EXHIBIT C5

Arkansas Department of Health

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The Arkansas Department of Health received your letter and petition on March 7, 2023. The petition requested that the Department remove mitragynine and 7-hydroxymitragynine (Kratom) from the Arkansas List of Controlled Substances.

After review of the material provided as exhibits to your petition, no change in scheduling is warranted at this time. Please also see the following findings after consideration of the eight factors found in Ark. Code Ann. §5-64-201(a)(2) (Supp. 2021):

1. **The actual or relative potential for abuse;**
    a. Studies indicate that Kratom has potential to produce physical dependence and withdrawal.
    b. Information received by ADH Pharmacy Services of significant amounts of substance indicated as Kratom seized at multiple shipping ports; however, containers were labeled as industrial products. This provides evidence of clandestine shipments of Kratom supplied to the United States, trying to circumvent legitimate importation channels. This would identify large scale attempted diversion for Kratom (mitragynine and 7-hydroxymitragynine).
    c. A survey report from New York University, using the 2019 National Survey on Drug Use and Health, indicated in part that *Kratom use was more prevalent among people who use other drugs, including cannabis, stimulants, and cocaine, and was particularly common among those who misuse prescription opioids, with 10.3 percent of people with opioid use disorder reporting kratom use. Men, white people, and those with depression and serious mental illness were also more likely to report using kratom. Teens and adults over 50 were less likely to report use.*[1]

2. **The scientific evidence of its pharmacological effect, if known;**
    a. The pharmacologic effects of morphine and kratom are similar. There is no established therapeutic benefit of kratom.
    b. A statement by Scott Gottlieb, M.D., FDA Commissioner, indicates in part *based on scientific information in the literature and further supported by our computational modeling and the reports on adverse effects in humans, we feel confident in calling compounds found in Kratom opiates.*[2]
    c. A comprehensive review of Kratom reported by Eastlack et al, indicate *both mitragynine and 7-OH-mitragynine target opioid receptors, albeit with significant differences in binding affinity. In fact, while the affinity of murrayanine for opioid receptors is less than that of morphine, 7-OH-mitragynine is far more potent than either, approximately 46 times that of murrayanine and 13 times that of morphine.* In addition, this review further indicates in part *competing evidence suggests a different model; rather than acting as simple agonists, mitragynine and 7-OH-mitragynine appear to demonstrate variable effects depending on the receptor. Specifically, the data show that both mitragynine and 7-OH-mitragynine are mixed opioid receptor agonists/antagonists, behaving as partial agonists at μ-receptors and competitive antagonists at δ-receptors, with negligible effects on κ-receptors.*[3]
    d. The University of Florida College of Pharmacy, Department of Pharmacodynamic also indicates Kratom has a number of reported adverse effects that include but are not limited to *nausea, vomiting, constipation, stomach upset, drowsiness, dizziness, irritability, and agitation.* Other more severe reported adverse effects with more *chronic consistent dosages such as elevated liver enzymes and intrahepatic cholestasis.*[4]
3. **The state of current scientific knowledge regarding the substance;**
    The scientific understanding of the pharmacological effect is rapidly advancing, however, the pharmacological effects of kratom alkaloids and metabolites are still to be defined. Due to limited data consisting of anecdotal evidence; case reports and surveys, more robust human clinical trials are necessary to update current scientific knowledge.

4. The history and current pattern of abuse; and

5. The scope, duration, and significance of abuse;

a. Kratom historically has been used in Southeast Asia as a stimulant for manual labor or as an opium substitute. According to a DEA document, 4x100 which is a mixture of Kratom leaves brewed in one or two ways: *The two "4x100" kratom formulas are described as a mixture of boiled kratom leaves, mosquito coils, and cola or a mixture of boiled cough syrup, kratom leaves, and cola served with ice.* A DEA report also indicated that Thai militants report this mixture make soldiers *more bold and fearless and easy to control.* [5]

The DEA report also indicates in part, *Kratom consumption can lead to addiction. In a study of Thai kratom addicts, it was observed that some addicts chewed kratom daily for 3 to 30 years (mean of 18.6 years). Long-term use of kratom produced anorexia, weight loss, insomnia, skin darkening, dry mouth, frequent urination, and constipation. A withdrawal syndrome was observed, consisting of symptoms of hostility, aggression, emotional lability, wet nose, achy muscles and bones, and jerky movement of the limbs. Furthermore, several cases of kratom psychosis were observed, where kratom addicts exhibited psychotic symptoms that included hallucinations, delusion and confusion. In the U.S., the use of kratom has been associated with numerous cases of overdose and fatalities.* [5]

b. The CDC reported d*uring 2011–2017, the national poison center reporting database documented 1,807 calls concerning reported exposure to kratom.* [6]

