

November 28, 2018

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U.S. Department of Health & Human
Services
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The Honorable Uttam Dhillon
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U.S. Department of Justice
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The Honorable Scott Gottlieb, MD
Commissioner
U.S. Food and Drug Administration
U.S. Department of Health & Human
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10903 New Hampshire Avenue
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The Honorable Nora D. Volkow, MD
Director
National Institute on Drug Abuse
National Institutes of Health
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Dear Health and Human Services and Drug Enforcement Administration:

We are writing to comment on the recently released October 17, 2017 letter “Basis for the recommendations to control mitragynine and 7-hydroxymitragynine in Schedule I of the Controlled Substances Act” (hereafter, “8-Factor Analysis” or “8-FA”) developed by the Food and Drug Administration (FDA), from the United States Department of Health and Human Services (DHHS) to the United States Drug Enforcement Administration (DEA) recommending the placement of mitragynine and 7-OH-mitragynine, the active alkaloids found in kratom, into Schedule I of the Controlled Substances Act. The cover letter is dated October 17, 2017. The letter and the 8-FA were made public by STAT News following their delivery from DHHS pursuant to a Freedom of Information Act request by STAT News (see <https://www.statnews.com/2018/11/09/hhs-recommended-dea-ban-kratom-documents-show/>). STAT News made the documents public at <https://www.documentcloud.org/documents/5031552-HHS-kratom-letter.html>.

Unfortunately, the disclosure omitted many pages of its 8-FA and the FDA has thus far declined to provide the full document stating as follows: “This document was inadvertently disclosed and should have been withheld as it is part of a pre-decisional, deliberative process rightfully protected by the Freedom of Information Act and implementing regulations,” said HHS spokesperson Caitlin Oakley. “That deliberative process is still ongoing, and therefore we have nothing further to add.” From STAT News at <https://www.statnews.com/2018/11/09/hhs-recommended-dea-ban-kratom-documents-show/>.

Nonetheless, what was disclosed provided the basis for evaluating its accuracy and determining if FDA’s approach met the standards of a reliable and valid decision-guiding document. It is possible that a review of the complete document would alter some of our specific comments, and therefore, we urge complete disclosure of the document. Whether its

release was intended or not, its findings and recommendations are now public and full disclosure would prevent misinterpretation of FDA's full evaluation due to omissions in the disclosure.

Based on our analysis of FDA's 8 FA, and with reference to the requirements of the Controlled Substances Act, we have major concerns about its conclusions, the actions that could be based upon it, and the implications for public health. We come to the following main conclusions and recommendations.

Main Conclusions:

- 1. FDA's 8-Factor Analysis does not constitute a reliable and valid scheduling decision guiding document.**
- 2. FDA clearly did not involve NIDA or kratom science experts, as revealed by its major deficiencies.**
- 3. The FDA analysis is incomplete, omitting key data sources routinely relied upon for identifying trends in abuse (e.g., the major federal surveys) and key scientific studies, AND is out-of-date as it does not refer to critical studies including those by NIDA (Yue et al., 2018) and Hemby et al., 2018.**
- 4. The evidence is sufficient to conclude that placement of kratom in Schedule I or any other approach that would ban kratom, would lead many kratom consumers to seek black market kratom and some to relapse to opioids and thus pose a serious risk of death.**

Main Recommendations:

- 1. DEA should ask FDA to reexamine the abuse potential of kratom and potential alternative regulatory approaches to kratom with involvement of NIDA and kratom experts, and stakeholders that have additional data and will be affected, namely kratom vendors and kratom consumers. This should be done transparently and include public meetings.**
- 2. Federal agencies should conduct a nationally representative survey to better understand how many people use kratom, use it in place of opioids and would be put at risk of relapse to opioids if kratom was banned, where they live geographically, and other information critical to understanding the nature and magnitude of a ban, as well as regulatory alternatives to a ban.**
- 3. We recommend that FDA propose a regulatory framework that will ensure that safely manufactured kratom products remain continuously available to consumers in natural leaf forms and manufactured extractions that are widely**

used by consumers, with regulations to ensure quality and appropriate standards for contents, labeling, and marketing. With an advance notice of proposed rulemaking (ANPR), the FDA could solicit comments, and perhaps plan a public hearing to obtain input from key stakeholders including consumers, vendors, experts, and kratom advocacy organizations. The leading kratom consumer advocacy group in the United States, the American Kratom Association, has issued a Statement of Principles on Regulating Kratom (at: <https://www.amerikankratom.org/abou-aka/statement-of-principles.html>) and a voluntary Good Manufacturing Processes (GMP) Standards Program (at: <https://www.amerikankratom.org/index.php/component/sppagebuilder/91-aka-gmp-certification-program>) that may be useful as both have been developed with consideration given to consumers, vendors and with expert input. The implementation of these standards by the FDA, as dietary ingredients/supplements are currently regulated, will offer consumers a safer supply chain for kratom products and help educate consumers on avoiding kratom products that are adulterated or misbranded.

General Comments

The FDA analysis is seriously deficient. Many points are at odds with the latest scientific evidence, some of which was mentioned in passing while other key evidence is not considered in the FDA's analysis. FDA's 8-FA fails to include the serious public health consequences that will result from scheduling kratom, including potential exacerbation of the opioid epidemic. These consequences are foreseeable based on four surveys of more than 20,000 kratom users, a survey of people in treatment for opioid use disorders, and more than 23,000 comments to DEA and FDA. The serious omissions of relevant data including critical studies published since October 2017, and other serious deficiencies summarized in this letter indicate that FDA's 8-FA does not meet the requirements for an abuse potential assessment embodied in the Controlled Substances Act and ordinarily relied upon by FDA and DEA in their scheduling recommendations. DEA should request that FDA develop a state-of-the-art 8-FA with input from NIDA, kratom experts, kratom consumers, and kratom product manufacturers and marketers, ideally facilitated by public meetings because the consequences of the regulatory approach could exacerbate the opioid epidemic, would be contrary to public health, and will put the lives of many current kratom users at risk.

In contrast to the abuse potential assessments ordinarily published in the Federal Register by DEA, which reflect FDA's 8-FA's and which are rigorous and follow the science which generally withstand expert review, this analysis appears to have been written to support a preordained conclusion for the following reasons. Contrary to its claim on page 1 of the 8-FA, that "FDA reviewed and evaluated all of the available data on the abuse potential of mitragynine and 7-hydroxymitragynine (hereafter "MG" and "7OHMG")" and the National Institute on Drug Abuse (NIDA) participated in the review (page 1 of the October 17, 2017 cover letter), the report is far from a comprehensive and objective review of the state of the

science pertaining to the abuse potential, public health impact of kratom, and public health impact of a kratom ban. It overstates analyses and opinions which support scheduling while mischaracterizing, minimizing, and/or omitting reports to the contrary.

Whether NIDA actually provided input to this 8-FA seems questionable given that it is not consistent with NIDA's Kratom Facts webpage that was available in October 2017, nor its most recently revised Kratom Facts webpage. Nor does the evaluation include mention of any of the major federal surveys conducted and/or paid for by NIDA or its collaborator in such surveillance, the Substance Abuse and Mental Health Services Administration (SAMHSA), which are routinely relied upon by NIDA, and usually FDA, for documenting substance abuse rates, trends and problems (more on this below). Nor did the document mention the more than 23,000 comments from kratom users and kratom experts to DEA that were publicly available by October 2017, and which are overwhelmingly at direct odds with FDA's analysis.

Of course, considerable research has been published in the scientific literature and presented at major national meetings convened and/or supported by NIDA since October 2017, and several key studies bearing on the abuse potential of kratom, include those conducted and/or supported by NIDA itself, have been published since October 2017. Whereas these would not have been available in October 2017, it would seem that if requested, NIDA could have informed FDA that the studies were ongoing so that FDA could have mentioned them because they included studies ordinarily considered critical in FDA evaluations of the abuse potential of substances.

