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May 18, 2018

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Via <https://www.regulations.gov/>

Re: FDA-2018-N-0987

Dear Food and Drug Administration

These comments are submitted in response to the April 17, 2018 Public Meeting on Patient-Focused Drug Development for Opioid Use Disorder (OUD).

I am Jack E. Henningfield, Vice President, Research and Health Policy at **Pinney Associates**, and Adjunct Professor of Behavioral Biology in the Department of Psychiatry and Behavioral Sciences at The Johns Hopkins University School of Medicine. Through **Pinney Associates**, I provide consultation to companies on issues including abuse potential assessments to support the development of safer medications for pain, addiction, and other disorders. We also provide advice to the dietary supplement industry, including to the American Kratom Association (see: www.pinneyassociates.com). No client had input into my comments or supported my attending this meeting.

Current treatments help, but increased capacity and diversity are needed

By way of additional disclosure, as well as the basis for some of my knowledge in this area, I have contributed to nearly every FDA approved treatment for OUD and other Substance Use Disorders (SUDs) through my research at NIDA and Johns Hopkins, and/or through my consulting work at **Pinney Associates**, which has helped bring many treatments through the FDA approval process and to market. I am proud of those efforts, and it was evident from the public hearing on April 17 where I gave a shorter version of these comments, that many people have benefitted from FDA approved treatments.

But it was also evident at that meeting that we have a long way to go with respect to the capacity of our treatment infrastructure, the accessibility and acceptability of our treatments, and the effectiveness of treatments. Some people reported being unable to get treatment when and where they needed it. Some did not like the side effects of offered treatments or found that a treatment that was helpful at one stage of recovery was not helpful or was not acceptable at another stage, putting them at risk of relapse. Some found benefits from approaches that are not FDA approved drugs and may never be. None of this was a surprise, and, indeed, awareness of such issues is part of the reason that FDA and NIDA convened the hearing and are to be commended for doing so.

Near-term help AND long-term MAT development are needed

This meeting gave people with OUD the opportunity to share their thinking with the two federal agencies that can help address many of their concerns and needs – hopefully in the near-term as well as the longer term. In the longer term we need new medicines and more, but with an average time of 10 years and a cost of 2.7 billion dollars per medicine, that path is not an answer for them now, so we must also be making every effort we can to do everything to help them in the near-term.

One of my mentors was Former Surgeon General C. Everett Koop. He was dedicated to advancing addiction science and making treatment as easy to access as are addicting drugs. I think he would have been pleased that the White House Opioid Report acknowledged the need to address shortcomings of our OUD treatment capacity, and its recommendations for research to “improve the range of medications to assist in treating OUD” to match the diversity of our treatment-related needs. However, he would also have been very frustrated at the slow pace of implementation and funding plans to more rapidly ramp up our nation’s treatment services.

Treatment needs to be more flexible including embracing harm reduction

We must also keep in mind that people with diagnosed OUD are just the tip of the iceberg of the opioid epidemic. Many people who are at risk and some who die of overdose do not have OUD but might also be helped by more flexible treatment approaches and programs to reduce the risk of transition from occasional use to addiction, as Dr. Thomas McLellan has long fought for (see bibliography).

We could also save more lives with broader acceptance and support of harm reduction approaches that reduce the risks for occasional nonmedical opioid users as well as for people with advanced OUDs. This is another area in which Dr. Koop was a leader. He embraced harm reduction for addictions to opioids, tobacco, and other substances, as well as for HIV AIDS. Regarding AIDS, whereas he made clear his moral and faith-based opposition to sex out of wedlock, he was a powerful advocate for the use of condoms when sex occurred outside of “monogamous” relationships. He put life and good health for All the People (the theme of his 90th birthday celebration) first and included access to addiction treatment in that concept (Koop, 2006).

Disparities in treatment of OUD and pain are interrelated and must be addressed

I am certain that Dr. Koop would have found it unconscionable that low income and minority people continue to face the greatest disparities in treatment of both pain and addiction—and that gap has actually been growing. He might have asked “Where is the outrage?” as he was wont to do faced with such inequities. I mention pain and addiction because these are frequently interrelated problems: inadequate treatment of pain can lead to illicit drug use, and concerns about addiction can contribute to inadequate treatment of pain in the people who are least likely to abuse opioids, namely properly diagnosed and monitored pain patients.

As evidenced by the April 17th hearing, we have great need for more diverse, affordable, acceptable, and accessible treatments; and, we need to address barriers to treatment access and reimbursement that hurt most those who are already hurting the most. At FDA’s January opioid prescribing meeting, I proposed a simple test for every policy pertaining to prescribing and opioid pain medicine access: Ask if it will help or hurt low

income and minority persons with pain. I suggest including this test for substance abuse policy ideas as well as ensuring that representatives of low income communities, minorities, youth, elderly, physically and mentally disabled, and other populations whose voices are too often left out be included in the evaluation of SUD treatment policies and approaches.

