November 20, 2025

via Electronic Submission

Office of Dietary Supplement Programs (HFS-810)
Human Foods Program
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION EXEMPT FROM DISCLOSURE

Subject: Catch-up New Dietary Ingredient Notification for 7-Hydroxymitragynine

Ladies and Gentlemen:

Shaman Botanicals, LLC ("SBL") hereby submits this new dietary ingredient notification ("NDIN") for 7-Hydroxymitragynine ("7-OH") under 21 C.F.R. § 190.6. SBL believes that the 7-OH in its dietary supplements is not a new dietary ingredient under 21 U.S.C. § 350b(d). Nevertheless, in an abundance of caution, SBL is submitting this catch-up NDIN, which contains information that is the basis on which SBL has concluded that its 7-OH dietary supplements are reasonably expected to be safe.

1. **The name and complete address of the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient.**

Shaman Botanicals, LLC
1501 Iron Street
North Kansas City, Missouri 64116

2. **The name of the new dietary ingredient that is the subject of the premarket notification, including the Latin binomial name (including the author) of any herb or other botanical.**

7-OH is the subject of this NDIN. As noted, SBL believes that 7-OH is not a new dietary ingredient but nevertheless is submitting this NDIN in an abundance of caution. 7-OH is a concentrate, metabolite, constituent, and/or extract of the botanical Kratom. The Latin

binomial name of Kratom is *Mitragyna speciosa* (authors Pieter Korthals and George Darby Haviland).

3. A description of the dietary supplement or dietary supplements that contain the new dietary ingredient including:

(i) The level of the new dietary ingredient in the dietary supplement.

The SBL dietary supplements contain 7.5 mg of 7-OH per serving (one tablet).

(ii) The conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement.

The conditions of use recommended or suggested in the labeling of SBL's 7-OH dietary supplements are as follows:

- "**AVERAGE REPORTED USE:** For adults, chew one (1) tablet in a 6 hour period. Do not take more than two (2) tablets in 24 hours. Do not exceed the average reported use."
- "Alkaloids may interact distinctively with pain relief remedies, opioids, anxiolytics, antidepressants, and soothing drugs, as it can modify certain bodily processes. Consult with your physician prior to using alkaloids, especially if you take any medications."
- "It is important to note that the use of alkaloids with alcohol or sleep-inducing drugs may exacerbate their effects, therefore it is not recommended. For safety reasons, it is recommended you abstain from combining alkaloids with other substances."
- "Although there aren't studies conclusively showing addiction related to alkaloids, there are anecdotal reports of people developing an addiction to alkaloid products. If you feel you are developing an addiction to this or any product, consult a physician or an addiction center immediately."
- "Do not use if pregnant or nursing."
- "Do not operate heavy machinery, watercraft or motor vehicles while using."
- "Regular use of alkaloids may lead to dependence and addiction for some users."[1]

The labeling of SBL's 7-OH dietary supplements also recommends or suggests the following conditions of use:

- "**HEALTH AND SAFETY WARNING:** This product contains psychoactive alkaloids, which may include mitragynine, 7-hydroxymitragynine, and mitragynine pseudoindoxyl, which interact with the human opioid system. These alkaloids are

[1] *See* label attached as Exhibit "A" hereto.

active at all known opioid receptors—mu, kappa and delta—each affecting them in various ways and with various potencies."

- "**WARNING:** This product may be habit-forming. Regular use can lead to physical and/or psychological dependence, addiction, and withdrawal symptoms may occur upon discontinuation. If you suspect addiction, seek medical help immediately."
- "**DO NOT** use if pregnant or nursing. Do not operate vehicles or machinery while using. Not for sale to persons under 21."
- "**DO NOT use this product if you are taking medications, especially opioid medications, other medications** (e.g., pain relievers, opioids, antidepressants, blood pressure drugs, MAO inhibitors, stimulants, antihistamines) or if you consume alcohol, as these interactions may increase health risks. This product should not be used daily or for prolonged periods. Consult your doctor before using if you have a medical condition or are on prescription medications."[2]

4. **The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer of the dietary supplement that contains the new dietary ingredient has concluded that the new dietary supplement will reasonably be expected to be safe.**

As set forth below, SBL has concluded that its 7-OH dietary supplements, when used under the conditions recommended or suggested in their labeling, are reasonably expected to be safe.

***Labeling*.** When used under the conditions recommended or suggested in labeling, only adults will consume SBL's 7-OH dietary supplements. Further, adult consumers will ingest no more than one serving (7.5 mg of 7-OH) in a 6-hour period, with no more than two servings (a total 15 mg of 7-OH) being consumed in any 24-hour period.

***History of Use*.** SBL and other dietary supplement manufacturers formulate 7-OH into commercial formulations. It is estimated that since 2023, no less than 200 million servings of 7-OH have been distributed in the United States. To date, there have been no reported deaths clearly attributed to 7-OH.

