of NTX®, used in the studies. Nor does the petition provide this information.

Based on the reasons FDA set forth in the CFSAN Memorandum, TTB determines that without information about the level of NTX® that was consumed in the studies, it is not possible to determine if any of the findings observed in the four studies are relevant to the amount of NTX® that would be found in the alcohol beverage products that the petitioners wish to market. Furthermore, TTB finds the continued references to the quantities set forth in the patent to be insufficient to determine the quantity of NTX and its individual components that were actually used in the studies.

This omission is particularly important in light of the limitations on the use of glycyrrhizin and mannitol in alcohol beverages. FDA has affirmed the use of glycyrrhizin as generally recognized as safe (GRAS) in alcohol beverages as a flavor enhancer or flavoring agent with a limitation of no more than 0.1 percent of the finished product. *See* 21 CFR 184.1408(c). With regard to mannitol, the limitation found in FDA regulations is not more than 2.5 percent of the finished product. *See* 21 CFR 180.25. It is not clear if the information from the published study, the patent, and the Stohs exhibit means that the studies tested NTX containing glycyrrhizin at levels exceeding 0.1 percent of the

finished product, which would be inconsistent with FDA's GRAS regulation. If so, such a use would not be authorized under FDA's GRAS regulations, and therefore TTB would not approve a formula for such an alcohol beverage product. Without more information on this issue, it is impossible to determine if the studies are at all relevant to the level of glycyrrhizin in alcohol beverages that may be lawfully sold in commerce.

As noted in the CFSAN Memorandum, "[w]hen evaluating a product, such as NTX, that has a specific composition and amount for each component, scientific conclusions about the product can be drawn only from studies that have evaluated that specific product (i.e., same composition and amount)." CFSAN Memorandum, p. 10.

This flaw in the studies makes it impossible to draw any valid scientific conclusions regarding the health effects of consumption of alcohol beverages containing NTX® in the quantities in which such an ingredient would be allowed in alcohol beverages. As noted previously, because of GRAS restrictions on glycyrrhizin and mannitol levels in alcohol beverages, there are limitations on how much NTX® would be allowed in an alcohol beverage product. The lack of specificity makes it impossible to draw conclusions from the evidence as to whether the evidence even applies to the levels of NTX ® that would be allowed in commercially available alcohol beverages.

The lack of dosage information from any of the four studies means that there is no credible evidence, let alone adequate substantiation, for any of the eight proposed specific health claims. Nonetheless, TTB has considered whether, even if the lack of dosage information were set aside, the evidence presented by the petitioners would otherwise constitute adequate substantiation for the claims. In carrying out that assessment, TTB relied on FDA's evaluation of the four studies with respect to each proposed specific health claim.

2. There is "no evidence" for five of the specific health claims.

With regard to five claims (Claims 2–6, as set forth in the petition), FDA concluded that "no evidence" was provided in the studies submitted with the petition to support the claims. The conclusions were presented in the CFSAN Memorandum on p. 11 as follows [with emphasis added]:

> 2) NTX helps protect against, i.e., reduces, alcohol-induced <u>oxidative damage</u> to the liver.
>
> *No evidence* was provided by Chigurupati, Udani/Chigurupati (2016), Pandit, Nobel, or England to demonstrate that NTX or mannitol helps protect against oxidative damage to the liver.
>
> 3) NTX helps maintain normal liver <u>enzyme production</u> and <u>function.</u>

No evidence was provided on the effect of NTX or mannitol on enzyme production. Furthermore, there are hundreds of enzymes present in the liver for which Udani only measured a few (and Chigurupati, Pandit, Nobel, and England measured none). Therefore, even if there was some evidence of an effect on enzyme production, this claim does not provide enough specificity as to which liver enzymes are being referred to.

One study (Nobel), representing 25 subjects, showed *no effect* of NTX administration on liver function.

4) NTX supports normal liver defenses and regenerative mechanisms.

The metabolites and enzymes measured by Chigurupati, Udani/Chigurupati (2016), Pandit, Nobel, and England are not measures of liver defense and regenerative mechanisms. *No evidence* was provided to demonstrate that NTX or mannitol supports normal liver defenses and regenerative mechanisms.

5) NTX reduces the risk of alcohol-induced liver disease, including fibrosis and cirrhosis.

