AMERICAN KRATOM ASSOCIATION

Memorandum

Date: **September 2018**

Subject: **Scientific and Policy Documents Supporting the Safety of Kratom**

The American Kratom Association (AKA), the largest consumer organization in the United States representing the nearly five million kratom users in the United States, provides the following information to state agencies that are receiving information from the U.S. Food and Drug Administration (FDA) and other federal agencies encouraging states to add the botanical kratom to their state-controlled substances lists. The AKA strongly opposes any unjustified regulatory actions because the science on the safety and the addiction profile of kratom does not support any scheduling policy.

Background:

Kratom has been used safely for centuries in the Southeast Asia region, where it grows in the wild, and for decades in the United States. Importantly, over that long history of centuries of use, Southeast Asian authorities have not reported any kratom overdose deaths. The reasons for kratom use in this region largely mirror those in the U.S., including use as a mild stimulant by agricultural workers and as a dietary ingredient/dietary supplement for pain relief. Such traditional use is reported to benefit quality of life, and improve social and occupational behavior, with little evidence of serious personal or social harm.

The "Ground Zero" event that appears to have triggered the interest of the FDA in kratom were 9 deaths that occurred in 2009 in Sweden that were attributed to the ingestion of a powdered kratom product known as "Krypton." Based on these deaths and the concerns about kratom flowing from those events, the FDA subsequently issued Import Alert 54-15 (2012; 2014; and 2016). These Krypton deaths were cited by the FDA in the recommendation to the DEA to schedule Mitragynine (MG) and 7-Hyroxymitragynine (7-OH) and were highlighted again in the August 31, 2016 Federal Register notice of intent to place MG and 7-OH into Schedule I. These deaths were also referenced by Dr. Scott Gottlieb in his November 14, 2017 Public Health Advisory on risks associated with the use of kratom as a part of a larger group of 44 total deaths the FDA maintains as being associated with the use of kratom. Dr. Gottlieb also stated on November 14 that the FDA had completed the required 8-Factor Analysis on kratom and had transmitted it to the DEA to support the recommendation for kratom being added to Schedule I.

To illustrate the flawed claims of the FDA, what is not disclosed is that a group of researchers investigated those nine deaths in Sweden and concluded they were not caused by powdered kratom, but rather because of a toxic dose of *O*-desmythltramadol that was deliberately added to the "Krypton" product rendering it a dangerous and lethal adulterated product. The FDA has never sought to schedule a substance that was adulterated by another toxic substance, but that is what is being proposed for kratom.

The DEA (1) withdrew the 2016 notice of intent to schedule kratom on October 13, 2016; and (2) has not taken any action on the November 14, 2017 request to place kratom into Schedule I. The AKA believes a large part of

the controversy surrounding kratom is based on the lack of understanding of the plant and its pharmacological activity, and any deaths and adverse events that are kratom specific are caused by adulterated and contaminated kratom products.

A substantial body of emerging science and research are validating both the basic safety of the natural plant for consumer use and documenting the fact that concerns about kratom are actually derivative of adulteration and contamination of kratom products, or deaths actually caused by polydrug use or unrelated health or social conditions of the decedents that do not support any regulatory action against kratom.

Use the following link to access a Dropbox folder which contains several critical reports and studies that have been conducted regarding kratom by industry experts:
https://www.dropbox.com/sh/5jv2k4cjjvb1nej/AACTg1jj6KrMyxeZ7a3ea4NOa?dl=0

With reference to each document provided, there is a description of the rationale we would hope will inform your consideration of any regulatory action impacting the availability of kratom to consumers.

- **There are 3 – 5 million kratom consumers in the United States, and surveys show that kratom is primarily used by a middle-aged (31 – 50 years), middle income ($35,000 and above) population for purposes of self-treating pain (68%) and emotional or mental conditions (66%). Kratom had only mild negative effects.**

    - **Document 1**: *Patterns of Kratom use and health impact in the US – results from an online survey*; Grundmann; Drug and Alcohol Dependence, 2017.