A review of the history of use data on 7-OH, including analyses of case reports, surveillance data, and clinical outcomes, reveals no credible evidence of acute poisoning or overdose death. 7-OH has "been used for years now in the United States, but there appears to be limited evidence for any widespread development of severe SUD [i.e., substance use

[2] *See* label attached as Exhibit "B" hereto.

disorder] or addiction."[3] Given the level of population exposure to date, the absence of safety signals for 7-OH indicates that currently there is no safety concern.[4]

The safety of 7-OH based on history of use can be ascertained by systematically searching the medical literature for published case reports of acute poisoning, overdose, or death attributable to the compound. This history of use information can be gathered from evaluating data contained in epidemiological surveillance systems, including the National Poison Data System ("NPDS"), the U.S. Drug Enforcement Administration's Toxicology Testing Program ("DEA TOX"), and the National Drug Early Warning System ("NDEWS"). History of use data and information can also be obtained by reviewing adverse event reporting databases, such as the FDA Adverse Event Reporting System ("FAERS"), and comparing the frequency and severity of 7-OH-related events to those of other psychoactive substances. The Researched Abuse, Diversion, and Addiction-Related Surveillance ("RADARS") system also contributes to the understanding current trends in substance abuse, misuse, and diversion.[5]

There appears to be an absence of published case reports documenting acute poisoning or overdose death directly attributable to 7-OH. According to one expert, the absence of case reports supports an inference of safety:

> The medical subspecialty that focuses on identifying new adverse effects from emerging use of substances, medical toxicology, has yet to publish acute poisoning or overdose death from 7-hydroxymitragynine. *Medical toxicologists are remarkably adept at identifying emerging adverse events from emerging substances*. For example, an oral anticoagulant poisoning outbreak among synthetic cannabinoid users from March 2018 was first identified *within 2 weeks* by toxicologists at the Illinois Poison Control Center. Medical toxicologists are also adept at prospectively identifying poisoning cases. Medical toxicologists in New Jersey identified the onset of the 2023 tianeptine outbreak in June, followed by prospective surveillance for the next several months. This prospective surveillance found 4.6 tianeptine cases per month compared against a background rate of 0.5 tianeptine cases per year. *Given the proven skill of medical toxicologists in identifying adverse events from a wide variety of potential intoxicants including opioids, the lack of a published signal suggests not that 7-hydroxymitragynine poisonings are missed, but that a signal does not exist*. As both of these outbreaks entailed new substances, the argument that medical toxicologists must know about a new drug class before its outbreak can be identified lacks merit.[6]

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[3] Expert Report of Kirsten E. Smith, Ph.D. (Aug. 18, 2025), at 10, attached as Exhibit "C" hereto (hereinafter "Smith Report").
[4] *See* Statement of Edward W. Boyer, M.D., Ph.D. (Aug. 18, 2025), at 14, attached as Exhibit "D" hereto (hereinafter "Boyer Statement"); *see also* Smith Report at 1.
[5] *See* Boyer Statement at 11.
[6] Boyer Statement at 7-8 (emphasis in original).

To date, a single letter to the editor—not a full publication—has attributed acute overdose to self-reported 7-OH ingestion. Notably, the individual described in the case report, who had a history of prior opioid abuse and claimed to be taking 7-OH, was resuscitated by administration of naloxone. Unfortunately, laboratory testing on this individual was inadequate (for example, the presence of fentanyl was not measured at any point, nor was 7-OH detected in his blood or urine).[7] The report lacks the scientific rigor to establish a relationship between 7-OH use and overdose.

Considered broadly, history of use data has not demonstrated significant or widespread respiratory depression in humans associated with 7-OH, and no confirmed cases of 7-OH-induced respiratory depression have been reported in the medical literature. These findings suggest that the overall clinical safety profile of 7-OH—particularly with oral use at typical serving sizes—appears favorable, with a low risk of serious respiratory depression. Current evidence does not indicate a significant clinical safety concern regarding respiratory depression for 7-OH when used as intended.[8]

Postmarketing surveillance further supports the lack of a safety signal from 7-OH. For example, the NPDS poison control data garnered only a small number of cases (N=118) between April 1, 2025, and July 31, 2025.[9] This time period[10] saw a 58% increase in 7-OH reports in the NPDS; over the same time period, however, the number of kratom reports increased 69%, with a total number of 1,116 cases. Subsequent analyses have confirmed that 7-OH and kratom cases were coded correctly, a quality control measure that increases the validity of the dataset.

Importantly, the "NPDS contains no reports of death attributable to 7-hydroxymitragynine, whereas 14 kratom deaths were reported April 1-July 31, 2025."[11] The single death in the NPDS dataset for this time period occurred in Mississippi in a person who had hyperventilation and alkalosis—the exact opposite physiology of the expected hypoventilation and acidosis caused by opioid overdose. In fact, the patient died of a pulmonary embolism after suffering a hemorrhagic complication from anticoagulation

[7] *See* Mallory K. Pullman et al., Letter to the Editor, *Cardio-pulmonary arrest in a patient revived with naloxone following reported use of 7-hydroxymitragynine*, Clinical Toxicology (2025), attached as Exhibit "E" hereto.
[8] Smith Report at 10-12.
[9] *See* NPDS data, available from America's Poison Center upon request.
[10] This date range is different than the date range referenced in FDA, *7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat* (July 29, 2025), https://www.fda.gov/files/drugs/published/7-hydroxymitragynin_7-oh_an_assessment_of_the_scientific_data_and_toxicological_concerns_around_an_emerging_opioid_threat.pdf (hereinafter "7-OH Report"). On February 15, 2025, a specific product code for 7-OH was established and adopted by Toxicall (and adopted by NPDS on July 16, 2025). The above analysis compares kratom and 7-OH mentions in the NPDS for the period of April 1, 2025, to July 31, 2025. This date range was selected to allow poison center staff to be trained on and become familiar with the new product code. By selecting a range of dates when 7-OH could not be properly coded, FDA's 7-OH Report exaggerates the rate of increase of 7-OH exposures reported to poison centers.
[11] Boyer Statement at 12.