The FDA analysis requires extensive revision and should be updated to actually reflect all relevant scientific evidence related to the abuse potential of MG and 7OHMG as required by the CSA in order to provide the basis for a scheduling recommendation. That analysis should also provide an evaluation of the consequences of banning kratom as it pertains to its foreseeable consequence of contributing to opioid overdose deaths.

Specifically, based on scientific evidence, including more than 43,000 responses to surveys from kratom users and comments to DEA and FDA on their dockets and in a public hearing on opioid use disorders, it is foreseeable that removing lawful and regulated kratom from public access by its placement along with heroin in Schedule I of the Controlled Substances Act (CSA) would lead to increases in opioid overdose deaths when thousands of former opioid users return to opioid use.

It is also foreseeable that a kratom ban would drive many kratom consumers (as indicated in the surveys and comments to DEA and FDA) to seek black market sources of kratom out of desperation because alternatives to kratom are either inaccessible, ineffective or unacceptable to them. Since black market kratom cannot be regulated by FDA, there will be no opportunity to evaluate or ensure the purity of what they purchase. Thus they will be at greater risk of exposure to kratom that may be adulterated with fentanyl and other substances than by their current purchases from kratom product marketers, the majority of which appear to be marketing products with high standards for kratom purity that they believe are consistent with

FDA guidance for foods and dietary products, as voluntary industry standards have been promulgated by the American Kratom Association (see AKA, Kratom Summit, May 2018; and AKA Voluntary Standards, 2018).

Additionally, a Schedule I placement will expose those who purchase kratom from any source to risk of arrest and prosecution as though it were possession of other Schedule I substances such as heroin. This is not a theoretical concern and has already occurred and disrupted families in states that have banned kratom (e.g., https://www.huffingtonpost.com/entry/kratom-ban-states_us_5b2bc298e4b00295f15a3b83; https://www.lehighvalleylive.com/slate-belt/index.ssf/2016/10/kilo_of_controversial_green_po.html; accessed Nov. 19, 2018).

A revised 8-FA should actively involve NIDA, and would likely benefit by soliciting information from kratom marketers and experts. This could be supported by public meetings as FDA frequently convenes such meetings when addressing controversial topics that affect millions of people. Examples of this include FDA's Center for Drug Evaluation and Research efforts to evaluate regulatory approaches to foster development of abuse-deterrent opioids, the Center for Tobacco Products efforts to evaluate the role of e-cigarettes in public health, and the Office of Dietary Supplements efforts to determine how Pre-DSHEA Dietary Ingredients (i.e., "old dietary ingredients") could be identified given that many (like and including kratom which were discussed in its October 3-4, 2017 public meeting) could be documented using more inclusive criteria given that they were less formally marketed than major brand products sold in mainstream retail stores.

The revised 8-FA should also provide an evaluation of the broader public health benefits of kratom access, in contrast to the actually documented present or "imminent hazard to public safety" (81 FR 59929). Such a balanced analysis is critical to determine whether public health and the well-being of people, including current kratom consumers, would be better served by banning kratom or by continuing to regulate it as a dietary ingredient, hopefully with more active regulatory oversight than FDA has provided to date.

With respect to kratom regulation by FDA, it should be noted that until the [November 2017 advisories of the FDA Commissioner](#) stating that kratom was a "narcotics like opioid" with respect to "addiction" and "deadly risks", its Office of Dietary Supplements seemed well underway toward developing standards for kratom product and acceptable dietary ingredient notifications that are desired by kratom consumers (see surveys) and kratom marketers. Whereas FDA's Office of Dietary Supplements has not announced that it is no longer considering such notifications, it does not seem that it would be in a position to accept notifications or issue product performance standards despite evidence it has received concerning kratom product safety that contradicts FDA's claims in this 8-FA that MG and 7OHMG should be considered as morphine and/or narcotic-like opioids.

Specific comments per factor of the FDA 8-FA.

Note, the following comments should not be considered comprehensive as FDA has yet to provide its complete 8-FA. However, these comments illustrate the serious deficiencies in the FDA analysis that should make clear to DEA that this cannot be considered a balanced, comprehensive evaluation of “all available data on the abuse potential of mitragynine and 7-OH-mitragynine” as is required by the CSA.

Introductory material, pages 1 & 3:

Page 1: “In assessing the relative abuse potential of mitragynine and 7-OH-mitragynine, FDA reviewed and evaluated all available data on the abuse potential of mitragynine and 7-OH-mitragynine.” And last introductory sentence on **page 3:** “This review evaluates data from the medical and scientific literature, from federal government reports, and databases on the subjective responses and adverse events that result from use of mitragynine and 7-OH-mitragynine.”

Comment: The statement that this 8-FA has “evaluated all available data on the abuse potential of mitragynine and 7-OH-mitragynine” and “federal reports” is a striking misrepresentation of the evidence. Multiple published peer-reviewed evaluations of kratom’s public health effects and abuse potential contain several times more citations and data sources including major sources such as the key federal substance abuse related surveys that were not mentioned or cited. Moreover, the scant evaluation of “subjective responses and adverse events” has selectively omitted data from peer-reviewed published surveys, misrepresented the totality of kratom user reports from the internet, surveys, and comments to DEA and FDA, and has relied upon unsubstantiated adverse event reports (Babin, 2018; Science letters to the White House Office on National Drug Control Policy, 2018, Science letters to Congressional Leadership, 2018; Grundmann et al., 2018). In addition, of course, are key abuse potential and safety-related studies published since October, 2017 (Hemby et al., 2018).

Factor 1 Comments

Page 5: “There is evidence that individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.”

Comment: The fact that some individuals might have taken sufficient amounts to constitute a health hazard (not documented with reliable evidence in this report) does not support this characterization. In fact, reports of adverse effects and effects in which people sought medical attention are apparently rare as evidenced by emergency room reports, poison control center data, surveys (e.g., Grundman et al., 2017; Garcia et al., 2018; Henningfield et al., 2018), and reports from Southeast Asia (SEA) (NIDA International Kratom Science Symposium, 2018). Furthermore, data from U.S. surveys and comments to DEA and FDA indicate that in the U.S. as in SEA, kratom use as an alternative to opioids, and in contrast to opioids, is associated with positive social, family and occupational outcomes and behavior (See also NIDA international Kratom Science Symposium, 2018; Swogger and Walsh, 2017; Henningfield, Fant and Wang, 2018)

Page 5: “The pharmacological effects of mitragynine and 7-OH-mitragynine are similar to those of morphine, a Schedule II drug with a high potential for abuse.”

Comment: This is a gross over generalization that does not distinguish morphine-like opioids from substances without the full spectrum of morphine effects. In fact, the pharmacological effects of MG and 7OHMG are fundamentally different from morphine. MG and 7OHMG are G-protein biased, partial agonists whereas morphine is a non-biased, full agonist at mu opiate receptors. Furthermore, the binding profiles of MG and 7OHMG differ from morphine in terms of their affinities and selectivities for opiate and other receptors. Thus, whereas morphine serves as a robust reinforcer for animals, MG did not serve as a reinforcer in the two animal intravenous self-administration studies that have evaluated it (Hemby et al., 2018; Yue et al., 2018).

Morphine-like opioids are powerful and reliable euphorants for recreational opioid users and whereas no formal human abuse potential studies have been conducted to support FDA’s conclusion, self-experimentation among recreational substance abuser as reported on internet sites indicate that kratom is not a morphine-like euphoriant.