None of the endpoints measured by Chigurupati, Udani/Chigurupati (2016), Pandit, Nobel and England are considered to be surrogate endpoints of liver disease risk, including cirrhosis and fibrosis. As such, there is *no evidence* to support this claim.

6) NTX helps maintain normal liver functions.

One study (Nobel), representing 25 subjects, showed no effect of NTX administration on liver function. Liver function was considered to be normal for both the control and NTX groups. As such, there is *no evidence* to support this claim.

Based on the above analysis in the CFSAN Memorandum, the above-referenced five claims are not “truthful and adequately substantiated by scientific or medical evidence” within the meaning of the TTB regulations. As reflected in FDA’s analysis, these claims are not supported by any credible evidence supplied by the petitioners at all, much less by adequate substantiation.

3. *If the lack of dosage information is set aside, then there is weak evidence tangentially related to the three remaining proposed specific health claims; however, there is still no credible evidence supporting the proposed claims themselves.*

With regard to the first, seventh, and eighth claims from the petition, the CFSAN memorandum analyzed the evidence in the four studies that related to those claims, as set forth below.

a. Claim 1 - "NTX® provides antioxidant and anti-inflammatory support."

With regard to the first claim, the CFSAN Memorandum (pp. 10–11) found as follows:

> Three studies measured the effect of NTX on GSH activity, a measure of antioxidant support (Chigurupati, Udani/Chigurupati (2016), and Pandit). The findings were mixed in two studies (Chigurupati and Udani/Chigurupati (2016)), collectively representing 24 subjects, with a significant increase seen at some but not all time points after administration of NTX when compared to the control. The third study (Pandit), representing 50 subjects, showed no effect of NTX on GSH activity. Two studies measured various markers of oxidant activity (Pandit and Nobel). For one study (Pandit) on 50 subjects, the findings were mixed, with a significant increase seen at some but not all time points (ROS, GSSG, MDA, PC, OH-dG) after administration of NTX when compared to the control. The second study (Nobel), representing 25 subjects, showed no effect of NTX on measures of oxidation (GSH/GSSG, MDA, PC, and ROS).
>
> Thus, regarding the claim that NTX provides antioxidant support, I have the following observations. As discussed above, none of the studies provided information on the amount of NTX consumed by the study subjects. It is therefore not possible to determine if the findings are relevant to the amount of NTX that is consumed in the commercially available alcohol products. Furthermore, none of the studies purported to assess long-term effects. The studies therefore can only be used to assess the possibility of short-term effects. Based on these studies, the short-term effect (if any) of NTX on various measures of antioxidant support/activity is not clear. As described above, some studies showed no effect on the measured endpoint(s), while some studies showed a significant difference between the NTX group and the control group at some, but not all time points.

> Two studies (Pandit and Nobel) measured the effect of NTX on dROM levels, a possible measure of inflammation. The findings were mixed in one study (Pandit), representing 50 subjects, with a significant increase in dROM levels found in only one of four time points. The second study (Nobel), representing 25 subjects, showed no effect on dROM levels for all time points measured after administration of NTX when compared to the control.
>
> Thus, regarding the claim that NTX provides anti-inflammatory support, I have the following observations. Many of the same limitations apply as are discussed above regarding the evidence for antioxidant support – specifically, the studies do not provide information on the amount of NTX consumed, and the studies do not purport to assess long-term effects. Based on these studies, the short-term effect (if any) of NTX on dROM levels, a possible measure of inflammation, is not clear. As described above, one study showed no effect, while another study showed a significant increase in dROM levels in only one of four time points. No other measures of inflammation were studied.

Additionally, TTB notes that of the studies cited in support of this claim, the only study that was published and peer reviewed, the Chigurupati study,[37] includes the following caveats about the preliminary nature of the evidence from the authors:

> The weaknesses of the study include the small number of subjects and the use of only a single endpoint of blood alcohol (0.12% per night). Furthermore, the study involved healthy nonalcoholic subjects who consumed alcohol for 12 days, and as a consequence, the long term effects are not known.
>
> The results of this study provide *preliminary evidence* regarding the potential protective effects of the proprietary glycyrrhizin/D-mannitol product against ethanol-induced hepatotoxicity. Larger, randomized, placebo-controlled clinical studies are required to further determine the effects of the product on liver protection during acute and chronic alcohol consumption. [Emphasis added.]