therapy, none of which are plausibly related to 7-OH use.[12] On August 12, 2025, the NPDS issued an alert regarding 7-OH that does not identify deaths following ingestion of 7-OH products.[13]

Case reports of severe toxicity attributed to 7-OH lack rigor. For example, one NPDS case described an individual who suffered cardiac arrest after the self-reported ingestion of 190 mg of 7-OH. The patient reported getting drunk on the day he was fired from his job before ingesting far more than the normal serving of 7-OH. The clinical and laboratory evaluation of this individual, who had a history of opioid abuse, did not include rigorous drugs-of-abuse testing, although the product he ingested was evaluated. He was resuscitated with two intravenous doses of 4.0 mg naloxone, a substantial dose of naloxone typically reserved for fentanyl intoxication. Considering that neither the presence of 7-OH (or its metabolites) nor fentanyl were confirmed in this patient, the extraordinary dose of naloxone needed for reversal suggests that a high-potency opioid, such as fentanyl (not a substance with the MOR binding affinity of 7-OH), was the cause.[14]

Additionally, DEA TOX and NDEWS, both designed to detect new and emerging drug threats, have not identified a pattern of serious or fatal outcomes linked to 7-OH, even as they have flagged other substances as public health concerns. "DEA TOX details emerging toxicologic threats in its publicly available content such as tianeptine, xylazines, and other substances, but 7-hydroxymitragynine, even after oral single-product formulations entered the marketplace, has never received comparable recognition."[15] NDEWS content concerning 7-OH is, for the most part, related to reporting of online material, research publications, and background material. One NDEWS data collection effort focusing on emergency medical services-run data combines kratom and 7-OH. Even so, NDEWS releases do not describe acute poisoning and overdose deaths.[16] Whereas case reports can function as a signal, the absence of case reports can plausibly be considered to constitute a lack of signal.

In general, when a substance poses a significant risk of overdose or death, multiple cases are rapidly detected and reported, generating a clear signal in these surveillance systems. Yet "[n]o clear signal for overdose death from 7-hydroxymitragynine exists. This finding holds

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[12] *See* Pullman, *supra* note 7.
[13] *See* Shuana Devitt, *Health Advisory: Serious Illnesses Associated with 7-OH Use*, America's Poison Centers (Aug. 12, 2025), https://poisoncenters.org/news-alerts/13531044, attached as Exhibit "F" hereto.
[14] *See* Mississippi Poison Control Center, Case No. 410848 (July 23, 2025), attached as Exhibit "G" hereto.
[15] Boyer Statement at 12; *see also* Smith Report at 17.
[16] *See* NDEWS, *Alert from the NDEWS Web Monitoring Team: Online mentions of 7-OH* (June 2024), https://ndews.org/wordpress/files/2024/11/6.21.24_7-OH_PDF.pdf; NDEWS, *Alert from the NDEWS Web Monitoring Team: Online mentions of 7-OH* (Aug. 2024), https://ndews.org/wordpress/files/2024/11/8.16.24_7-OH_PDF.pdf; NDEWS, *Alert from the NDEWS Web Monitoring Team: 7-OH* (Nov. 2024), https://ndews.org/newsletter/ndews-weekly-briefing-issue-208/; NDEWS, *NDEWS Special Report: EMS Encounters for Kratom/7-OH-related Overdoses (nonfatal or fatal) in the US January 1, 2023-April 30, 2025* (May 2025), https://ndews.org/newsletter/ndews-weekly-briefing-issue-233/ (hereinafter "*NDEWS Press Releases*"), attached as Exhibit "H" hereto (combined).

true across multiple nationwide overdose surveillance systems. The lack of a signal is important. In general, multiple overdoses do not go unnoticed; multiple overdoses generate signals."[17] Indeed, the "lack of signal from even a single 7-hydroxymitragnine overdose death is important."[18] This absence is not due to underreporting or lack of awareness among clinicians or surveillance systems but rather reflects the true risk profile of the compound. "A signal arising from overdose death from 7-hydroxymitragynine is absent. Based upon data available at this time, the lack of findings suggests that 7-hydroxymitragynine carries no undue or unreasonable risk of overdose death."[19]

The argument that data collection systems are unaware of 7-OH and therefore miss adverse events lacks merit. Leading surveillance systems (e.g., poison control centers, DEA TOX, and NDEWS) are well aware of the distinction between kratom and 7-OH. Furthermore, the way NPDS operates *increases* the accuracy of identifying death from a specific chemical. For example, poisoning death in a patient in a healthcare facility (i.e., the sort of individual about whom NPDS collects data) is rarely immediate. The period from presentation to death allows medical toxicologists time to obtain substantial information about the intoxication; this, in turn, leads to greater precision in attributing poisoning death—and minimizing underreporting—to a specific substance. NPDS has not identified any deaths that are solely attributable to 7-OH.[20] NDEWS investigators knew of the differences between kratom and 7-OH but provided only aggregated data of "kratom/7-OH" exposure.[21] This research strategy potentially overrepresents the impact of 7-OH in NDEWS reporting.