Critically relevant to the inappropriate characterization of kratom as a morphine-like opioid is its respiratory depressing and overdose risk – or lack thereof. Although kratom is estimated to be used by 5 million or more people in the U.S., in contrast to approximately 49,000 actually documented opioid deaths in 2017 (not known to include any in which kratom was the primary cause), it is not clear if there have been any direct kratom-related deaths in which pure kratom, MG, and/or 7OHMG were the primary cause of death, though the possibility that there has been one or more cannot be ruled out. This is consistent with data from SEA, which was reported as follows at the NIDA International Kratom Science Symposium: “There are no known reported severe toxicity or fatality incidents in Malaysia or Thailand where there are large populations of long-term daily users of kratom”. Moreover, animal safety and toxicology studies that have been published and/or known to have been provided to FDA’s own Office of Dietary Supplements in support of New Dietary Ingredient Notifications have exposed several species of animal to doses of 100 or more times greater than human equivalent doses without evidence of respiratory overdose death.

Note, we do not contend that kratom has never caused or contributed to death, that kratom carries no risks, or that kratom and specific alkaloids cannot under some conditions cause respiratory depression. However, the science does not support the conclusion that it is a morphine-like opioid on this critical aspect of opioid pharmacology and toxicology.

The pharmacology of kratom is also at odds with the classic powerful soporific (i.e., “narcotic”) effects of morphine that are among its defining characteristics for millennia. Although kratom can have relaxing effects that some people report are useful in helping to get to sleep, kratom is well known from decades of study in SEA, and surveys in the U.S. to be more commonly

used for alerting and focusing effects and sustaining occupational performance much as coffee and tea are used.

**See also NIDA’s statement on kratom overdose risk on its Kratom Facts page
NIDA’s 2017 version**

“Kratom by itself is not associated with fatal overdose, but commercial forms of the drug are sometimes laced with other compounds that have caused deaths.”

NIDA’s updated July 2018 version was revised following its International Kratom Symposium and possibly other data

“Kratom by itself is not associated with fatal overdose, but some forms of the drug packaged as dietary supplements or dietary ingredients can be laced with other compounds that have caused deaths.”

NIDA’s more nuanced September, 2018 version that apparently reflected reconciliation with FDA

“Can a person overdose on kratom?”

In 2017, the Food and Drug Administration (FDA) began issuing a series of warnings about kratom and now identifies at least 44 deaths related to its use, with at least one case being investigated as possible use of pure kratom. Most kratom associated deaths appear to have resulted from adulterated products (other drugs mixed in with the kratom) or taking kratom along with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there have been some reports of kratom packaged as dietary supplements or dietary ingredients that were laced with other compounds that caused deaths.”

NIDA’s most recent update would appear to be a reasonable and appropriately cautious statement relevant to kratom safety and overdose risk putting kratom starkly in contrast with opioids that kill 134 or more people per day, and appear on course to account for 50,000 or more fatalities in 2018 based on current trends (Jalal et al., 2018)

Factor 2

Page 5 Central Nervous System Effects: “Mitragynine and 7-OH-mitragynine have been shown in binding studies to have high affinity for human mu opioid receptors ($K_i = 233$ nM and 47 nM, respectively) (Kruegel et al., 2016). Functional studies with these compounds showed that they are acting as partial agonists in human tissue, with maximal effects in G-protein activation of 34 percent for mitragynine and 47 percent for 7-OH-mitragynine (Kruegel et al., 2016). Mu opioid partial agonists are able to produce significant mu opioid agonist activity, as long as the dose is not increased beyond a certain level. At high doses, a mu opioid partial agonist may act as an antagonist.”

Comment: This paragraph misrepresents the pharmacology of partial agonists as well as kratom in its statement that “Mu opioid partial agonists are able to produce significant mu opioid agonist activity, as long as the dose is not increased beyond a certain level.” In fact, as explained on NIDA’s website and is well known in pharmacology, a partial agonist has “less strong” or lower maximal effects, often referred to as a “ceiling” effect that is not overcome by increasing the dose.

The paragraph does mention the percent G-protein activation of MG and 7OHMG but fails to mention the favorable potential safety and abuse potential related implications (see Varadi et al, 2017; Kruegel et al., 2017). Specifically, available evidence supports the conclusion that that G-protein bias may reduce the risk of harmful adverse effects (Schmid et al. 2017), and that the partial agonist profile may limit adverse effects of use because as dose escalates, analgesic and possible respiratory depressing effects plateau (e.g., Vardi et al., 2017; Kruegel et al., 2017). Regardless of the specific mechanisms of the partial agonist effects, which FDA seems to concur with, this is also consistent with the fact that acute respiratory depression overdose death has not been reported in SEA or documented in the U.S.

Page 9: Discussion of CPP (conditioned place preference) study.

Comment: FDA did not mention the fact that there was no dose-dependency that would support the interpretation of positive conditioned effects, nor that the dose suggestive of a CPP effect occurred at dose equivalents 100 times or greater than people take in the community. Also, since the dose at which a potential CPP effect occurred was also producing increased locomotor activity, it cannot be ruled out that it was simply a nonspecific effect.

Most importantly, FDA does not mention that two intravenous rodent self-administration studies found that over a broad range of doses, MG did not serve as a reinforcer like morphine (Hemby et al. 2018) or heroin (Yue et al., 2018). Intravenous self-administration studies are the gold standard animal tests for assessing whether a drug is characterized as one with reinforcing properties. The Hemby study was available online at least by October 2017 and was presented at the Society for Neuroscience meeting in Washington DC the first week of November, 2017. Yue et al. was not mentioned at a scientific meeting until the June, 2018 College on Problems of Drug Dependence Meeting, but this study was conducted in the NIDA’s own Intramural Research Program laboratory and likely would have been shared with FDA had FDA inquired of NIDA. That absence suggests FDA did not involve NIDA.

Two other findings by Hemby et al. and Yue et al. are also relevant. The first is that both found that MG pretreatment reduced self-administration of the reinforcing opioid: namely morphine in the Hemby et al. study, and heroin in the Yue et al. study. Whereas this does not confirm that such an efficacious effect would occur in humans, it is consistent with reports by former opioid users that (a) kratom does not provide the euphoriant effects of opioids, but (b) does relieve cravings and help them abstain from opioids. Yue et al. concluded as follows: “The present study suggests that mitragynine has limited abuse liability from the perspective of self-administration procedures.... it appears at present that mitragynine is deserving of more

extensive exploration for the development of a therapeutic use for treating opioid abuse.” (Yue et al., 2018, page 2828). We concur with that conclusion but not that development of mitragynine or an analog may be a \$2-3 billion path taking a decade or more.

The second finding of relevance was that at intravenous dose equivalents of 100 times or greater than those likely obtained by kratom users, 7OHMG did serve as a positive reinforcer for the rats in the Hemby et al. study. Because these doses were extraordinarily high as compared to those obtainable from naturally-derived products, they suggest that a maximum allowable 7OHMG concentration might be set by FDA to not exceed the absolute or proportional content of the alkaloids present in the natural plant

Failure to understand or report dose throughout. FDA’s failure to report MG and 7OHMG doses or relate them to meaningful human equivalents is a failure to recognize the principle that “The dose makes the poison” – or an accepted drug or dietary ingredient – recognized by its drug and food regulations and regulatory experts.

In fact, as was observed nearly 500 years ago and accepted globally today was the statement by the Swiss chemist and medical doctor, Paracelsus, who stated “All things are poison and nothing is without poison; only the dose makes a thing not a poison.” In fact, for example, doses that might cause discriminative effects similar to opioids in animals are 100 times or more the equivalent of doses that are consumed by humans. For FDA to generalize, as it does throughout its 8-FA from few scientific and anecdotal observations of theoretical, impractical, and extraordinarily high doses is misleading at best but misrepresentative in any case.

Page 9: “Activation of 5-HT₂ receptors by 5-methoxy-dimethyltryptamine (a Schedule I hallucinogen) produces head twitches in mice. This behavior is known to be blocked by 5-HT₂ antagonists and by alpha-2 adrenergic antagonists. When mice were pre-treated with mitragynine, there was a dose-dependent reduction in 5-MeO-DMT-induced head twitches (Matsumoto et al., 1997). This suggests that mitragynine has antagonistic activity at 5-HT₂ or alpha-2 adrenergic receptors.”