In addition, the CDC report also indicated in part, *data on 27,338 overdose deaths that occurred during July 2016–December 2017 were entered into SUDORS, and 152 (0.56%) of these decedents tested positive for kratom on postmortem toxicology (kratom-positive). Postmortem toxicology testing protocols were not documented and varied among and within states. Kratom was determined to be a cause of death (i.e., kratom-involved) by a medical examiner or coroner for 91 (59.9%) of the 152 kratom-positive decedents, including seven for whom kratom was the only substance to test positive on postmortem toxicology, although the presence of additional substances cannot be ruled out.*[6]

The CDC report further indicated in part, in *approximately 80% of kratom-positive and kratom-involved deaths in this analysis, the decedents had a history of substance misuse, and approximately 90% had no evidence that they were currently receiving medically supervised treatment for pain. Postmortem toxicology testing detected multiple substances for almost all decedents. Fentanyl and fentanyl analogs were the most frequently identified co-occurring substances; any fentanyl was listed as a cause of death for 65.1% of kratom-positive decedents and 56.0% of kratom-involved decedents. Heroin was the second most frequent substance listed as a cause of death (32.9% of kratom-positive decedents), followed by benzodiazepines (22.4%), prescription opioids (19.7%),and cocaine (18.4%).*[6]

c. Even as a scheduled substance, the Arkansas Poison and Drug Information Center reported 19 exposure case calls and 1 information call related to Kratom (mitragynine/7-hydroxymitragynine) from 2021 to early March 2023.

d. In 2022, the Arkansas State Crime Laboratory indicated mitragynine was identified in 3 mixed drug overdose deaths.

6. The risk to public health;

a. Definitive safety studies of kratom have not yet been published, and until then the

adverse effects of kratom have not been sufficiently studied. In addition to the safety concern, the level of risk for unintended consequences for transitioning to riskier alternatives to kratom has not been established and is therefore a public health concern.

b. Kratom interacts with various liver enzyme systems which include Cytochrome-P450 1A2, 2C19, 2D6 and 3A4 as well as P-glycoprotein transport system could lead to increased concentrations of various medications. There are potential additive effects when combined with alcohol, opioids, barbiturates and alcohol.[4] More studies are needed to protect public from unintentional alterations of medication concentrations which could have dangerous consequences.
c. Lack of local sourced products has resulted in adulterated products reported by FDA containing contaminants that includes harmful bacteria specifically *salmonella* and heavy metals which also poses a public health risk. [7, 8]
d. According to the National Institute on Drug Abuse website, documentation indicates in part *long-term health and safety effects are not well understood. Because kratom research is relatively new compared to research on more widely used drugs, there is little evidence to determine how kratom use may affect someone over time. Case reports do show regular, long-term, kratom use in large amounts may be associated with serious liver problems. These cases appear to occur unpredictably in a small minority of people who use kratom, and it is unclear what role other substances and underlying health conditions may play.* [9]
e. Utilizing unapproved medical treatment for Opioid Use Disorder could cause unnecessary delays in individuals obtaining known effective treatment.

7. The potential of the substance to produce psychic or physiological dependence liability;

a. According to National Institute on Drug Abuse website, *studies suggest people may experience mild to moderate withdrawal symptoms when they stop regular kratom use, but more research is needed to understand to what extent people develop substance use disorder symptoms related to kratom.* [9]

b. Case reports related reported kratom addiction are included which warrant further studies to further determine risk factors associated with Kratom use vs abuse.

1. Case Report: Treatment of Kratom Use Disorder With a Classical Tricyclic Antidepressant. [10]

2. A Case Report: Potential pharmacokinetic Kratom-drug interactions resulting in toxicity and subsequent treatment of Kratom use disorder with Buprenorphine/Naloxone [11]

3. Neonatal Abstinence Syndrome Due to Maternal Kratom Use. [12]

The case studies of reported kratom addiction in adults and neonatal abstinence syndrome in newborns suggest the ability of mitragynine and 7-hydroxymitragynine to produce

psychic and physiological withdrawal. Subsequent data and studies are required better understanding of extent and risk factors association with Kratom dependance.

8. Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

Although there no other immediate precursors previous listed on the controlled substances list, it should be noted, the immediate precursor of 7-hydroxymitragyine is mitragynine. Both mitragynine and 7-hydroxymitragynine are currently on the controlled substances list for the state of Arkansas both promulgated in November 2015.

Accordingly, the petition to remove mitragynine and 7-hydroxymitragynine from the Scheduled List of Controlled Substances is denied.

Sincerely,

Renee Mallory

Renee Mallory, RN, BSN

Interim Secretary of Health

Sources:

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4. **https://pd.pharmacy.ufl.edu/research/kratom/**
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12. Whitney B. Eldridge, Cherie Foster, Lance Wyble; Neonatal Abstinence Syndrome Due to Maternal Kratom Use. *Pediatrics* December 2018; 142 (6): e20181839. 10.1542/peds.2018-1839 **https://publications.aap.org/pediatrics/article/142/6/e20181839/37470/Neonatal-Abstinence-Syndrome-Due-to-Maternal**