An online survey of 278 U.S. adults who had used 7-OH products found no evidence of widespread or severe illness, injury, or SUD associated with 7-OH use. Most survey respondents reported positive experiences, and qualitative interviews with 23 users further supported the finding that the majority perceived a net benefit rather than harm from 7-OH consumption. These results are consistent with a related finding indicating that most users are highly functioning and do not experience significant adverse effects.[22]

In summary, review of the literature, surveillance data, and adverse event reports does not reveal evidence of acute poisoning or overdose death attributable to 7-OH. While cases of 7-OH use have been reported to overdose surveillance systems, they are scattered, sporadic,

[17] Boyer Statement at 13 (citations omitted).
[18] *Id.*
[19] *Id.* at 14. Research has identified that notification of upcoming scheduling of a substance leads to increased overdose from that substance; for example, DEA's announcement in 2001 that gamma-hydroxybutyrate ("GHB") would be placed in Schedule I led to an immediate surge of severe GHB overdoses in the weeks prior to scheduling. *See 2001 North American Congress of Clinical Toxicology Annual Meeting*, 39 J. of Clinical Toxicology 455, 541-42 (2001). By contrast, NPDS data demonstrates that FDA's issuance of a warning letter on June 25, 2025, has not triggered a comparable surge of severe 7-OH poisoning, overdose, or death.
[20] A single death reported to NPDS occurred in a hospice patient who died after several days in the hospital of complications from a pulmonary embolism, not 7-OH. *See* Pullman, *supra* note 7; Mississippi Poison Control Center, *supra* note 14.
[21] *See* NDEWS Press Releases, *supra* note 16.
[22] Smith Report at 10-12.

and uncommon. The lack of signal arising from the estimated one billion servings of 7-OH distributed since 2023 strongly suggests that the threat of inadvertent overdose, toxicity, and poisoning at recommended serving sizes is minimal.

Other Evidence. In addition, other evidence suggests that 7-OH, when used under the conditions recommended or suggested in the labeling of the SBL dietary supplements, is reasonably expected to be safe. Exposure, not dose, predicts toxicity. Pharmacokinetic measurements demonstrate that 7-OH has low systemic exposure making acute toxicity unlikely. Following oral administration, 7-OH is rapidly absorbed, with maximum serum concentrations achieved in only 20 minutes. 7-OH then undergoes substantial first pass metabolism to yield a bioavailability of approximately 2.7%. Of the molecules that survive biodegradation in the liver and enter the bloodstream, an estimated 50% distribute into red blood cells where they cannot produce biological activity. Together, these pharmacokinetic actions contribute to 7-OH's brief elimination half-life of 1.7 hours, as well as to a mean residence time of 1.2 to 2.0 hours.[23]

7-OH molecules that enter the blood stream must survive plasma esterase-based degradation in addition to non-enzymatic breakdown before reaching the target organ. If 7-OH reaches the brain, it is as a substrate for p-glycoprotein, so that brain penetrance is the lowest of all organs tested and it is net exported with an efflux ratio of 1.4, meaning that 7-OH is removed from cells more efficiently than it enters them. This process further decreases the risk of acute toxicity, such as respiratory depression.[24]

In addition, the binding profile of 7-OH is almost identical to that of buprenorphine, a partial mu-opioid receptor ("MOR") agonist with respiratory ceiling effects where administration of additional doses of substance, beyond a certain point, produces no additional respiratory depression.[25] The respiratory depression identified by laboratory chemists arises only in the setting of intravenous administration 7-OH, a route that is not used by consumers. Moreover, investigators compared the respiratory depression produced by 7-OH to that produced by morphine, but they did not compare 7-OH against oxycodone (a more common comparator in pharmacokinetic studies) or fentanyl, more realistic comparators given current trends in non-medical opioid use. Respiratory depression following 7-OH administration was, therefore, identified only in an inappropriate model using an incorrect route of administration and an unrealistic opioid for comparison.[26]

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[23] *See* Yi-Hua Chiang et al., *In Vitro and In Vivo Pharmacokinetic Characterization of 7-Hydroxymitragynine, an Active Metabolite of Mitragynine, in Sprague-Dawley Rats*, 50 European J. of Drug Metabolism and Pharmacokinetics 205, 218 (2025), attached as Exhibit "I" hereto.
[24] *See id.* at 213.
[25] *See id.* at 205.
[26] *See id.* Interestingly, buprenorphine (like 7-OH, another partial MOR agonist with respiratory ceiling effects) is used clinically to reverse respiratory depression from complete MOR agonists. *See* Nasim Zamani, et al., *Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial* 24 Critical Care 44 (2020), https://doi.org/10.1186/s13054-020-2740-y, attached as Exhibit "J" hereto. These findings are consistent with the reported bi-exponential distribution of 7-OH (meaning, 7-OH distributes into two compartments in the body, such as body water and tissues), where

On July 29, 2025, FDA released a report entitled, "7-Hydroxymitragynine (7-OH): An Assessment of the Scientific Data and Toxicological Concerns Around an Emerging Opioid Threat" (hereinafter "7-OH Report"). FDA's 7-OH Report contains several misstatements of science and epidemiology.

- With regard to science, the 7-OH Report incorrectly conflates 7-OH's MOR receptor affinity with lack of safety. Exposure, not potency of binding alone, predicts toxicity.[27] As FDA has stated, "[e]xposure-response information is at the heart of any determination of . . . safety."[28] While the binding of a substrate to its receptor is useful information, it is only one aspect to consider when assessing potential adverse effects.[29] FDA's 7-OH Report not only overlooks the importance of assessing human exposure to 7-OH following ingestion of that substance in its analysis, but it also disregards existing data that could better inform policymaking decisions.