Comment: Again, these studies failed to relate dosing to human exposure. Furthermore, the implication that kratom might have hallucinogenic effects is at odds with human experience including self-experimentation by experienced polydrug users who do not describe kratom’s effects as hallucinogenic; therefore, the relevance of the studies with mice to human use and effects is not clear.

Page 9: “Cross tolerance was also observed with 7-OH-mitragynine and morphine (Matsumoto et al., 2005). Thus, once tolerance developed to one drug (such that a larger dose was necessary to produce analgesia), then a larger dose of the other drug was also needed in that animal to produce analgesia. This phenomenon occurs when drugs have overlapping mechanisms of action. Thus, these results suggest that 7-OH-mitragynine has mu opioid agonist effects similar to that of morphine.”

Comment: From the 2017 Food and Drug Administration (FDA) Guidance for Industry: Assessment of Abuse Potential of Drugs: “The presence of physical dependence or tolerance does not determine whether a drug has abuse potential. Many medications that are not associated with abuse, such as antidepressants, betablockers, and centrally acting antihypertensive drugs, can produce physical dependence and/or tolerance after chronic use. However, if a drug has rewarding properties, the ability of that drug to induce physical dependence or tolerance may influence its overall abuse potential.” Mitragynine has not been demonstrated to have “reinforcing properties” as the term is used in the guidance, and 7OHMG only at doses for rats of 100 times or more equivalent to what humans consume (Hemby et al., 2018; Yue et al. 2018), and so the finding that tolerance and/or physical dependence may occur is not of clear relevance and certainly is not indicative that “that 7-OH-mitragynine has mu opioid agonist effects similar to that of morphine.”

Page 9: FDA states: “Cross-tolerance was observed with 7-OH-mitragynine and morphine... Thus, these results suggest that 7-OH-mitragynine has mu opioid agonist effects similar to that of morphine”

Comment: This is a rather remarkably speculative leap that flies in the face of the differences in the pharmacologic effects of 7OHMG and morphine. It has long been known, as stated elegantly by addiction research pioneer Herbert Kalant that “drugs sharing a common effect, even by different mechanisms, might show cross-tolerance for that effect” (Le et al. 1980 <https://www.ncbi.nlm.nih.gov/pubmed/7424739>; see also Kalant, 1988 <https://www.ncbi.nlm.nih.gov/pubmed/7424739>).

We frankly do not understand this and other leaps from bits of data to the repetitive conclusion that 7OHMG and MG have “mu opioid agonist effects similar to that of morphine” other than to fit a preordained conclusion.

Page 13 Currently Accepted Medical Use

Comment: The only relevance of this discussion by FDA is that IF kratom was to be placed in the CSA, Schedule I is the only place allowed by law because it is not recognized by FDA as safe and effective for therapeutic purposes, i.e., an approved drug – a fact that we do not dispute. This extensive section could be shortened to a few sentences along the following lines: Neither kratom products, nor MG or 7OHMG have been evaluated in multi-center clinical trials and/or been submitted for approval to FDA for therapeutic use. That is, they do not meet the accepted standards for therapeutic use, nor have kratom experts including these authors, or contemporary scientific and medical articles made such claims.

In fact, this is the case with most dietary ingredients and part of the basis for the Dietary Supplement Health and Education Act of 1994, established to define and regulate dietary supplements including herbs and other botanicals, and support their access to consumers on the assumption that most would never undergo the multi-billion-dollar decade long path to approval as drugs. On the other hand, to ignore reasons for occasional or daily use by millions

of people in the U.S. and SEA that has been well documented is to ignore reality, decades of traditional use, and pharmacological activity. Furthermore, as recently recognized by FDA Commissioner Gottlieb (see page 16 of this letter), with respect to electronic nicotine delivery systems, which do carry risks and raise public health problems that FDA is addressing, they must be kept available but regulated so to minimize risks and increase their potential as assets in combatting the tobacco epidemic.

Factor 5. The drug's scope, duration, and significance of abuse

Comment: The authoritative databases that are usually relied upon for such information and conclusions (e.g. The Drug Abuse Warning Network (DAWN), the Treatment Episode Data Set (TEDS), the National Survey on Drug Use and Health (NSDUH), Monitoring the Future (MTF), etc.) were not included in this analysis, probably because they do not support FDA's conclusion. All of these can potentially detect emerging trends with new substances and forms of substances. In the case of DAWN, data were collected only through 2011 but that period included the first decade that kratom use appeared to have been rapidly increasing in the U.S.

Notably, in its October 2, 2018 National Drug Threat Assessment (NDTA), kratom and its constituent alkaloids did not even warrant a mention

([https://www.dea.gov/sites/default/files/2018-11/DIR-032-](https://www.dea.gov/sites/default/files/2018-11/DIR-032-18%202018%20NDTA%20%5Bfinal%5D%20low%20resolution11-20.pdf)

[18%202018%20NDTA%20%5Bfinal%5D%20low%20resolution11-20.pdf](https://www.dea.gov/sites/default/files/2018-11/DIR-032-18%202018%20NDTA%20%5Bfinal%5D%20low%20resolution11-20.pdf)). Similarly, "The DEA's most recent, 2017 National Forensic Laboratory Information System (NFLIS) reports of laboratory identifications of substances collected in law enforcement operations and cases nationwide included no mention of kratom/mitragynines.

(<https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS-Drug-AR2017.pdf>). That does not mean there were zero reports but the highest signal from earlier reports was only 0.01% of all reports, i.e., a very small signal that was far lower than the lowest of the top 25 substances reported."

With respect to the poison control center data that FDA cites with concern due to the "ten-fold increase", it should be noted that this was an increase from 26 in 2010 to 263 in 2015, which remains miniscule in absolute numbers as compared to many other dietary supplements, over-the-counter medicines and household cleaning products.

The DEA's most recent 2017 National Forensic Laboratory Information System (NFLIS) reports of laboratory identifications of substances collected in law enforcement operations and cases nationwide included no mention of kratom/mitragynines

(<https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS-Drug-AR2017.pdf>). That does not mean there were zero reports but the highest signal from earlier reports was only 0.01% of all reports, i.e., a very small signal that was far lower than the lowest of the top 25 substances reported.

The Grundmann survey of 2017 and other surveys summarized in Henningfield et al (2018a,b) provide a more accurate characterization of the general safety of kratom. FDA would also do well to consider new dietary ingredient notifications that have been submitted to its own Office

of Dietary Supplements because from what is publicly known about several of these, they make credible cases that kratom safety is well within the range of what is considered acceptably safe by FDA for acceptance of the notifications. Note as mentioned before, the fact that none have been accepted is considered by sponsors who have submitted applications, and have publicly discussed some of their safety data and interactions with FDA Dietary Supplement staff as potentially meeting FDA's standards, but recognizing that acceptance is not an option while the FDA Commissioner's Office is taking the position that kratom is a narcotic-like opioid.

Page 11: "The content of mitragynine found naturally in *M. speciosa* is variable. The total alkaloid content in *M. speciosa* leaves usually ranges from 0.5 to 1.5 percent (Hassan et al., 2013). Plants from Thailand were found to have a mitragynine content of 66 percent of the total alkaloid contents (or approximately 3-9 mg/g in leaves), while leaves from trees in Malaysia were found to have a mitragynine content of 12 percent of the total alkaloid contents (Takayama et al., 1998; Chittrakam et al., 2008; Ponglux et al., 1994; Hassan et al., 2013; Harun et al., 2015). In contrast, the 7-OH-mitragynine content comprises up to 1.6 percent of the total alkaloid content of the plant (or approximately 0.1-0.3 mg/g in *M. speciosa* leaves) (Kruegel et al., 2016; Warner et al., 2016; Ponglux et al., 1994)."