As set forth above, the CFSAN Memorandum notes that the studies submitted in support of the claim regarding antioxidant support and anti-inflammatory support do not purport to assess long-term effects. Thus, according to the CFSAN

[37] Chigurupati H, Auddy B, Biyani M, Stochs SJ. Hepatoprotective effects of a proprietary glycyrrhizin product during alcohol consumption: A randomized, double-blind, placebo-controlled, crossover study. Phytotherapy Research. 2016.

Memorandum, the "studies therefore can only be used to assess the possibility of short-term effects." However, as discussed earlier in this document, TTB has determined that this claim implies that the antioxidant and anti-inflammatory support provided by NTX® will protect the liver from alcohol-induced damage, and U.S. Government publications indicate that alcohol-induced liver damage generally results from long-term, heavy consumption of alcohol, meaning that the implication is that NTX® will have the long-term effect of providing antioxidant and anti-inflammatory support in a way that meaningfully protects consumers from alcohol-induced liver damage.

The studies submitted in support of this claim do not address the long-term hepatoprotective effects implied by the claim, and thus they provide no credible evidence to support such a claim.[38] As noted earlier, the CFSAN Memorandum (p. 5) concluded that none of the studies at issue measured risk biomarkers that are considered surrogate endpoints of liver disease. Because the studies do not provide credible evidence to support the first proposed claim, it is TTB's conclusion that the claim is not adequately substantiated by the evidence presented by the petitioners.

b. Claims 7 and 8 – "NTX® helps protect DNA from alcohol-induced damage" and "NTX® reduces alcohol-induced DNA damage."

With regard to the seventh claim, the CFSAN Memorandum (p. 12) provides as follows:

> The evidence was mixed for NTX in protecting DNA from alcohol-induced damage, with one study (Pandit), representing 50 subjects, showing a significant reduction in certain measures of DNA damage at some but not all time points after administration of NTX, and a second study (Nobel), representing 25 subjects, showing no effect on protecting DNA.
>
> Many of the same limitations apply as are discussed above regarding the evidence for antioxidant support and anti-inflammatory support – specifically, the studies do not provide information on the amount of NTX consumed, and the studies do not purport to assess long-term effects. Based on these studies, the short-term ability of NTX to protect DNA from alcohol-induced damage is not clear. As described above, one study

[38] While TTB does not find it necessary to determine whether the evidence submitted would adequately substantiate *a* differently worded claim regarding short-term antioxidant support and short-term anti-inflammatory support, we note that there are significant issues there as well. As noted above, the CFSAN Memorandum found that "[b]ased on these studies, the short-term effect (if any) of NTX on various measures of antioxidant support/activity is not clear. As described above, some studies showed no effect on the measured endpoint(s), while some studies showed a significant difference between the NTX group and the control group at some, but not all time points." The CFSAN Memorandum made the same finding with regard to the claim regarding anti-inflammatory support.

> showed no effect, while a second study showed an effect at some but not all time points.

With regard to the eighth claim, the CFSAN Memorandum (p. 12) provides as follows:

> The evidence was mixed for NTX in reducing alcohol-induced DNA damage, with one study (Pandit), representing 50 subjects, showing a significant reduction in certain measures of DNA damage at some but not all time points after administration of NTX, and a second study (Nobel), representing 25 subjects, showing no effect on protecting DNA.
>
> Many of the same limitations apply as are discussed above regarding the evidence for antioxidant support and anti-inflammatory support – specifically, the studies do not provide information on the amount of NTX consumed, and the studies do not purport to assess long-term effects. Based on these studies, the short-term ability of NTX to reduce alcohol-induced damage is not clear. As described above, one study showed no effect, while a second study showed an effect at some but not all time points.

As set forth above, the CFSAN Memorandum notes that the studies submitted in support of these claims do not purport to assess long-term effects. As discussed earlier in this document, TTB has determined that these two claims imply that consuming an alcohol beverage infused with NTX® will provide a reduction of risk from alcohol-induced damage to DNA, and thus protect from alcohol-induced damage to the liver and the brain. U.S. Government publications indicate that alcohol-induced liver damage generally results from long-term, heavy consumption of alcohol, meaning that the implication is that NTX® will have the long-term effect of protecting DNA from alcohol-induced damage and reducing alcohol-induced DNA damage in a way that meaningfully protects consumers from alcohol-induced liver and brain damage.