  Recognizing that data related to administration of 7-OH in humans is limited, FDA's 7-OH Report relies on existing studies and animal models to infer (rather than prove) the potential for toxicity in humans. Unfortunately, FDA makes two errors in its assessment. First, FDA attempts to extend information derived from kratom use studies to oral 7-OH. Substantial differences exist in several pharmacokinetic and pharmacodynamic parameters in animal models between 7-OH from kratom use and oral use of 7-OH. Many of these parameters arising from oral 7-OH administration in animal models (e.g., the limited bioavailability of <3%, limited volume of distribution, extrahepatic elimination by enzymatic and non-enzymatic means, extensive distribution of 7-OH into red blood cells, short elimination half-life, brief mean residence time (i.e., the time a molecule such as 7-OH spends in the body), and

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oral dosing produced mono-exponential distribution, or a one-compartment model. 7-OH penetrates the brain the least of all tissues, a finding that suggests that body water is the predominant compartment for 7-OH distribution.

[27] "Exposure" in this context is different from NPDS usage; here, exposure refers to the concentration and persistence of a substance in the body. The amount of a substance that is absorbed into the body, how long the body takes to metabolize and excrete it, metabolite-to-parent ratio, protein binding, and how long a substance persists in target organs, among other parameters, all contribute to the extent of exposure to that substance. Response can be assessed in terms of therapeutic effect or safety. *See id.*

[28] FDA, Guidance for Industry, *Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* (Apr. 2003), attached as Exhibit "K" hereto.

[29] The same features that make 7-OH difficult to detect in forensic testing—its instability in plasma—also *limit the exposure of the person ingesting 7-OH*. 7-OH contains a conjugated methyl ester that is of heightened chemical reactivity; hence, the observed instability of 7-OH in plasma, blood, urine, and gastric fluid. The stability of orally administered 7-OH is actually worse than research suggests; incubation of 7-OH without protease inhibitors leads to greater-than-expected destruction of the molecule than from simple ester hydrolysis alone. *See* Shyam H. Kamble, et al., *Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases Its Opioid Potency and Efficacy*, 3 ACS Pharmacology & Translational Science 1063, 1063-68 (2020), attached as Exhibit "L" hereto. Moreover, this analysis did not include the impact on hepatic metabolism—a recognized pathway for 7-OH metabolism. Together, these effects, unconsidered by the FDA in its report, limit human exposure to ingested 7-OH. *See id.*

poor brain penetrance) could contribute to an understanding of the observed lack of signal for acute poisoning and overdose death.[30] Second, FDA relies on animal studies with unclear translational value to identify respiratory depression. The relied-upon study used intravenous 7-OH consumption—a route of administration of 7-OH that has not been observed among consumers. At no point does FDA's 7-OH Report acknowledge the importance of pharmacokinetic and pharmacodynamic parameters that limit exposure and mitigate toxicity from 7-OH, or rely upon optimal scientific methodology in attempts to demonstrate toxicity.

- With regard to epidemiology, FDA's 7-OH Report acknowledges the considerable shortcomings of several epidemiologic datasets—and ignores the shortcomings of others. For example, the 7-OH Report notes, correctly, that due to its shortcomings the FAERS database is not worthy of further analysis. Notably, however, the report ignores the fact that through the first quarter of 2025, none of FDA's own quarterly reports describe 7-OH as presenting a safety signal for serious risk.[31] FDA places the greatest emphasis on NPDS data but reports only 7-OH exposures. This approach contains considerable bias due to the lack of a comparator. A more scientifically rigorous approach would compare the number and rate of change of NPDS-reported exposures to 7-OH versus another psychoactive substance, such as ingestible delta-9 tetrahydrocannabinol ("Δ-9 THC") formulations. Comparing the reports for 7-OH to other substances likely would have identified a much stronger signal for substances other than 7-OH.

Finally, although FDA's 7-OH Report does not specifically address SBL's dietary supplements, it cites surveillance data from various sources that purport to show a rising trend in exposures to 7-OH linked to negative health outcomes. FDA, however, did not adequately consider real-world use of 7-OH, which—as set forth above—has not been shown to pose a significant risk of acute toxicity (such as overdose), respiratory depression, other types of morbidity or mortality.

5. The signature of the person designated by the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient.

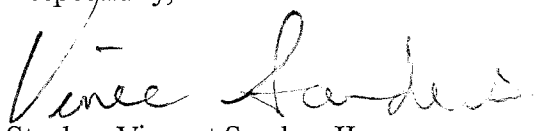
The signature of Stephen Vincent Sanders II, the person designated by SBL, is set forth below.

* * *

[30] *See* Chiang, *supra* note 23, at 213.
[31] *See* FDA, *Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)* (updated Sep. 30, 2025), https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system, attached as Exhibit "M" hereto.

If you have questions or need any clarification, please do not hesitate to contact me at vince@cbdamericanshaman.com.

Respectfully,



Stephen Vincent Sanders II
Chief Executive Officer
Shaman Botanicals, LLC

Attachments

U.S. FOOD & DRUG ADMINISTRATION

December 3, 2025

(b)(4)

Dear (b)(4):

Questions have arisen during FDA's review of your new dietary ingredient (NDI) notification concerning your new ingredient, "7-Hydroxymitragynine", that you intend to market as a bulk dietary ingredient, about matters that, if unresolved, are likely to cause FDA to object to the marketing of your ingredient. Please provide an amendment addressing the following issues, including the appropriate documentation.