Comment: Overall, the discussion of FDA concerning the variability in alkaloid levels appears consistent with our interpretation of the literature, though it would be helpful to have pages 10 and 12 which were not provided by FDA. Moreover, the levels cited in these studies indicate that naturally occurring levels of 7-OH-mitragynine are so low as to be unlikely to account for any substantial effects of kratom in humans based on the animal studies FDA has cited and based on low rates of serious morphine-like adverse events in humans. Thus, 7OHMG should not be considered relevant in FDA's analysis except possibly for a kratom product performance standard that would be reasonable to set the maximum allowable level of 7OHMG as no higher than the 1.5 -2% of the highest naturally occurring levels in leaves because intake of leaf-based kratom products has never been demonstrated to be lethal in humans.

Page 13: "Tmax for mitragynine was determined to be 0.83±0.35 hours, with a half-life ($t_{1/2}$) of 23±16 hours. The authors caution that these data may not be representative of individuals who do not have chronic experience with *M. speciosa*".

Comment: All seem to agree that further study should be performed on the pharmacokinetics of mitragynine and possibly other kratom alkaloids; however, this half-life estimate does not necessarily reflect on the safety or abuse potential of kratom.

Page 19: "Kratom is a botanical that qualifies as a dietary ingredient under section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)). When marketed as a dietary ingredient, FDA also considers kratom to be a new dietary ingredient under section 413(d) of the Act (21 U.S.C. 350b(d)) because, to the best of the Agency's knowledge, there is no information demonstrating that this substance was marketed as a dietary ingredient in the United States before October 15, 1994. Furthermore, based on FDA's review of the publicly available

information regarding kratom, there does not appear to be a history of use or other evidence of safety establishing that kratom will reasonably be expected to be safe as a dietary ingredient. In the absence of a history of use or other evidence of safety establishing that kratom will reasonably be expected to be safe as a dietary ingredient, kratom and kratom-containing dietary supplements and bulk dietary ingredients are adulterated under section 402(f)(1)(B) of the FD&C Act (21 U.S.C. 342(f)(1)(B)) because they contain a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury.”

Comment: There are currently several New Dietary Ingredient applications for kratom and kratom-containing products under consideration by FDA. There is also extensive anecdotal evidence that kratom marketing and use certainly predated the October 15, 1994 DSHEA grandfather date. Kratom and its traditional use was brought to the US at least by the 1970s and 1980s by waves of immigration from SEA where the plant grows naturally, and is part of daily life for millions of people based on its wide prevalence of use throughout SEA and Malaysia as discussed in NIDA’s International Kratom Science Symposium in June, 2018. Additionally, the applications provide evidence for safe marketing and use of kratom products, depending on formulation, upon approval.

Page 21: “Epileptic Seizures Associated with Mitragynine and *M. speciosa*”

Comment: The following case studies include a wide range of disorders and individuals. This evidence should be evaluated as a starting point for research, not conclusions or warnings – any more than the fact that these individuals might have been daily consumers of eggs, caffeine, or NSAIDs.

The first two cases were instances of combination use while the third was with kratom alone. It is not possible to draw any conclusions from a single case of seizure after exposure to kratom, given the millions of people who regularly use the product and do not have seizures.

Page 21: “A 58-year old man with schizoaffective disorder experienced jaundice and liver injury on two separate occasions (separated by a year apart) following regular use of powdered *M. speciosa* for anti-anxiety purposes (Dorman et al., 2015). In both instances, the man continued taking his psychotropic medication, which was identified as quetiapine (100 mg daily) in the first instance and sertraline (50 mg daily) in the second instance. Liver bilirubin, ammonia, and enzyme levels were all determined to be abnormal and medication was discontinued temporarily. Upon discontinuation of *M. speciosa* in both instances, liver tests were returning to normal after several days. Evaluation of body fluids for mitragynine and 7-OH-mitragynine was not conducted.

Comment: This patient was consuming other drugs as well, and stopping ALL drugs resulted in a return to normal liver function. It is unclear whether it was kratom or other drugs, or some combination, causing the liver issues. Both quetiapine and sertraline have been documented to be associated with hepatotoxicity in the scientific literature.

Page 23: “Of the 24 fatal cases associated with mitragynine, 7 were published as case reports in the medical literature. These 5 published reports demonstrate the variety of multiple drugs taken in conjunction with mitragynine, which include:” [Note the authors of this letter do not know if the FDA meant “7” or “5” in these two sentences which are shown as they appear in FDA’s 8-FA.]

Comment: The intended significance of multiple drug consumption in FDA’s analysis is unclear. It is difficult to identify the cause of death in cases where multiple drugs are involved, and consumption of kratom is not unique to multi-drug toxicity deaths. Deaths involving many medications that don’t include kratom are commonly reported to poison control centers every year. It is not possible to analyze the “24 fatal cases” FDA refers to as it has publicly announced various numbers of cases attributed to kratom since October, 2017. Many, if not most, cases FDA has identified publicly have been discredited as having a cause of death unrelated to kratom consumption, such as deaths by suicide, homicide, trauma, and where consumption of kratom was merely incidental to co-consumption of an undeniably lethal amount of another substance such as U-47700 (Babin, 2018).

FDA’s analysis does not meet its own standards for ascertaining cause of death as applied to other substances (Babin, 2018). Specifically, it has relied on unsubstantiated and incomplete reports, along with opinions of family members who may not have access to or a full understanding of the decedent’s medical history or the circumstances surrounding the death, and suffer from undeniable bias. In depending on unverified third-party sources of information, FDA has apparently made no attempt to independently investigate or verify even the most basic information related to any individual death. Often investigative reports and medical history, if considered, would shed further light on cause of death not apparent from simple toxicology, such as the suicide by hanging of a troubled teen concurrently using kratom, Zolpidem, Quetiapine and alcohol (FAERS ID 12639556).

Moreover, in the cases of multi-drug consumption described, FDA has represented to DEA positions on cause of death which conflict with those in possession of greater knowledge of the relevant facts and circumstances. In the case reported by McIntyre et al., the authors of the case report made inferences that exceeded those in official documents. While the Medical Examiner concluded that “Based on the autopsy findings and the circumstances surrounding the death, as currently understood, the cause of death is best listed as ‘mitragynine, diphenhydramine, mirtazapine, ethanol, and venlafaxine toxicity.’” (Autopsy Report 14-01250, County of San Diego, Office of Medical Examiner), McIntyre et al. added that the cause of death was “predominantly mitragynine.” This appears to be related to the common assumption by some Medical Examiners that medications detected at therapeutic levels can be dismissed as causing or contributing to a death, as in this case the contributions of diphenhydramine, mirtazapine, and venlafaxine were relegated to a role inferior to MG. The FDA fails to report that between 2008 and 2016, venlafaxine was implicated in 283 multi-drug-related deaths including 107 cases where it was first-ranked as the cause of death, and in an additional 23 cases where it was the only drug detected (2008-2016 Annual Reports of the American

Association of Poison Control Centers' National Poison Data published in Clinical Toxicology). Regarding the propylhexedrine death reported by Holler et al., FDA implies that the only reason MG was not considered the cause of death was because "there were, at the time, no published toxic levels of mitragynine." FDA fails to mention that the level of propylhexedrine alone in the decedent's blood was sufficient to cause death. (Holler et al.: "The propylhexedrine blood and tissue concentrations were in range of previously reported deaths **caused** by propylhexedrine. The autopsy findings of bilateral pulmonary edema are also consistent with other reports for propylhexedrine toxicity deaths." [emphasis added, citations omitted]). Neither did the FDA mention the possible contribution of the "[t]hirty-nine separate nutritional supplements, herbal supplements, and prescription and nonprescription medications" found at the scene.

Similarly, FDA vastly overstates the contribution of MG in the death of a husband and wife from loperamide abuse in the case reported by Bishop-Freeman et al. Investigators found evidence on the decedents' computer that the couple had researched methods to get high by potentiating loperamide opioid-like CNS activity with "cocktails" including quinine/quinidine (also detected in decedents' blood) and other substances of which mitragynine was but one. One of these two decedents had the highest blood concentration of loperamide detected amongst the 21 cases of loperamide toxicity studied by the authors, leading to the unequivocal conclusion that loperamide was the primary cause of death.