Substance use problems are complex and will not be solved by simple solutions

Many people on opioids have poly-drug use problems and/or other mental health disorders. Let's keep in mind HL Mencken's aphorism that "for every complex human problem there is a simple solution that is neat, plausible, and wrong." The opioid epidemic is not just an opioid problem; it did not have a simple cause and it certainly does not have a simple solution. OUDs typically involve multiple drugs, psychiatric disorders, social factors, and economic factors. Drug development must recognize that; treatment programs must recognize that; the reimbursement system must recognize that; and governmental policies and actions must recognize that from the local to federal levels. The science shows that both pain and SUDs have better outcomes when treatment approaches are comprehensive. Unfortunately, most pain management programs provide prescriptions with little by way of individually tailored multi-modal programs, and medication-assisted treatment programs for SUDs often provide little of the comprehensive behavioral treatment with which the medication was intended to work because there is inadequate funding for multi-modal behavioral support.

Kratom is an in-hand asset: will its potential be realized or will this asset be unfathomably rejected?

Some of the research and development efforts under discussion, including vaccines, are important to pursue but are far from emerging as assets in the near-term. It was pointed out that that we do have assets that are not being utilized and some that are threatened. I will comment only on kratom in this regard. Kratom is presently being used by an estimated 3-5 million Americans to improve their health and well-being, and by many people as a preferred alternative to conventional medicines for various disorders including OUDs.

Kratom is a tree in the coffee family and so it is not surprising that its leaves provide some of the alerting and focusing effects of caffeine that are reported by many consumers to be their main reason for using kratom. Many others report use to relieve symptoms of anxiety, depression, pain, and to reduce or eliminate opioid use whether their use was for pain or addiction. These effects and reasons for use have been known for a century or more in South East Asia and were recently well-documented by four US-focused internet surveys that together included more than 20,000 respondents and more than 20,000 comments to FDA, as well as in global review of the mental health effects of kratom (see reports below).

With respect to the opioid epidemic and people with OUDs, kratom is an in-hand asset, and for many people it is their life line because FDA-approved treatments were either not accessible, not effective, or were not acceptable to them due to side effects and other reasons. This was commented on in the April 17th public hearing. Some kratom users report that methadone or buprenorphine helped break their addiction cycle but that at some point in their recovery, those drugs were not acceptable, and they found that kratom was more helpful and tolerable. Telling them they should go back to methadone or buprenorphine because kratom has not been proven effective to FDA's standards

rings hollow: for them kratom is working and has helped give their lives back to themselves, their families, friends, and co-workers.

Though the science is at an early stage, it supports the conclusion that kratom is far less harmful and addictive than narcotic-like opioids and does not support claims to the contrary

As compared to narcotic-like opioids such as morphine, fentanyl, and heroin, kratom is far less harmful, and its main ingredient, mitragynine, is far less addicting and with little of the signature respiratory-depressing effects of morphine-like opioids that kill more than 115 people every day. This has been demonstrated in laboratory studies for decades, including more recent studies to support the safety of kratom and guide its regulation by FDA's Office of Dietary Supplements. Also, in contrast to opioids, is the absence of documented deaths—in South East Asia or the US—due to kratom-caused respiratory depression. This does not mean there has never been an actual kratom-caused death or serious respiratory depression or that kratom is without risks, but it supports the conclusion that the harmfulness of kratom is far lower than that of narcotic-like opioids. Nor is there is evidence that kratom is feeding the opioid epidemic. Rather, thousands of comments to DEA and FDA and the 4 surveys I mentioned earlier make clear that kratom is a path away from opioids for many people.

Scientific studies are beginning to unravel how kratom's main active ingredient, mitragynine, actually works, and why it is so much lower in the addictive euphoria and deadly respiratory depressing effects than morphine-like opioids. The science and epidemiology indicate that it makes no more sense to place kratom in the same categorical bucket as narcotic-like opioids as it would to place caffeine in the same category with crack cocaine, even though caffeine can cause physical dependence, withdrawal, addiction, mood alteration, is sometimes abused, and sometimes contributes to death. In fact, analogs of mitragynine, as opposed to analogs of opioids, may be among the safer pain relievers and OUD treatments of the future. This is being investigated by several laboratories in the US, though any such medicines are likely many years and many billions of dollars away. These researchers are concerned about efforts to put kratom in Schedule I of the Controlled Substances Act because that would grind their research to a halt.