Identity Concerns:

1. Your notification included two labels for your proposed NDI in finished dietary supplements (Exhibits A and B). Further, you provide a brief description on page 2, #3 of the NDI in the dietary supplement. However, your notification did not provide a full description of the NDI nor the quantity of each ingredient (i.e., "Other Ingredients") in the dietary supplement(s). Please provide a full description of the NDI (e.g., chemical formula and source information) as well as the concentration of each ingredient in your proposed dietary supplements. This information is requested to verify the identity of your proposed NDI and dietary supplements.

2. Your notification indicates that your 7-OH is manufactured from kratom. However, your notification did not contain your manufacturing processes and specifications for your proposed NDI and dietary supplements. Please provide the following:
    - A complete description of your raw materials and formulation ingredients as well as material/ingredient verifications (e.g., certificates of analysis, evidence that processing materials and formulation ingredients are food grade).
    - A complete, detailed narrative and flowchart of the manufacturing processes of your proposed NDI and dietary supplements.
    - A list of the NDI and dietary supplement specifications as well as detailed protocols of the analytical methods used to support these acceptance criteria including data, calculations, and/or results used to confirm that the NDI and products meet specifications.

   This information is important to establish the identity of your proposed NDI.

Because FDA is obligated to complete its review and send a response to your notification within 75 days of the filing date of November 21, 2025, I urge you to review these concerns and then

U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740
www.fda.gov

upload an amendment to your notification within three business days. If you do not understand how to document the concerns discussed, FDA is prepared to make the scientists who are reviewing your notification available to you and/or your scientific staff during a telephone conference to help you understand our concerns and discuss responses that might address our concerns.

Note that any amendment will have to comply with all requirements of 21 CFR 190.6 including the requirement that it consist of a signed original document. FDA could consider the amendment a substantive amendment, which would result in resetting the original filing date for your notification (see 21 CFR 190.6(d)).

If you have any questions about this request or how to document your response, email us at NDITEAM@fda.hhs.gov.

Best regards,

Markeesa Scales, MPH
Identity and Status Branch
Division of Research and Evaluation
Office of Dietary Supplement Programs
Office of Food Chemical Safety, Dietary Supplements, and Innovation
Human Foods Program

SHAMAN
BOTANICALS

December 12, 2025

via Electronic Submission

Office of Dietary Supplement Programs (HFS-810)
Human Foods Program
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740

CONTAINS CONFIDENTIAL COMMERCIAL INFORMATION EXEMPT FROM DISCLOSURE

Subject: Amendment: Catch-Up New Dietary Ingredient Notification for 7-Hydroxymitragynine

Dear Ms. Scales:

This amendment to the New Dietary Ingredient Notification ("NDIN") submitted on November 20, 2025, by Shaman Botanicals, LLC ("SBL") for 7-Hydroxymitragynine ("7-OH") provides information in response to your request for more information dated December 3, 2025. In the response below, we have listed each request in bold font, followed by SBL's response.

1. **Your notification did not provide a full description of the NDI nor the quantity of each ingredient (i.e., "Other Ingredients") in the dietary supplement(s). Please provide a full description of the NDI (e.g., chemical formula and source information) as well as the concentration of each ingredient in your proposed dietary supplements. This information is requested to verify the identity of your proposed NDI and dietary supplements.**

(b)(4)