An unfortunate and erroneous consequence of reporting blood MG concentrations in cases where an individual died after consuming kratom, without a definitive link to causation, is that reference laboratories testing for kratom alkaloids now report a range of MG concentrations from post mortem toxicology testing (e.g., 20-600 ng/mL listed by NMS labs) without adequately informing medical examiners of the significance of these observations. This has led to determinations that MG was the cause of death even when the level of MG detected was at the low end of the reported range—a range that coincides with clearly non-toxic MG levels determined by Trakulsrichai et al. resulting from human consumption of a mere 1-2 g of kratom. Moreover, it is unclear whether recent high reported levels of MG in excess of 1,000 ng/mL or more could have resulted from consumption of kratom powder alone as this would appear to exceed the quantity of kratom powder that an individual could consume without vomiting. As discussed herein, this distinction suggests the need to independently regulate the amount of MG in whole leaf kratom, extracts and purified kratom alkaloid preparations rather than ban kratom altogether.

It must be emphasized that even if FDA had established a firm link between kratom and any one or more deaths, the paucity of "kratom-associated" death reports must be considered when FDA attempts to compare kratom to more deadly opioids such as heroin. It is reasonable to conclude that if MG and 7OHMG were comparable in toxicity to heroin or fentanyl, the annual number of deaths would be orders of magnitude greater. Instead, FDA strains to find two dozen deaths that are unequivocally attributable to kratom consumption over the past decade.

General comment pertaining to factors 4, 5, and 6 which address public health risks, scope and impact

Because the even numbered pages of its 8-FA have not been provided by FDA, we cannot be certain that FDA did not address critical information that is not evident in what was disclosed. However, there is no evidence that FDA considered major public health surveys ordinarily relied upon by FDA and DEA for estimating the nature and magnitude of problems associated with substance use (e.g., DAWN for information through 2011, Monitoring the Future, National Survey on Drug Use and Health, and the Treatment Episodes Data Monitoring Set) nor the published and presented surveys and comments to DEA and FDA discussed elsewhere and in this letter that address the public health risks and benefits of kratom use.

With respect to kratom for which there is strong evidence that many former opioid users are successfully sustaining abstinence through their kratom consumption, the stakes are too high for FDA to do anything less than to transparently and with stakeholder involvement, examine all available evidence concerning patterns of kratom use, and effects, desired and undesired. Such information would help better understand the potential magnitude of the foreseeable risk of exacerbating the opioid crisis and contributing to overdose deaths of former kratom users by a kratom ban.

Such an evaluation should include information from outside the US as was done in the June 2018 NIDA International Kratom Science Symposium. Such an evaluation should also document the history of kratom use in the U.S. that likely began at least with the 1970s and 1980s waves of immigration from SEA but with little evidence in major surveys because of the absence of associated problems. This would also be useful to FDA's Office of Dietary Supplements to determine how Pre-DSHEA Dietary Ingredients (i.e., "old dietary ingredients") could be identified given that many (like kratom which was discussed in its October 3, 2017 meeting) were less formally marketed and documented than major brand products in mainstream retail stores.

FDA would likely be most comprehensively informed by a transparent approach with public hearings and involvement of kratom consumers and organizations, kratom vendors, and kratom experts. There is ample precedent for such an approach by FDA. This includes FDA's Center for Drug Evaluation and Research efforts to evaluate regulatory approaches to better understand opioid use and foster abuse deterrent opioids, and the Center for Tobacco Products efforts to evaluate the place of e-cigarettes in public health.

Page 25: "Anecdotal Case Reports of Physical Dependence of Mitragynine and 7-OH-Mitragynine"

Comment: Physical dependence and withdrawal are not only plausible but reasonably well documented. However, as recognized by people who use kratom and use it in place of opioids in the U.S. and SEA, kratom withdrawal is readily self-manageable for most people.

Furthermore, as recognized by FDA in its 2017 Guidance for Industry: Assessment of Abuse Potential of Drugs: “The presence of physical dependence or tolerance does not determine whether a drug has abuse potential. Many medications that are not associated with abuse, such as antidepressants, beta-blockers, and centrally acting antihypertensive drugs, can produce physical dependence and/or tolerance after chronic use. However, if a drug has rewarding properties, the ability of that drug to induce physical dependence or tolerance may influence its overall abuse potential.” Furthermore, physical dependence occurs with a number of consumer health, food, and beverage products such as caffeine and does not necessarily indicate harm or addiction risk.

Comments on other issues relevant to this analysis

Estimates of the numbers of kratom consumers including how many use it in place of opioids and how many are at risk of seeking black market kratom and/or relapse to opioid use if lawful kratom was banned

The evidence is strong and supported by surveys of more than 20,000 kratom consumers, more than 23,000 comments to DEA and FDA, and other surveys and information source that suggest that there are more than 5 million kratom consumers (American Kratom Association, 2018; Henningfield et al., 2018; Swogger and Walsh, 2017; Grundman, 2017). This same evidence indicates that many kratom users would seek black market kratom and/or relapse to opioid use if lawful kratom was banned. Placing kratom in Schedule I and banning kratom in light of this evidence poses an imminent serious public health risk and would be an unconscionable act by federal agencies that is amplified by an opioid crisis that is accounting for more than 49,000 deaths per year and showing no evidence of near term abatement (Jalal et al. 2018; NIDA, 2018 at <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>).

But there is some critical information that is not known to either federal agencies, experts, or kratom vendors that is readily knowable and which FDA and other federal agencies should collect before any ban of kratom is considered. That is information that could be collected by major nationally representative federal surveys to go beyond the surveys that have been conducted to date with the power of federal surveys to provide nationally projectable estimates of at least the following information:

- How many people use kratom including how many are using in place of opioids?
- What kinds of products are most commonly used for those using kratom in place of opioids?
- What are the numbers of people using kratom in place of opioids for different reasons including, they preferred kratom for pain, they preferred kratom to FDA approved medications for treating opioid use disorders (OUD), they use kratom for their OUDs because medication assisted therapy (MAT) is not effective or accessible or affordable to them?

- What percentage of people using kratom for various reasons report that they would consider, and are fearful, of black market kratom or relapse to opioids if kratom was banned?

The foregoing is a starting point but such a survey could be quickly designed and conducted by agencies such as NIDA and SAMHSA with input from kratom experts, vendors, and kratom consumer serving organizations such as the American Kratom Association. Such information would help FDA and DEA better understand the magnitude of the consequences of a ban and how to prepare for a ban if a ban was ever implemented.

Comment on Scheduling MG and/or 7OHMG vs performance standards and other regulatory approaches such as FDA uses for caffeinated and nicotine-containing products, and industrial hemp

FDA has many precedents to draw from for addressing concerns about a wide range of substances, to enable consumers to make informed choices to buy and use products for health and well-being and for other uses.

Banning MG and/or 7OHMG carries foreseeable serious and life-threatening risks because banning either or both would be tantamount to a ban on natural kratom leaf-based products which constitute the vast majority of the consumer market and which are by far the dominant category of kratom product used by people in place of opioids. In contrast, manufactured extract products (often sold in small single dose containers similar to “5 Hour Energy” bottles), although being preferred by many people for occasional use and use in place of coffee are not typically used to replace opioids in people who were frequent opioid users. Banning them would be the equivalent of a ban on caffeine in manufactured beverages that are marketed and used for wakefulness, energy, mood modulation, and a variety of other reasons that consumers report.

Regulations that banned natural kratom leaf products containing MG and/or 7OHMG would be analogous to allowing only decaffeinated coffee beans, ground coffee and coffee, and would remove what appear to be the most widely used category of kratom products, i.e., natural leaf in powdered and sometime encapsulated form. The most serious public health consequences of a ban of either MG or 7OHMG would be to put current users at risk of turning to the black market that would quickly emerge to replace the lawful market, and in the case of former opioid users, a return to opioids.

