A review of the FDA FAERS data on the referenced death reports the FDA relied upon in issuing the Public Health Advisory on kratom confirmed that all of the disclaimers warning of the deficiencies in the accuracy of the data were applicable in every single one of the claimed kratom associated deaths. There are no credible conclusions that can or should be drawn from these uncorroborated reports unless and until a full investigation using accepted scientific methods to verify the association that is alleged in these deaths.

Yet, Dr. Gottlieb doubled-down on promoting his "Junk Science" on kratom in his February 6, 2018 statement when he increased the number of reported deaths to a total of 44.[xxi]

> Now, I'd like to share more information about the tragic reports we have received of additional deaths involving the use of kratom. Looking at the information we have received – including academic research, poison control data, medical examiner reports, social science research and adverse event reports – we now have 44 reported deaths associated with the use of kratom. This is an increase since our November advisory, which noted 36 deaths associated with these products. We're continuing to review the newly received reports and will release those soon. But it's important to note that these new reports include information consistent with the previous reports.

The only part of Dr. Gottlieb's statement about the new reports that can be verified is his claim that "these new reports include information consistent with the previous reports." However, the common consistency is that the reports are equally unreliable in validating any scientific conclusions about kratom being dangerous.

Dr. Gottlieb attempted to address the deficiencies in the FAERS data by disclosing the lack of specific information in "many of the cases," but his statement opened up a whole new set of questions about why the FDA is selectively investigating some deaths and not others.

> Today, we're releasing the reports of the 36 deaths we referenced in November. These reports underscore the serious and sometimes deadly risks of using kratom and the potential interactions associated with this drug. Overall, many of the cases received could not be fully assessed because of limited information provided; however, one new report of death was of particular concern. This individual had no known historical or toxicologic evidence of opioid use, except for kratom. We're continuing to investigate this report, but the information we have so far reinforces our concerns about the use of kratom.

On one hand, Dr. Gottlieb acknowledges that many of the reports could not be fully assessed because of the limited information provided, but he then cites a new case where, according to the report, one death had "no known historical or toxicological evidence of opioid use, except for kratom." Dr. Gottlieb indicated the FDA was continuing to investigate that report, but it ignores the fact that none of the other death reports was being investigated by the FDA to verify the accuracy of the report.

Indeed, in many cases that had previously been reported in the published scientific literature following evaluation of the available facts and circumstances, including toxicology, autopsy and investigative reports, the FDA simply dismissed the fact-finders' expert analysis and conclusions on cause of death and inserted their own conclusion of kratom causation without so much as a footnote.

The FDA has an army of scientists, investigators, analysts, and lab technicians who are fully capable of conducting a rigorous scientific review of each of the alleged deaths associated with kratom. Such an effort may not be necessary if the FDA simply intended for the public to make their own assessment of risks of using kratom by reviewing the data on the FAERS database, but when the FDA determines to use the FAERS information to formally issue a Public Health Alert, and uses that same deeply-flawed data as the basis for recommending the scheduling kratom as a Schedule I substance under the CSA, removing kratom from the marketplace and essentially criminalizing any future use, the FDA has a clear obligation to base that recommendation on real science, not an amalgamation of duplicative, uncorroborated, and woefully deficient records of those deaths.

While mistakes in data entry into the FAERs database may be attributed to clerical error, and the lengthy disclaimer cautions against drawing conclusions on causation, incidence or frequency of association between a drug or substance reported in conjunction with an adverse effect in FAERS, the Commissioner's personal statements that FDA had received reports of 36 and subsequently 44 deaths associated with kratom, and the implication that such reports were credible, must be held to a higher standard. It should rightfully be expected that allegations from the leader of the agency that includes the most highly regarded expertise on food and drugs in world would have been thoroughly vetted, analyzed and evaluated before they were disseminated through public address and press release. Those expectations have not been fulfilled. Instead, the documents released by FDA and relied upon by the Commissioner, are riddled with inconsistencies and direct contradictions to the position espoused by the Commissioner and summarized in the FAERS database. Instead of documenting relevant relationships between 44 reported deaths and consumption of kratom, the documents reveal a lack of honesty and a complete disregard for objective scientific inquiry. We can but hope that Dr. Gottlieb failed to bring his A team to the meeting on kratom.