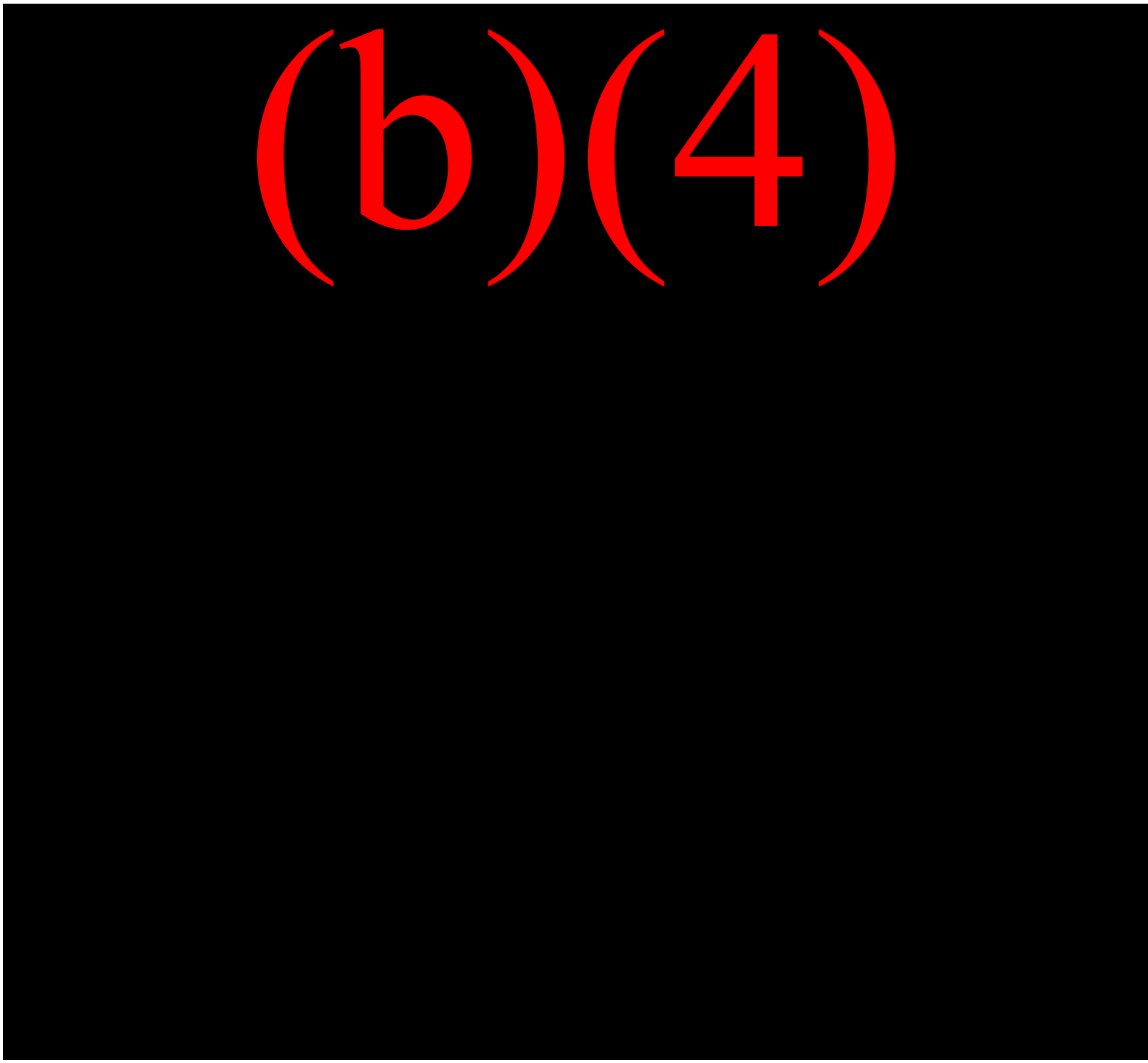
(b)(4)

(b)(4)

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2. **Your notification did not contain your manufacturing processes and specifications for your proposed NDI and dietary supplements. Please provide the following:**

    - **A complete description of your raw materials and formulation ingredients as well as material/ingredient verifications (e.g., certificates of analysis, evidence that processing materials and formulation ingredients are food grade).**

