SAM Smart Approaches to Marijuana
preventing another big tobacco

July 16, 2019

Ned Sharpless, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Acting Commissioner Sharpless,

I write on behalf of Smart Approaches to Marijuana (SAM) to submit comments on FDA-2019-N-1482. SAM is the leading, non-partisan national organization offering a science-based approach to marijuana policy, founded by former Congressman Patrick Kennedy, senior editor of *The Atlantic* David Frum, and myself, a White House advisor to three U.S. administrations.

SAM urges the Food and Drug Administration (FDA) to preserve the integrity of the FDA process in regulating medicines as proven safe and effective through double-blind, placebo-controlled clinical trials.

While cannabidiol (CBD) does not have the same abuse potential as delta-9-tetrahydrocannabinol (THC), it is important to take into account the known pharmacology of CBD, the importance of known ingredients, the potential for drug interactions, risks from cumulative exposure, and the possibility of THC content allowed under the dry-weight definition of hemp in the 2018 Farm Bill.

Known Pharmacology

The warning label for Epidiolex, a high-dose, purified CBD oil recently approved by the FDA, lists warnings for side effects including liver damage, somnolence and sedation (with warnings not to drive or operate machinery), and suicidal behavior and ideation[i]. The risk of these effects is balanced against the benefit of treatment for severe medical conditions, and patients are carefully monitored to determine the correct dose with a managed risk of negative side effects.

At lower doses, the risk of negative side effects may be reduced, but it's possible that any corresponding benefit will also be reduced. However, one study offers a note of caution, pointing out that "low concentrations of CBD and CBDV cause damage of the genetic material in human-derived cells… Fixation of damage of the DNA in the form of chromosomal damage is generally considered to be essential in the multistep process of malignancy, therefore the currently available data are indicative for potential carcinogenic properties of the cannabinoids."[ii]

Known Ingredients

The FDA process is designed to protect patients from unscrupulous operators, like Chinese companies peddling fake cancer medications. Patients with side effects from unapproved, untested marijuana products have no recourse against the fly-by-night companies that produce

them. Purified CBD that has been produced with Good Manufacturing Practices and has gone through clinical trials to understand its interactions with other drugs and side effects is very different than marijuana or CBD products sold in marijuana stores, many of which have been shown by the FDA to be lacking the active ingredient, contain large amounts of THC, or be contaminated with mold or pesticides.[iii] In all of these cases, the products are very dangerous to give to children or immunocompromised patients.

Drug Interactions

The warning label for Epidiolex[i] also lists a number of drugs with which higher-dose CBD will interact, including alcohol, caffeine, opiates, clobazam, and warfarin, a common blood thinner. It is not yet clear whether lower-dose CBD would have a similar interaction.

Cumulative Exposure

Similar to other cannabinoids, CBD is absorbed by fatty tissue until it is metabolized, and so can accumulate in the body over time if the daily dose is higher than the subject's ability to metabolize it. We do not yet understand what the long-term effects of regular CBD use are on the liver or the endocannabinoid system. Similarly, THC that may be present in these products may also accumulate in the subject's system, causing other unintended effects or drug interactions.

THC Content

Under the Farm Bill, finished CBD products are allowed to contain up to 0.3% THC based on the dry weight of the finished products, which for some products could be a significant amount. For example, a standard 30mL container of "CBD oil" could contain as much as 82mg of THC under the Farm Bill definition, and an average CBD gummy bear could contain as much as 12mg of THC. This is not how the definition was advertised under the justification for the Farm Bill, and so SAM urges the FDA to place tighter restrictions on the allowable THC content of consumer products potentially available from major retailers.

Upholding the Integrity of the FDA Process

While many states have adjusted their drug formulary by ballot initiative or a vote of the state legislature, federal law is clear that the Food, Drug, and Cosmetics Act defines the process for discovery and approval of a medicine.

This has been further clarified through the denial of the petition to reschedule marijuana (57 Federal Register 10499, 10504-10506 (1992)), which lays out five common-sense tests: First, a drug's chemistry must be known and reproducible. Doctors must know how much and of what they are giving their patients. If the researchers don't know what they are giving test subjects, they cannot record meaningful observations. Second, there must be adequate safety studies. Measured doses must be tested for safety, usually in animal studies and pre-clinical human trials, to ascertain the pharmacological and toxicological effects of the drug. Third, there must be adequate and well-controlled studies proving efficacy. Measured doses must be tested and provide evidence of efficacy in treating the intended condition. Double-blind, placebo-controlled clinical trials are the gold standard for ascertaining medicinal safety and effectiveness. Fourth, there must be acceptance by qualified experts. The Food, Drug, and Cosmetics Act requires

those with scientific training in pharmacology and toxicology to evaluate the safety and effectiveness of drugs before they can be sold to the general public. Finally, the scientific evidence must be widely available. The supporting scientific evidence must be published in scientific and medical journals so that other experts may evaluate and test the assumptions made in the clinical trials.