Caffeine and nicotine meet all pharmacological criteria as substances that could be placed in the CSA. They are used for pleasure, mood modulation, and a wide array of reported benefits that are not recognized by FDA as meeting standards for safe and effective therapeutic agents. They can produce tolerance, physical dependence, reinforcing effects, withdrawal and toxicity in animals and humans. Both are often used with other substances and in forms that are concerning to FDA and to other medical and public health authorities.

With respect to caffeine, FDA and other authorities have concluded that high acute caffeine doses and high daily caffeine intake pose serious health risks including addiction and death. Thus, educational efforts from FDA and other agencies inform consumers about maximum recommended levels in general and in special circumstances such as during pregnancy, and FDA thus bans the sale of overly concentrated dietary supplements and beverages and bulk caffeine powder and provides advice on daily caffeine intake (see <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm604485.htm> and <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm350570.htm>).

Although a single serving of coffee as sold in many coffee shops and as brewed by consumers greatly exceeds FDA's allowable limits for manufactured products, the amount of ground or powdered or whole coffee beans that may be sold or purchased by consumers and their caffeine content is not regulated by FDA. By setting standards for maximum levels of alkaloids in manufactured products, extracts, dietary supplements, and other products, FDA gives consumers the right to make informed choices and address their needs and desires with regulated products.

FDA has demonstrated considerable and constantly evolving regulatory flexibility with respect to nicotine products. Nicotine is a substance long recognized as a potentially deadly poison in which a package of conventional cigarettes contains 4 or more potentially lethal doses of nicotine and some nicotine patches, several potentially lethal doses of nicotine. Nicotine can produce psychoactive and rewarding effects in humans and animals with approximately 10 times greater potency than cocaine (Surgeon General's Report, 1988, 2014); and was determined by FDA to meet criteria for placement in the CSA as a schedule III drug for nicotine-containing drug products, e.g. nasal nicotine spray, gum and patch, though nicotine-containing tobacco products are exempt from scheduling by a provision in the CSA (FDA, 1995, 1996). When the scheduling of nicotine in the form of gum, then patch, then nasal spray was considered by FDA in 1984, 1990, and 1995, respectively, FDA held public advisory committee hearings and agreed with experts that it made no sense to schedule nicotine despite its ability to cause addiction and potency as a poison when it could serve as a path away from the far deadlier and more addictive tobacco products (FDA, 1995, 1996; Henningfield et al. 2016). In fact, despite nicotine's dependence potential and potential toxicity, gum and patch were allowed for over-the-counter marketing in 1996, and later nicotine lozenges.

Recently, FDA Commissioner Gottlieb and FDA's Center for Tobacco Products Director Zeller have made clear that to address the tobacco epidemic, alternatives to medicines that are not recognized for therapeutic use or as safe and effective for any use, such as the rapidly proliferating electronic cigarettes, have an important role in addressing the tobacco epidemic (Gottlieb and Zeller, 2017, page 1111), and thereby contribute to the migration away from the deadlier and more addictive combusted products as also discussed by the Surgeon General (2014). The devices are not considered safe but are less harmful than cigarettes and there are problems that consumers, vendors, and experts agree need to be addressed by balanced regulation while keeping them available, e.g., variable contents, quality, harmful additives in

some products, youth-attracting flavors and marketing, and increasing use by young people (Gottlieb, 2018; Abrams et al., 2018).

However, FDA has been steadfast in declining to ban or highly restrict nicotine products as called for by some, recognizing their value in achieving broader health goals, and have instead opted to regulate the products through marketing and performance standards without prohibiting access to adults (Gottlieb 2018). Specifically, Gottlieb and Zeller (2017, p. 1111) stated as follows: “The agency’s new tobacco strategy has two primary parts: reducing the addictiveness of combustible cigarettes **while recognizing and clarifying the role that potentially less harmful tobacco products could play in improving public health**” and recognizing that “**potentially less harmful tobacco products could reduce risk while delivering satisfying levels of nicotine for adults who still need or want it.**”(bold emphasis added).

Industrial hemp provides yet another example of maximum levels standard setting to support the use of hemp-based products that actually may contain THC that could theoretically be extracted for use for psychoactive effects but which pose low risks. Thus, the U.S. Department of Agriculture, in collaboration with the DEA and FDA came to agreement on standards that allow the cultivation and a variety of uses and marketing the category of marijuana defined as Industrial hemp which is defined in statute as "the plant *Cannabis sativa* L. and any part of such plant, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis."

Hemp posed a more complex challenge because it is a lower THC-containing form of a Schedule I drug-marijuana or cannabis. Industrial hemp is cannabis that contains less than 0.3% tetrahydrocannabinol (“THC”) based on dry weight (see <https://nifa.usda.gov/industrial-hemp>). The term “industrial hemp” includes the plant *Cannabis sativa* L. and any part or derivative of such plant, including seeds of such plant, whether growing or not, that is used exclusively for industrial purposes (fiber and seed) with a tetrahydrocannabinols concentration that contains less than 0.3 percent THC. The term “tetrahydrocannabinols” includes all isomers, acids, salts, and salts of isomers of tetrahydrocannabinols. The U.S. Department of Agriculture in consultation with the DEA and FDA developed a Statement of Principles on Industrial Hemp and published it in the Federal Register (August 12, 2016; 81 FR 53395; link at <https://www.gpo.gov/fdsys/pkg/FR-2016-08-12/pdf/2016-19146.pdf>).

Conclusions and recommendations

Based on our analysis of FDA’s 8 FA, and with reference to the requirements of the Controlled Substances Act, we have major concerns about its conclusions, the actions that could be based upon it, and the implications for public health. We come to the following main conclusions and recommendations:

Main Conclusions:

- 1. FDA's 8-Factor Analysis does not constitute a reliable and valid scheduling decision guiding document.**
- 2. FDA clearly did not involve NIDA or kratom science experts, as revealed by its major deficiencies.**
- 3. The FDA analysis is incomplete, omitting key data sources routinely relied upon for identifying trends in abuse (e.g., the major federal surveys) and key scientific studies, AND is out-of-date as it does not refer to critical studies including those by NIDA (Yue et al., 2018) and Hemby et al., 2018.**
- 4. The evidence is sufficient to conclude that placement of kratom in Schedule I or any other approach that would ban kratom, would lead many kratom consumers to seek black market kratom and some to relapse to opioids and thus pose a serious risk of death.**

Main Recommendations:

- 1. DEA should ask FDA to reexamine the abuse potential of kratom and potential alternative regulatory approaches to kratom with involvement of NIDA and kratom experts, and stakeholders that have additional data and will be affected, namely kratom vendors and kratom consumers. This should be done transparently and include public meetings.**
- 2. Federal agencies should conduct a nationally representative survey to better understand how many people use kratom, use it in place of opioids and would be put at risk of relapse to opioids if kratom was banned, where they live geographically, and other information critical to understanding the nature and magnitude of a ban, as well as regulatory alternatives to a ban.**
- 3. We recommend that FDA propose a regulatory framework that will ensure that safely manufactured kratom products remain continuously available to consumers in natural leaf forms and manufactured extractions that are widely used by consumers, with regulations to ensure quality and appropriate standards for contents, labeling, and marketing. With an advance notice of proposed rulemaking (ANPR), the FDA could solicit comments, and perhaps plan a public hearing to obtain input from key stakeholders including, consumers, vendors, experts, and kratom advocacy organizations. The leading kratom consumer advocacy group in the United States, the American Kratom Association, has issued a Statement of Principles on Regulating Kratom (at: <https://www.amerikankratom.org/abou-aka/statement-of-principles.html>) and a voluntary Good Manufacturing Processes (GMP) Standards Program (at:**

<https://www.amerikankratom.org/index.php/component/sppagebuilder/91-aka-gmp-certification-program>) that may be useful as both have been developed with consideration given to consumers, vendors and with expert input. The implementation of these standards by the FDA, as dietary ingredients/supplements are currently regulated, will offer consumers a safer supply chain for kratom products and help educate consumers on avoiding kratom products that are adulterated or misbranded.