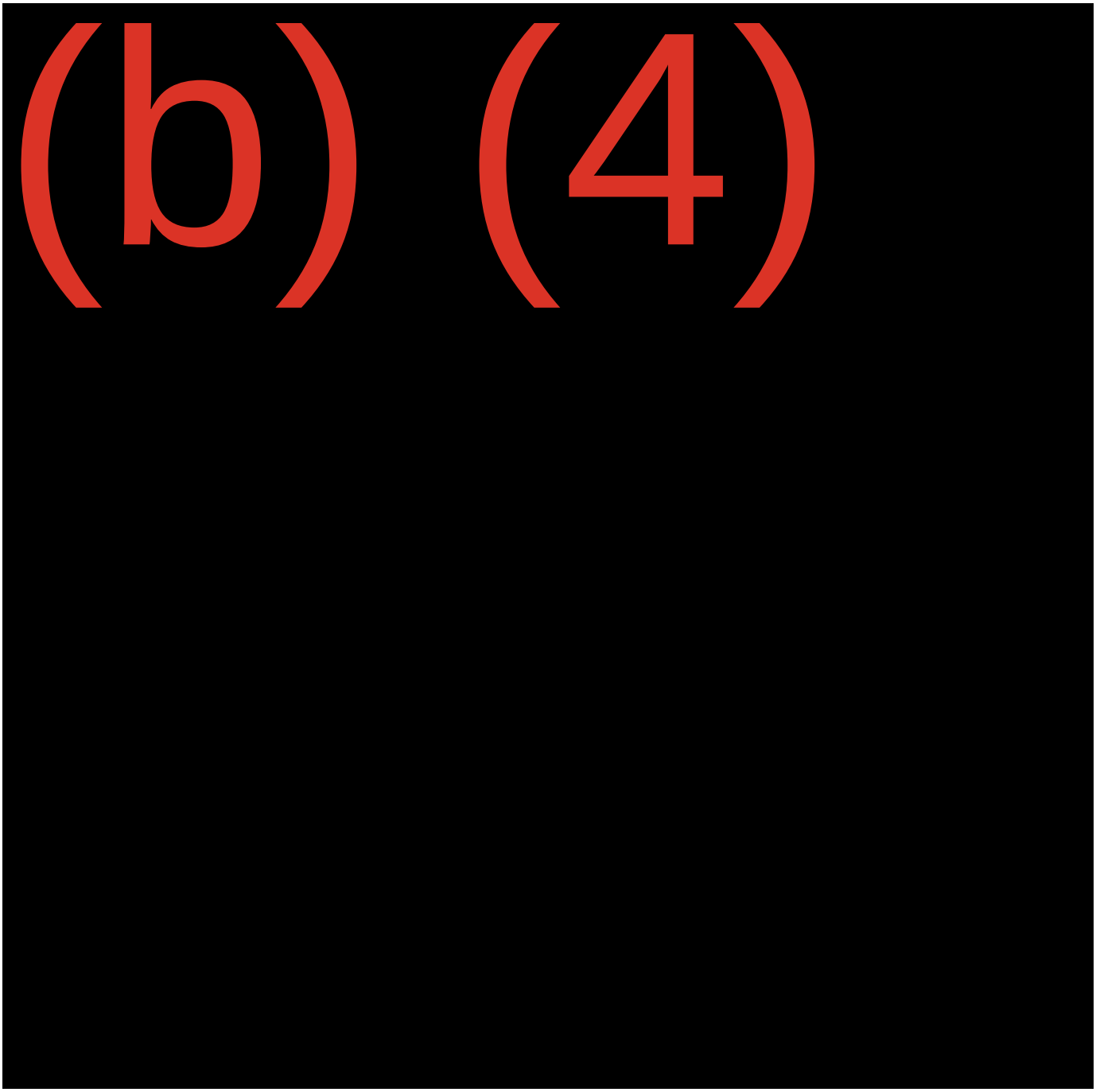


- **A complete, detailed narrative and flowchart of the manufacturing processes of your proposed NDI and dietary supplements.**

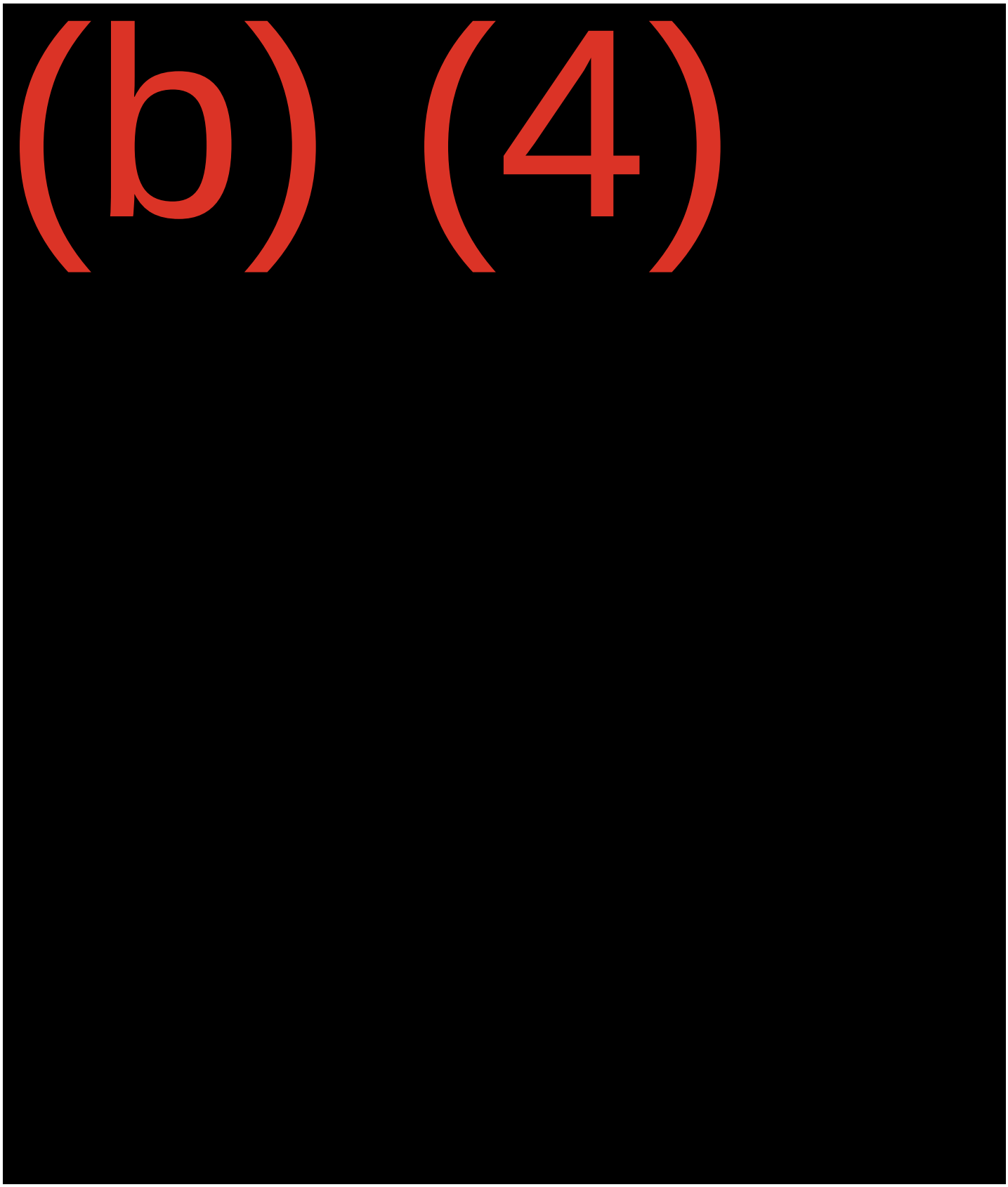


- **A list of the NDI and dietary supplement specifications as well as detailed protocols of the analytical methods used to support these acceptance criteria including data, calculations, and/or results used to confirm that the NDI and products meet specifications.**





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If you have any questions or need any clarification, please do not hesitate to contact me at vince@cbdamericanshaman.com.

Respectfully,

Vince Sanders

Stephen Vincent Sanders II
Chief Executive Officer
Shaman Botanicals, LLC

Attachments

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