THE FDA USE OF THE SWEDISH DEATH REPORTS ON KRYTON TO IMPOSE IMPORT ALERTS IS DECEPTIVE

The FDA has targeted kratom for prohibition and has repeatedly circulated reports that can at best be described as incomplete, in an effort to associate nine deaths that occurred in Sweden over a 12-month period beginning in 2009 as its bedrock evidence of kratom's threat to public safety. The FDA's first Import Alert on kratom in 2012 (#54-15), and subsequent import alerts in 2014 (#54-15) and 2015 (#66-41) [xxii], included the justification that "scientific literature disclosed serious concerns regarding toxicity of

kratom in multiple organ systems." Yet FDA did not disclose the scientific literature it relied on to reach that conclusion.

The Dietary Supplement Health and Education Act of 1994 (DSHEA) places the burden on FDA to demonstrate that a dietary supplement is unsafe before it can remove a product from the marketplace. In a perverse twist, when FDA invoked its authority to impose an Import Alert on kratom, it shifted the burden to the importer to demonstrate safety. FDA can impose an Import Alert and a "Detention Without Physical Examination" order with a much lower evidentiary burden than required for demonstrating that dietary supplements in the market are unsafe. Import Alerts identify companies, which are placed on an FDA "Red List". If a company is placed on the FDA's Red List, it cannot be removed until sufficient evidence is produced by the company to demonstrate that the imported product(s) meets FDA requirements. A simple allusion to scant scientific associations, allegations and suggestions is sufficient to Red List kratom importers, but a much higher level of proof is required by the importer to have their product released.

However, when FDA issues an Import Alert through misrepresentation, deception and willful disregard of relevant evidence that is inconsistent with its established narrative, the exercise of that authority is illegitimate and must be voided.

Despite its statutory obligation to ensure and maximize the quality, objectivity, utility, and integrity of the information it disseminates[xxiii], the FDA has either ignored or deliberately withheld material scientific information that contradicts the conclusion that the nine deaths in Sweden resulted from the use of kratom.

- The FDA relied on autopsy and toxicology information from the nine Swedish deaths in its 2012 Import Alert on kratom and subsequent updates.

- The FDA perpetuated half-truths and mischaracterizations of the Swedish deaths in the report provided to the Drug Enforcement Administration to justify its own desire to schedule the two primary alkaloids of the botanical plant kratom, mitragynine and 7-hydroxymitragynine, as Schedule I substances under the Controlled Substances Act (CSA) in its initial recommendation to the DEA.

- The FDA included Swedish deaths amongst the group of 36 deaths allegedly "associated with the use of kratom" in issuing its Public Health Advisory on kratom on November 14, 2017. Based on statements to media by FDA Commissioner Scott Gottlieb the inaccurate representation of these deaths was included in the FDA's recommendation for DEA to publish a ***new*** Notice of Intent to place kratom and/or its constituent alkaloids into Schedule I substance under the CSA.

The critical science that has been excluded, referenced in passing without proper acknowledgment of its significance, or dismissed entirely as irrelevant was the more detailed analysis of these deaths published in May 2011 in the Journal of Analytical Toxicology.[xxiv] The peer-reviewed Case Report included

important scientific information that should have been disclosed and appropriately considered by the FDA in both its 3-Factor Analysis supporting a recommendation to schedule kratom in 2016, and in the 8-Factor Analysis believed to have been prepared by FDA and submitted to DEA in November 2017 to justify scheduling of kratom.

The Kronstrand Case Report concludes:

> "We believe that the addition of the potent mu-receptor agonist *O*-desmethyltramadol to powdered leaves from Kratom contributed to the unintentional death of the nine cases presented. We conclude that intake of the herbal blend ***Krypton*** is not as harmless as it often is described on internet websites, and the large packages sold increase the risk for unintentional overdose." [xxv] (emphasis added).