The studies submitted in support of these claims do not address the long-term hepatoprotective effects implied by these two claims, and thus they provide no credible evidence to support such claims.[39] As noted earlier, the CFSAN Memorandum (p. 5) concluded that none of the studies at issue measured risk biomarkers that are considered surrogate endpoints of liver disease. Because the studies do not provide credible evidence to support the seventh and eighth proposed claims, it is TTB's

[39] While TTB does not find it necessary to determine whether the evidence submitted would adequately substantiate a differently worded claim regarding short-term DNA protection, we note that there are significant issues there as well. As noted above, the CFSAN Memorandum found that the evidence was "mixed" in that the Nobel study (representing 25 subjects) showed no effect in protecting DNA, while the Pandit study (representing 50 subjects) showed "a significant reduction in certain measures of DNA damage at some but not all time points after administration of NTX." CFSAN Memorandum, p. 12.

conclusion that these claims are not adequately substantiated by the evidence presented by the petitioners.

4. *TTB concludes that the eight proposed specific health claims are not adequately substantiated by scientific or medical evidence.*

Based on the reasons set forth above, it is TTB's conclusion that the studies reviewed by FDA did not "adequately substantiate" any of the eight specific health claims at issue, within the meaning of TTB regulations. As discussed earlier, TTB concludes that each of these claims conveys the message that NTX® provides a real and meaningful reduction in the long-term health risks posed by moderate and heavy levels of alcohol consumption. It is TTB's determination that this message is not supported by credible evidence and therefore is not adequately substantiated by the evidence provided by the petitioners, and thus does not pass the threshold inquiry under TTB regulations.

C. The Eight Proposed Claims Tend to Create a Misleading Impression as to the Effects on Health of Alcohol Consumption

Even if TTB did not consider the eight proposed claims from the petition to be specific health claims, and instead classified them only as health-related statements, it would still decline to approve the claims. That is because the statements do not comply with TTB's regulation for health-related statements, which provides that "labels may not contain any health-related statement that is untrue in any particular or tends to create a misleading impression as to the effects on health of alcohol consumption." 27 CFR 5.42(b)(8)(ii)(A).

As discussed earlier in this document, TTB has determined that all eight of the proposed claims, when read in conjunction with the proposed disclaimer, convey the message that consumption of alcohol beverages infused with NTX® will somehow reduce the long-term health risks otherwise associated with both moderate and heavy levels of alcohol consumption, specifically liver disease and brain damage. The existence of these health risks is well established; however, the alleged protective effects of NTX® are not adequately substantiated. It is clearly misleading to explicitly or implicitly claim that an alcohol beverage infused with NTX® will reduce the serious long-term health risks posed by alcohol consumption and abuse without credible evidence.

VIII. The Petitioners' Proposed Disclaimer Does Not Cure, and in Fact Compounds, the Misleading Nature of the Eight Proposed Claims.

As mentioned earlier, TTB's regulations on health-related statements provide that TTB may require the use of disclaimers for such statements. Specifically, the regulations state that "TTB will evaluate such statements on a case-by-case basis and may require as part of the health-related statement a disclaimer or some other qualifying statement to dispel any misleading impression conveyed by the health-related statement."

However, alcohol beverage labels may not contain any health-related statement "that is untrue in any particular or tends to create a misleading impression as to the effects of alcohol consumption."

The TTB regulations for specific health claims provide that any such claim, in order to be approved, must satisfy a number of conditions.[40] As previously noted, the claim must be “truthful and adequately substantiated by scientific or medical evidence.” Furthermore, the claim must be "sufficiently detailed and qualified with respect to the categories of individuals to whom the claim applies." The claim must also "adequately disclose[] the health risks associated with both moderate and heavier levels of alcohol consumption[] and outline[] the categories of individuals for whom any levels of alcohol consumption may cause health risks." It is important to note that specific health claims must satisfy all of these regulatory conditions. In other words, TTB regulations do not require TTB to allow the use of disclaimers to cure specific health claims that are not adequately substantiated by scientific or medical evidence.

In any case, the disclaimer that the petitioners have put forward does not cure the misleading nature of the proposed claims or adequately address the requirements for qualifying language that must be present for specific health claims. In fact, the proposed disclaimer increases the misleading nature of the proposed claims. Specifically, the proposed disclaimer does not characterize the level of evidence to support the claims, and it reinforces the most misleading aspects of the claims —the unsubstantiated premise that the infusion of NTX® in alcohol beverages somehow protects consumers from the numerous and real health risks associated with alcohol consumption and abuse, in particular liver disease and damage and brain damage. Accordingly, the proposed disclaimer fails to qualify the proposed claims in a manner that would mitigate, much less overcome, their inherently misleading nature.