- **Research confirms that MG, the main kratom alkaloid, does not have abuse or addiction potential and actually reduces morphine intake – a desired characteristic for any candidate pharmacotherapies for opiate addiction and withdrawal. The potential bad-actor 7-OH alkaloid constitutes only 2% of the alkaloid content of the kratom plant and has no significant pharmacological effect on consumers.**

  This is an important study that addresses the addictive potential of kratom using the most well-accepted and relied upon animal model. It shows that the major naturally occurring constituent responsible for the health-related effects of kratom, mitragynine, is of very low abuse potential. A second substance, 7-hydroxymitragyine, that naturally occurs at such low levels in kratom that it might be of minimal health consequence, has higher abuse potential.

  This has at least two regulatory implications: (1) the finding does not support FDA's claim that kratom is a narcotic-like opioid, and (2) in regulating kratom products, FDA could set standards to ensure that no kratom product contain levels of 7-hydroxymitraginine exceeding those that are commonly present in kratom leaves and products. The study also showed that mitragynine treatment reduced morphine self-administration, an effect consistent with the self-reported use of kratom to reduce opioid craving and use, and consistent with the conclusion that mitragynine is the predominant active constituent in kratom.

    - **Document 2**: *Abuse Liability and therapeutic potential of the Mitragyna speciosa (kratom) alkaloids mitragynine and 7-hydroxymitragynine*, Addiction Biology; Hemby, McIntosh, Leon, Cutler & McCurdy, published on June 27, 2018.

- **Despite assertions by the FDA, research confirms that kratom and its alkaloids are not functionally identical to opioids, and their mechanisms of action are distinctly different.**

    - **Document 3**: Addiction: Society for the Study of Addiction, Letter to the Editor, *The Therapeutic potential of kratom*, June 28, 2018, Oliver Grundmann, Paula Brown, Jack Henningfield, Marc Swogger, Zach Walsh.

    - **Document 4**: *Synthetic and Receptor Signaling Explorations of the Mitragyna Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators,* Journal of the American Chemical Society, Kruegel, Gassaway, Kapoor, Varadi, Majumdar, Filizola, Javitch, and Sames, December 2016.

    - **Document 5**: *The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse,* Kruegel, Grundmann, Neuropharmacology, 2017.

- **The nine Sweden deaths actually were the result of the contamination and adulteration of the powdered kratom product with a toxic dose of *O*-desmethyltramadol, a chemical formulation of the opioid Tramadol.**

    - **Document 6**: *Unintentional Fatal Intoxications with Mitragynine and O-Desmethyltramadol from the Herbal Blend Krypton*; Kronstrand, Roman, Thelander, and Eriksson, Journal of Analytical Toxicology, Vol. 35, May 2011.

- **Kratom does not cause deaths and does not have the same effects of classic opioids on the respiratory system that would support any scheduling of kratom.**

    - **Document 7**: *Henningfield 8-Factor Analysis* addressing the requirements for scheduling under the CSA, submitted to the DEA in November 2016.

    - **Document 8**: *The abuse potential of kratom according to the 8 factors of the controlled substances act: implications for regulation and research*, Psychopharmacology, 23 December 2017.

- **The FDA death reports do not document any death exclusively caused by kratom.**

  Any deaths alleged to be associated to the use of kratom merely document the possible use of kratom products at the time of the occurrence of a death caused by other specific factors, i.e., where the cause of death is related to a gunshot wound; a suicide related to mental health issues; physical injuries that caused ancillary medial issues resulting in a fatality; use of an illegal drug; polydrug use of prescription and/or illegal drugs as toxic dose levels; and deaths that are related to other unrelated medical conditions that have no relationship to kratom use, i.e., a death from deep vein thrombosis.

  Of the 44 claimed deaths, the FDA identifies only a single death as being kratom-related involving an individual who "had no known historical or toxicologic evidence of opioid use, except for kratom." The FDA refuses to release any additional information on the death other than the subject's age and ethnicity and provides no information on how kratom was determined to have contributed to the death.

- **Document 9**: Raw data file issued by the FDA on November 14, 2017.

- **Document 10**: Raw data file issued by the FDA on February 14, 2017.

- **Document 11**: *The FDA Kratom Death Data: Exaggerated Claims, Discredited Research, and Distorted Data Fail to Meet the Evidentiary Standard for Placing Kratom as a Schedule I Controlled Substance*, March 2018, Jane Babin, Ph.D., Esq., University of San Diego School of Law, J.D., Purdue University, Ph.D., Molecular Biology.