Additional conclusions and recommendations

Regulate, don't ban, kratom: We urge FDA regulation of kratom, not banning of kratom. Regulation has the potential to protect public health, whereas banning kratom poses foreseeable deadly risks, particularly to people using kratom in place of opioids. Relegating kratom to the black-market will not address the problems that FDA, kratom consumers and kratom vendors agree should be addressed, e.g., unsubstantiated and unauthorized health claims, adulterated products, lack of standardized labeling and warnings, and product performance standards (e.g., maximum alkaloid levels). None of this will be addressed by the black market and the many kratom users who will then be hostage to only the black market for their kratom will be put at serious risk. See examples of regulatory principles and voluntary GMP standards that are already being adopted by kratom vendors, as promulgated by the American Kratom Association (see: <https://www.amerikankratom.org/index.php/component/sppagebuilder/41-good-manufacturing-processes>)

Regarding MG and the diversity of natural and manufactured products, what FDA Commissioner Gottlieb stated about the role of electronic cigarettes in combatting the tobacco epidemic would seem to apply equally to the potential role of kratom products in combatting the opioid epidemic (see page 16 of this letter). “The agency’s new tobacco strategy has two primary parts: reducing the addictiveness of combustible cigarettes ***while recognizing and clarifying the role that potentially less harmful tobacco products could play in improving public health.***” And recognizing that ***“potentially less harmful tobacco products could reduce risk while delivering satisfying levels of nicotine for adults who still need or want it.”*** (bold italic font added). (Gottlieb and Zeller, 2017, p. 1111) Appropriately, in our opinion, the Commissioner did not label or imply that electronic cigarettes should be considered safe and effective for therapeutic purposes by FDA standards and did emphasize the importance of other factors in addressing the epidemic including the need for expanded treatment options and access. Such an approach recognizes the public health value of regulating and not banning potential public health assets in the face of an epidemic, which the FDA’s kratom 8-FA did not.

Regulation as a food and dietary ingredient: The FDA has been granted sufficient statutory authority by the Congress to regulate dietary ingredients/supplements including herbs and botanicals to protect public safety in the use of these products, including the specific authority to remove adulterated and contaminated products to protect public safety. Inexplicably, despite

clear evidence of adulteration of kratom products that has caused adverse events and deaths, the FDA has elected to focus on the scheduling of kratom's alkaloids instead of regulation that could address such problems. There is no record of the FDA ever seeking to schedule any substance that is found to be harmful because unscrupulous actors adulterate a substance purely for economic gain except for their current scheduling recommendation for kratom.

The rational regulatory response should be to seize the adulterated products and remove them from the marketplace, and to identify the corporations or individuals responsible for adulteration and refer them for prosecution by the Department of Justice as provided in statute. Congress clearly intended for the scheduling of substances under the CSA to be reserved for those substances that themselves pose a serious public health threat and high level of potential for abuse and dependence, neither of which has been demonstrated for kratom. Kratom is currently not adequately regulated by the FDA as a dietary ingredient/supplement. It is evident that the FDA's condemnation of kratom has stalled constructive regulation by its own Office of Dietary Supplements. We urge that FDA resume and accelerate good faith efforts to work with kratom vendors, experts, and consumers to develop kratom product performance standards, and marketing and labeling guidelines.

Research and drug development: FDA and NIDA could do much to accelerate research and potential development of mitragynine analogs for treatment of pain, opioid and other substance use disorders, and other conditions. This is already occurring but should be accelerated; the opioid epidemic adds urgency. This recognizes that this is a 2-3-billion-dollar, decades long path that will not address the present epidemic or needs of people struggling with pain, opioid use, and other disorders. Schedule I placement would severely hinder such research (See comment on this by the American Society of Pharmacology and Experimental Therapeutics at: <https://www.aspet.org/aspet/advocacy/advocacy/aspet-addresses-proposed-dea-scheduling-action-on-kratom>).

Minimum age of procurement: Despite the absence of evidence of a trending youth problem, FDA might consider additional approaches such as a minimum procurement age as required for over-the counter (OTC) nicotine gum and patches and other products.

Pregnancy and other conditions of potential concern: Also learning from OTC nicotine product regulation, FDA might require warnings that have been used for OTC nicotine products related to pregnancy and lactation, which are intended to discourage use, but not risk prohibiting use for those for whom kratom is used in place of opioids. Schedule I placement would likely not eliminate such use, but it would likely make such kratom-using pregnant and lactating women less likely to admit this to their healthcare providers before or during delivery out of fear of losing custody of their child since this could legally be treated the same as a heroin violation

Product Standards: Develop standards for lawfully marketed products that could include "not to exceed levels" of MG and 7OHMG, and other substances based on the proportional content of the alkaloids present in the natural plant. For example, this might include a maximum

allowable content of 7OHMG of 2% by weight. Actual standards should be developed with input from stakeholders through the rule-making process with contributions from experts and vendors to ensure they are viable and will support public health.

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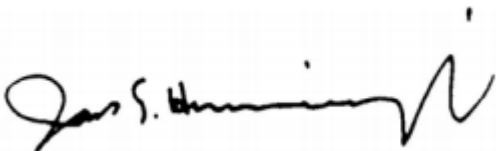
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Sincerely (See disclosures for all beneath signatures),



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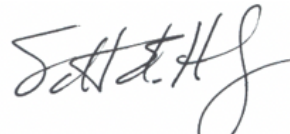
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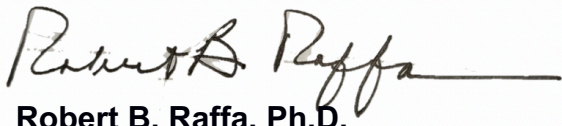
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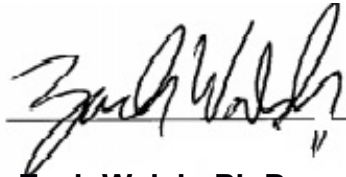


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DISCLOSURES

Jack E. Henningfield provides consulting support through **PinneyAssociates**, on the development of abuse potential assessments and eight factor analyses according to the Controlled Substances Act pertaining to the development and regulation of new medicines and formulations for pain, addiction, epilepsy, and other central nervous system disorders, and also to the dietary industry including the American Kratom Association (see more at www.pinneyassociates.com).

Jane Babin is a California Attorney, registered to practice before the U.S. Patent Office, who represents clients in the biotechnology, pharmaceutical, chemical and other industries in patent, trademark and licensing matters. She has counseled the American Kratom Association on a variety of legal and scientific issues, with and without compensation. The views

expressed in this letter are her own and she has received no compensation for her contributions to this letter.

The views expressed in this document by Dr. Oliver Grundmann do represent his personal and professional views and not the views of his employer, the University of Florida. He did not receive any funding for contributing to this document.

Robert B. Raffa was a previous employee of Johnson & Johnson (analgesics drug discovery) and received preclinical research support and honoraria from several pharmaceutical companies involved in analgesics research and development – but he receives no remuneration based on sales of any product. He is a cofounder of CaRafe Drug Innovation (involved in the discovery of non-opioid analgesics) and is a current advisor/investor, and Chief Scientific Officer with Neumentum (non-opioid analgesics). He currently lectures, writes, and consults for several pharmaceutical companies involved with the discovery and development of analgesics (opioid and non-opioid).

Marc T. Swogger has consulted without compensation for the American Kratom Association.

Scott E. Hemby, PhD, has no conflicts to disclose. Dr. Hemby has received research funding support from NIDA but not for research related to kratom.

Paula N. Brown provides scientific research guidance on dietary supplement manufacture and regulatory compliance to companies, associations and government.