Additionally, TTB considered but rejected use of a different disclaimer to accompany the proposed claims. Adding a disclaimer that effectively characterizes the claim as baseless is not a viable regulatory alternative because a disclaimer cannot rectify the message conveyed by inherently misleading claims.

IX. TTB Response to Remaining Legal Arguments Raised by Petitioners

A. Alleged Deficiencies in TTB's Health Claims Regulations

The petition argues that TTB’s regulations are inadequate to address the approval of health claims in labeling and advertising, and it thus has the right to file a petition on this matter. See Petition, pp. 13–17. Because TTB has reviewed and acted on this petition, there is no need to address those arguments. TTB does not believe that the petition

[40] See 27 CFR 5.42(b)(8)(ii)(B)(2); 4.39(h)(2)(ii)(B); and 7.29(e)(2)(ii)(B) (use of specific health claims on distilled spirits, wine and malt beverage labels).

process is the exclusive means of obtaining TTB review of a proposed labeling or advertising health claim, but TTB agrees that industry members may petition TTB for a ruling on a proposed health claim.

The petitioners argue that "TTB has yet to implement the administrative process or structure needed to consider a properly noticed health claim petition." Petition, p. 17. TTB does not agree — TTB may interpret its regulations governing health-related statements, including specific health claims, on a case-by-case basis, to address issues that have not previously been addressed in TTB's enforcement of its regulations.[41] An agency's interpretation of its regulations is not subject to notice and comment rulemaking requirements. *Perez v. Mortgage Bankers Assn.*, 135 S. Ct. 1199, 1206 (2015) ("Because an agency is not required to use notice-and-comment procedures to issue an initial interpretive rule, it is also not required to use those procedures when it amends or repeals that interpretive rule.") The Supreme Court has recognized further that agencies, such as TTB, are entitled to a degree of deference in interpreting their own regulations. *See Auer v. Robbins*, 519 U.S. 452, 461 (1997) ("Because the salary-basis test is a creature of the Secretary's own regulations, his interpretation of it is, under our jurisprudence, controlling unless plainly erroneous or inconsistent with the regulation.") (internal quotations omitted).

B. Petitioners' First Amendment Arguments

The petition (p. 33) argues that the proposed health claims are commercial speech that is protected by the First Amendment. The petition suggests that in order to prohibit the health claims, TTB "must show either that the language is not protected speech or that TTB's interest in government censorship is substantial and the method of censorship advances those interests in a direct and material way and that there are no obvious, less speech-restrictive alternatives (such as claim qualifications)." Petition, pp. 34–35 (citations omitted). It is TTB's view that the speech at issue in this petition response is not protected speech.

In *Central Hudson Gas & Electric Corp. v. Public Services Commission,* 447 U.S. 557, 563-566 (1980), the Supreme Court held that in order to regulate commercial speech, the Government must satisfy a four-prong test. First, the expression is protected by the First Amendment only if it concerns lawful activity and is not misleading. Second, the Government must establish a substantial interest. Third, the regulation must directly advance the governmental interest asserted. Finally, the regulation must be no more extensive than necessary to serve the interest asserted.[42]

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[41] For example, courts have recognized that "it is well settled that an agency is not precluded from announcing new principles in an adjudicative proceeding." *POM Wonderful, LLC v. FTC*, 777 F.3d 478, 497 (D.C. Cir. 2015), *cert. denied*, 136 S. Ct. 1839 (2016) (internal quotations omitted).

[42] In two cases involving alcohol beverages, the Supreme Court struck down bans on *truthful and non-misleading* commercial speech. In *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 491 (1995), the Supreme Court applied the

Here, the claims in question are properly restricted based on the first prong – i.e., the proposed health claims are inherently misleading because they are not supported by credible evidence. *See Alliance for Natural Health v. Sebelius*, 786 F. Supp. 2d 1, 17 (D.D.C. 2011) ("Claims which are not supported by credible evidence are misleading commercial speech and may be prohibited under the threshold step of the *Central Hudson* test."). Thus, the claims are not protected by the First Amendment.[43]

The petitioners argue that TTB cannot conclude that a statement is misleading, or otherwise restrict the use of such a claim on a label, without evidence such as a consumer survey. Petition, p. 36. A consumer survey is not necessary, however, to prohibit labeling and advertising health claims about alcohol beverages that lack any credible support. *See Alliance for Natural Health v. Sebelius*, 786 F. Supp. 2d 1, 14 (D.D.C. 2011) (FDA need not "make an empirical showing of the inefficacy of a disclaimer before prohibiting a claim that is not supported by credible evidence").