More importantly for the near-term efforts to address the opioid epidemic and help people with OUDs, kratom is an in-hand asset that is helping many people. These people and their families are rightfully terrified of the possibility that legal sale and possession would be banned by scheduling kratom. Banning kratom would be like taking life preservers away from people struggling in the ocean because they were not Coast Guard approved.

Kratom is helping now, but could help more, and with even less risk if appropriately regulated by FDA: FDA's Office of Dietary Supplements should be encouraged and supported to expedite reviews and work with stakeholders

The public would be far better served by FDA using its broad and flexible regulatory tools to resume the course that its Office of Dietary Supplements had been on (at least through last November) to work with kratom product suppliers, marketers, and makers to set standards for kratom and regulate it to the same standards of other dietary supplements and foods. FDA could set the standards desired by consumers and responsible manufactures alike for product purity, packaging, labeling, claims, and even

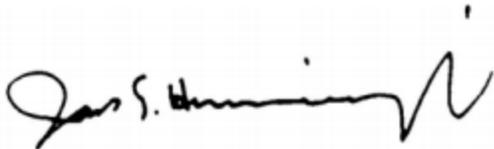
maximum allowable levels of mitragynine and other constituents. It can warn and even ban irresponsible marketers. With registered products, it could more quickly track and trace those brands and batches that are problematic. Those actions will serve kratom users and public health. But there can be no such consumer or public health protections if the lawful kratom market is banned. Instead, more serious problems and less controllable problems would be created by such a ban, as the lawful and regulatable market would be quickly replaced by the truly deadly black market.

Kratom use has been increasing since its introduction to the US by about the 1980s. Many of us in addiction science and medicine and many with OUDs are thankful that we have it as a valuable asset for combatting the surging opioid epidemic. Rather than killing this asset and putting its users at resumed risk of opioid use, and/or black market kratom, I hope that FDA will bring relevant stakeholders (including consumers, kratom vendors, other natural products organizations, scientists and addiction treatment professionals, and NIDA representatives) together to preserve and develop consumer and public health serving regulations while we continue to explore additional longer-term solutions that are supported by appropriate research and surveillance. That approach would be in the interest of people with OUDs and public health.

We appreciate the Food and Drug Administration's effort to organize this public meeting. Thank you very much for the opportunity to provide these comments. Please contact me at **Pinney**Associates at jhenning@pinneyassociates.com or 301-718-8440 if you have any questions or need further information.

Oral Comment for April 17, 2018 At: <https://www.regulations.gov/document?D=FDA-2018-N-0987-0001>

Sincerely,



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And
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For additional information on kratom safety, how it works, and its potential in the opioid epidemic see:

Babin, J. (2018). The FDA Kratom Death Data: Exaggerated Claims, Discredited Research, and Distorted Data Fail to Meet the Evidentiary Standard for Placing Kratom as a Schedule I Controlled Substance. *American Kratom Association Policy Report, 1*.

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Grundmann, O. (2017). Patterns of Kratom use and health impact in the US-Results from an online survey. *Drug and Alcohol Dependence*, 176, 63-70.

Henningfield, J.E., Fant, R.V., and Wang, D.W. (2018). The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. *Psychopharmacology (Berlin)*, 235(2), 573-589. Note that this includes a summary of the 4 US focused internet surveys mentioned above see Factor 5, section 1.5.2)

Kruegel, A.C., Gassaway, M.M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Javitch, J.A., and Sames, D. (2016). Synthetic and receptor signaling explorations of the mitragyna alkaloids: Mitragynine as an atypical molecular framework for opioid receptor modulators. *Journal of the American Chemical Society*, 138(21), 6754-64.

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Warner, M.L., Kaufman, N.C., and Grundmann, O. (2016). The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. *The International Journal of Legal Medicine*, 130(1), 127-38.

For additional information on some of the general addiction research and treatment issues mentioned in this comment see the National Institute on Drug Abuse Website at www.drugabuse.gov and the following:

Henningfield, J.E. (2017). Comment on Docket No. FDA-2017-N-2903.

Koop, C. E. (2006). Health and Health Care for the 21st Century: For All the People. *American Journal of Public Health*, 96, 290-292.

McLellan, A.T., Lewis, D.C., O'Brien, C.P., and Kleber, H.D. (2000). Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA*, 284(13), 1689-95.

Vallerand, A.H., Cosler, P., Henningfield, J.E., and Galassini, P. (2015). Pain management strategies and lessons from the military: A narrative review. *Pain Research & Management*, 20(5), 261-8.

Volkow, N.D. and McLellan, A.T. (2016) Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. *New England Journal of Medicine*, 374(13), 1253-63.

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