The commercial marijuana products available in marijuana stores do not pass the five tests to be considered a medicine. The chemistry of these products have not been dosed or standardized. Approved medicines are the same wherever one buys them. The penicillin tablet bought in a Boston pharmacy is the same as one purchased in San Diego. Not so with marijuana. The marijuana plant grown in Seattle is different from the one grown in Denver. No two are the same—and unlike a pharmacist, the "budtender" selling the product cannot recite all of the chemicals each plant contained or the drug interactions that might result from other medications.

Indeed, raw marijuana contains hundreds of compounds in unknown quantities. Even if some compounds, if extracted, purified, and standardized, have been approved by the FDA in treating certain conditions like childhood seizures, raw marijuana contains so many unknown compounds that we do not yet understand their overall effect on animals or humans. That's why even the most basic over-the-counter drugs have a more complex label than marijuana sold in dispensaries.

Raw marijuana is inherently difficult to standardize and dose, which is an obvious impediment to rigorous clinical trials. As late as 2016, raw marijuana failed the FDA's scientific review to be considered a medicine. Aside from a handful of anecdotal studies, all successful, large-scale clinical trials have been with isolated compounds from the marijuana plant, not raw marijuana itself. It is not marijuana's Schedule I status that makes it difficult to conduct a clinical trial—all botanicals face this difficulty.

Legitimate Research

SAM and our partners in the research community have identified barriers that could be reduced to enhance research opportunities in the United States into medicines derived from compounds within the marijuana plant. SAM has published guidelines to reducing these barriers,[iv] and also advocates for legislation, such as the Marijuana Effective Drug Studies (MEDS) Act and the Medical Marijuana Research Act, to improve the research process without rescheduling marijuana. SAM supports the recommendations of the National Academy of Sciences[v] and the National Institutes of Health[vi] on reducing the barriers to legitimate research into marijuana and its constituent compounds.

Conclusion

Sometime in the future, we will look back on the mania of putting CBD in every conceivable product as a fad in a long line of wellness cure-alls. In the meantime, it is the responsibility of

the FDA to preserve the safety of food from adulterants and unsafe additives, and the integrity of prescription medicines as safe and effective.

To that end, SAM urges the FDA to insist on the gold standard for approved medications: double-blind, placebo-controlled clinical trials so that science will govern our understanding of the effects and side effects of compounds like cannabinoids on the body and brain.

SAM also urges FDA to step up its enforcement of THC infused products and vaping devices under the Food, Drug, and Cosmetic Act, similar to the initial steps it has taken with CBD. THC vaping companies are still actively executing the Juul social media advertising strategy, with much more disastrous effects on the mental health of young people.

Dr. Nora Volkow and her co-authors offer a potent warning of what is to come should we continue down this path: "Repeated marijuana use during adolescence may result in long-lasting changes in brain function that can jeopardize educational, professional, and social achievements. However, the effects of a drug (legal or illegal) on individual health are determined not only by its pharmacologic properties **but also by its availability and social acceptability.** In this respect, legal drugs (alcohol and tobacco) offer a sobering perspective, accounting for the greatest burden of disease associated with drugs ***not because they are more dangerous than illegal drugs*** but because their legal status allows for more widespread exposure."[vii]

SAM echoes this warning, as we witness market dynamics encouraging marijuana businesses to increase potency and pursue young people while they are most susceptible to becoming heavy users. SAM urges the Food and Drug Administration to take action to mitigate the societal damage of expanded drug use and maintain a scientific understanding of drug use and its harms.

Sincerely,

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President, Smart Approaches to Marijuana (SAM)

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[i] https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

[ii] Russo, et al., Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells. *Archives of Toxicology*. January 2019, Volume 93, Issue 1, pp 179-188. https://link.springer.com/article/10.1007%2Fs00204-018-2322-9

[iii] https://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm

[iv] https://learnaboutsam.org/researching-marijuanas-medical-potential-responsibly-a-six-point-plan/

[v] http://nationalacademies.org/hmd/~/media/Files/Report%20Files/2017/Cannabis-Health-Effects/Cannabis-report-highlights.pdf

[vi] https://www.drugabuse.gov/drugs-abuse/marijuana/nih-research-marijuana-cannabinoids ; https://www.drugabuse.gov/about-nida/noras-blog/2017/02/nasem-report-recommends-removing-barriers-to-cannabis-research

[vii] Volkow, et. al. Adverse Health Effects of Marijuana Use. *New England Journal of Medicine*. 2014 Jun 5; 370(23): 2219–2227. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827335/