Finally, TTB notes that although a disclaimer may be appropriate in the context of certain commercial speech, adding a disclaimer is not curative when the disclaimer does not provide additional information to help consumer understanding but merely contradicts an explicit or implicit claim.[44] The proposed disclaimer set forth in the

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Central Hudson analysis in striking down the FAA Act's prohibition against statements of alcohol content on malt beverage labels unless required by State law. In *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484 (1996), the Supreme Court struck down Rhode Island's ban on advertising the price of alcohol beverages on First Amendment grounds. However, these decisions did not address the Government's authority to regulate actually or potentially misleading commercial speech regarding alcohol consumption.

[43] TTB notes that even if the remaining prongs of the *Central Hudson* test applied, the Government clearly has a substantial interest in ensuring that alcohol beverage consumers are not misled about the significant health risks associated with alcohol consumption and abuse, and that requiring specific health claims on labels and advertisements to be adequately substantiated by scientific or medical evidence directly advances the asserted governmental interest, and is no more extensive than necessary to serve that interest. *See POM Wonderful,* 777 F.3d 478, 502 ("the injunctive order's requirement of *some* [randomized and controlled human clinical trial] substantiation for disease claims directly advances, and is not more extensive than necessary to serve, the interest in preventing misleading commercial speech."). TTB also notes that in *Pearson v. Shalala*, 164 F.3d 650, 656 (DC Cir. 1999), the D.C. Circuit recognized that there is a more substantial interest in preventing consumer fraud or confusion where the product poses potential harm to consumers' health and safety.

[44] *See, e.g., In re Warner-Lambert Co.,* 86 F.T.C. 1398, 1414 (1975), *aff'd,* 562 F.2d 749 (D.C. Cir. 1977) (pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds); *Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."); *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir. 1975) *(per curiam)* (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has a decisive connotation for which qualifying language would result in a contradiction in terms."), *cert denied,* 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC,* 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States,* 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g., United States v. Millpax, Inc.,* 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that "no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer

petition does not relate to the *strength* of the evidence submitted by the petitioners, but instead purportedly advises consumers of the health risks associated with alcohol consumption. And as previously explained, the proposed disclaimer's commentary on those health risks actually reinforces the unsubstantiated claims proposed in the petition.

X. Conclusion

For the reasons set forth in this letter, TTB is denying your request to issue a ruling that would authorize the use of the eight claims identified in the petition on labels or in advertisements. It is TTB's position that the proposed claims are not truthful and they are not adequately substantiated by scientific or medical evidence. Accordingly, the claims would not comply with TTB regulations regarding the use of general statements, health-related statements, or specific health claims in the labeling or advertising of wine, distilled spirits, or malt beverages.

Furthermore, it is TTB's position that the proposed disclaimer would not in any way alter its conclusion that the claims would violate the FAA Act and its implementing regulations by misleading consumers as to the health consequences of consumption of alcohol beverages containing NTX®. Furthermore, TTB regulations do not require TTB to consider the use of disclaimers for specific health claims that are not adequately substantiated by scientific or medical evidence.

In light of these conclusions, TTB is also denying your request to initiate rulemaking with respect to the eight proposed claims. TTB does not believe that it would be useful to solicit comments on proposed claims that are not supported by credible scientific or medical evidence.

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cure); *United States v. Kasz Enters., Inc.,* 855 F. Supp. 534, 543 (D.R.I.) ("The intent and effect of the FDCA in protecting consumers from . . . claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds,* 862 F. Supp. 717 (1994).

Jonathan W. Emord, Esq.

If you have any questions about this letter, please contact Andrew Malone at Andrew.Malone@ttb.gov.

Sincerely,

(b) (6) [redacted]

Amy R. Greenberg
Director
Regulations and Rulings Division

Enclosures: FDA Cover Memorandum
CFSAN Memorandum
Attachment 1 to CFSAN Memorandum (CDER Memorandum)
Attachment 2 to CFSAN Memorandum (Categorization of Articles)

cc: Mr. Michael Sullivan