Notably, this Case Report detailed the following observations:

1. Each of the nine decedents had toxic or near toxic doses *O*-desmethyltramadol in peripheral blood, suggesting overdose on *O*-desmethyltramadol alone was sufficient to cause death.[xxvi]

2. None of the decedents had unmodified tramadol or *N*-desmethyltramadol in their blood, excluding the possibility that they consumed analgesic medication containing tramadol.[xxvii]

3. Each of the decedents had consumed at least one other psychoactive substance in addition to mitragynine and *O*-desmethyltramadol; as many as six other substances and alcohol were detected in blood from these individuals.[xxviii]

4. Mitragynine was detected, but its contribution to death could not be ascertained due to a lack of reference data on mitragynine blood concentrations at the time.[xxix] Blood concentrations ranged from 0.02 to 0.18 µg/g, with only two exceeding 0.10 µg/g.[xxx]

Significantly, after publication of the Kronstrand Case Note, Trakulsrichai et al. published the first report of blood concentrations of mitragynine in human subjects following consumption of unadulterated kratom tea. [xxxi] In this study, tea prepared from low doses (about 1-3 g/dose) of kratom containing 6.25 to 23 mg mitragynine, resulted in maximal blood concentrations of 0.0185 to 0.105 µg/mL mitragynine in these subjects without serious side effects.[xxxii] Seven of the nine decedents in Kronstrand had blood concentrations within this clearly non-toxic range.

The nine deaths in Sweden that the FDA repeatedly uses as a justification to ban kratom, were actually caused by an adulterated kratom product laced with a toxic dose of *O*-desmethyltramadol. Neither FDA nor DEA has taken any action to schedule *O*-desmethyltramadol.

Kratom consumers advocate for use of pure, unadulterated whole leaf kratom and assistance from the federal government in ensuring that the kratom available for consumption in the U.S. is not contaminated with harmful substances like *O*-desmethyltramadol. The FDA has the authority to provide this needed assistance under the Federal Food Drug and Cosmetic Act (FDCA), which prescribes criminal penalties for the introduction into interstate commerce of adulterated or misbranded foods, drugs, cosmetics, or medical devices; and is an enforcement tool the FDA currently has at its disposal to remove such products from the marketplace.[xxxiii] Instead, FDA has abandoned kratom users and all those who might benefit from kratom, by insisting that kratom itself is deadly, despite mounting evidence to the contrary from its own archives, which it has deliberately hidden from public view.

The FDA, in its self-proclaimed war on kratom, has engaged in a clear pattern of deceit in its public statements to support both its Import Alerts on kratom and its recommendations to the Drug Enforcement Administration (DEA) to schedule the key alkaloids of kratom, mytragynine and 7-hydroxymitragyine, as Schedule I substances under the Controlled Substances Act (CSA). The effect of these misleading and often false public statements by the FDA on kratom has resulted in significant policy decisions that reach into states and local communities across America.

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[iii] *See* Public Database entry for FAERS ID No. 808389 viewed by querying the FAERS Public Dashboard at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm070093.htm.

[iv] *See* Public Database entries for FAERS ID Nos. 8121536, 8121551, 8121559, 8121566, 8124388, 8124494, and 8132531 viewed by querying the FAERS Public Dashboard at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm070093.htm.

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[xvi] Bishop -Freeman et al. "Loperamide-Related Deaths in North Carolina," J Anal Toxicol 40:677-86 (2016).

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[xviii] Wing "FDA Releases Kratom Death Data, Undermines Its Own Claims About Drug's Deadly Harms", Huffington Post, February 7, 2018, viewed at https://www.huffingtonpost.com/entry/kratom-deaths-fda_us_5a7a3549e4b07af4e81eda8b.

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[xxi] https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm595622.htm

[xxii] https://www.accessdata.fda.gov/cms_ia/importalert_1137.html4

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[xxv] *Id. at* 247.

[xxvi] *See id*. at Table II; p. 246, right column, first full paragraph under "Discussion" (suggesting 0.5 µg/g peripheral blood is a toxic if not fatal concentration of *O*-desmethyltramadol).

[xxvii] *See id.* at p. 246, right column, second full paragraph.

[xxviii] *Id.*, Table II.

[xxix] *Id.,* paragraph bridging pp. 246-47.

[xxx] *Id.*, Table II.

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[xxxii] *See id*. at p. 2423 (Preparation of Kratom Tea); p. 2424, right column including Table 2.

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