- **Document 12**: *FDA Fails to Follow the Science***,** August 2018, Jane Babin, Ph.D., Esq., University of San Diego School of Law, J.D., Purdue University, Ph.D., Molecular Biology.

- **Kratom use produces a similar addiction profile to caffeine, and its effects are mild in contrast to the psychosocial and physiological effects relative to that of opioids.**

  - **Document 13**: *Kratom use and mental health: A systematic review*; Swogger, and Walsh; Drug and Alcohol Dependence, 2018.

  - **Document 14**: CPDD/NIDA International Kratom Symposium Summary Slides, June 9, 2018.

- **A ban on kratom actually increases the public safety risk as patients using kratom are forced to (1) use NSAID medications that have serious documented adverse health risks; (2) use dangerously addictive and potentially deadly opioids; or (3) seek kratom on the black market where adulteration, contamination, and dangerously formulated kratom products have been identified.**

  - **Document 15**: FDA Docket FDA-2018-N-0987 comments submitted by Jack E. Henningfield, VP of Research and Policy at PinneyAssociates, and Adjunct Professor of Behavioral Sciences at The Johns Hopkins University School of Medicine, May 18, 2018.

  - **Document 16**: CPDD 2018, Poster on *Kratom and its Mitragynines in the Opioid Crisis: A Path to or Away from Opioids,* Henningfield, Raffa, Garcia-Romeu, Doshi.

- **Additional research and documents of interest:**

  - **Document 17**: Science Letter to Leader McConnell, Minority Leader Schumer, Speaker Ryan, Minority Leader Pelosi, requesting the DEA return the FDA scheduling recommendation for further review and study, June 21, 2018.

  - **Document 18**: NCSL State Legislatures Magazine, April 2018, *Kratom Concerns*.

  - **Document 19**: Science Letter to Kellyanne Conway, Counselor to the President, and Robert W. Patterson, Acting Administrator of the Drug Enforcement Administration, February 8, 2018.

  - **Document 20**: American Society for Pharmacology and Experimental Therapeutics (ASPET) letter (representing 5,000 members) letter to Acting Administrator Robert W. Patterson of the DEA, arguing that placing kratom on Schedule I would "effectively eliminate an important avenue of research that has the potential to ameliorate the effects of the ongoing opioid crisis and possible lead to more effective treatments of pain."

- **Document 21**: DEA 2016 Docket, "Schedules of Controlled Substances: Temporary Placement of Mitragynine and 7-Hydroxymitragynine into Schedule I; Withdrawal" @https://www.regulations.gov/docket?D=DEA-2016-0015

- **Document 22**: FDA 2018 Docket, "Patient-Focused Drug Development on Opioid Use Disorder; Public Meeting; Request for Comments" @https://www.federalregister.gov/documents/2018/03/14/2018-05119/patient-focused-drug-development-on-opioid-use-disorder-public-meeting-request-for-comments

- **The AKA Supports Appropriate FDA Regulation of Kratom:**

  - The natural botanical kratom is and should be subject to existing dietary supplement and dietary ingredients regulations that prohibit marketing of products that are adulterated or misbranded.

    - AKA fully supports FDA taking immediate action against any adulterated or misbranded dietary supplement product when it reaches the market.

  - Any chemical reformulation of the natural plant kratom or its alkaloids that alters the purity, concentration, or designed to enhance the effects should be subject to new dietary ingredient regulations as provided in the Dietary Supplement Health and Education Act of 1994 (DSHEA).

  - Kratom products are subject to FDA regulations limiting health claims, Nutrient Content Claims, and Structure/Function Claims and Related Dietary Supplement Claims, and any violators should be prosecuted.

  - Because there are no safety studies documenting safe use for children, the sale of kratom could be restricted for purchase by children under the age of 18, and the product labeling could require an advisory for pregnant women to not consume kratom products.

The AKA has published a set of good manufacturing standards and labeling requirements as a part of its effort to provide consumers with a list of compliant kratom vendors who market safe and unadulterated kratom products.

- **Document 23**: AKA GMP Standards Program