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July 11, 2019

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Principal Associate Commissioner for Policy  
Food and Drug Administration  
10903 New Hampshire Ave.  
Bldg. 32, Rm. 5308  
Silver Spring, MD 20993

**RE: Docket Number: FDA-2019-N-1482 – Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds Request for Comments**

Dear Mr. Schiller,

On behalf of the American Psychiatric Association (APA), the medical specialty society representing over 38,500 physicians who specialize in the treatment of mental illnesses, including substance use disorders, we thank you for the opportunity to provide comments for consideration by Food and Drug Administration (FDA) on products containing cannabis or cannabis-derived compounds. We appreciate the FDA's focus on the safety, manufacturing, product quality and marketing of these products. Given the range in the current state and federal policy landscape regarding cannabis, we encourage the FDA to move swiftly to provide regulatory guidance on cannabis products. As the front-line physicians who treat patients with substance use disorders every day, we are concerned that absent FDA's oversight of cannabis products, the consequences could be devastating for patients, families, and communities across the country.

*Concerns About Cannabis Products to Treat Psychiatric Disorders*

As an organization, APA does not endorse cannabis as medicine.<sup>1</sup> Regarding psychiatric disorders, there is no current scientific evidence that cannabis is beneficial for treatment. In fact, several studies have shown that cannabis use may exacerbate or hasten the onset of psychiatric illnesses.<sup>2,3,4</sup> For those with a family history of mood

<sup>1</sup> American Psychiatric Association. Position Statement on Marijuana as Medicine (2013).

<https://www.psychiatry.org/File%20Library/About-APA/Organization-Documents-Policies/Policies/Position-2013-Marijuana-As-Medicine.pdf>

<sup>2</sup> Moore TH, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007 Jul 28;370(9584):319-28.

<sup>3</sup> Large M, Sharama S, Comptom MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch Gen Psychiatry*. 2011 Jun;68(6): 555-61.

<sup>4</sup> van Laar M, van Dorsselaer S, Monshouwer K, de Graaf R. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction*. 2007 Aug;102(8): 1251-60

disorders, cannabis use is associated with the emergence of mood disorders, particularly symptoms of bipolar disorder.<sup>5</sup> Cannabis use is also associated with poorer outcomes among patients with mental illness. Among individuals with schizophrenia, cannabis use is associated with poorer long-term clinical outcomes.<sup>6</sup> For those with major depressive disorder, co-morbid cannabis use is associated with increased rates of both suicidal ideation and attempts, raising grave safety concerns.<sup>7</sup> Individuals with psychotic illness may be more sensitive to both the psychosis-inducing and mood-altering effects of cannabis.<sup>8</sup> This may explain why even among those taking medications for psychotic disorders, cannabis use is associated with an increased risk of relapse into psychotic symptoms.<sup>9</sup>

Additionally, as cannabis-derived products become more accessible and the perceived risks of use are reduced, it is important to note that individuals can develop an addiction to cannabis. Studies indicate that 9% of users become dependent on cannabis, and this number increases to 25-50% among daily users and to 1 in 6 among adolescents.<sup>10</sup> Adolescents remain at particular risk for cannabis use disorder and can experience significant withdrawal symptoms, including appetite changes, restlessness, irritability, depression, twitches and shakes, perspiration, and thoughts/cravings of cannabis.<sup>11</sup>

**While there is no current evidence pointing to its effectiveness to treat psychiatric disorders, we cannot ignore the current surge of cannabis-derived products available to the public. We urge FDA to take bold action to strengthen its infrastructure for regulating the current market.**

#### *The Need for Stronger Research on Cannabis Products*

Further research on the use of cannabis-derived substances as medicine should be facilitated by the federal government. While most of the data highlights the risks associated with cannabis products, some evidence indicates that pure, pharmaceutical cannabidiol (CBD) may have benefits as an adjunctive pharmacotherapy for some psychiatric conditions. Among patients with schizophrenia already stabilized on antipsychotic medication, CBD compared to placebo in a double-blind, placebo-controlled trial demonstrated improvements in positive psychotic symptoms on the Positive and Negative Syndrome

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<sup>5</sup> Lynskey M, Glowinski A, Todorov A, Bucholz K, Madden P, Nelson E, Statham D, Martin N, Heath A, Phil D. Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Arch Gen Psychiatry*. 2004 Oct;61(10): 1026-32.

<sup>6</sup> Henquet C, van Os J, Kuepper R, Delespaul P, Smits M, à Campo J, Myin-Germeys I. Psychosis reactivity to cannabis use in daily life: an experience sampling study. *Br J Psychiatry*. 2010 Jun; 196(6): 447-453.

<sup>7</sup> Kahn RS, Linszen DH, van Os J, Wiersma D, Bruggerman R, Cahn W, de Haan L, Krabbendam L, Myin-Germeys O. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: An analysis of patient-sibling and sibling-control pairs. *Arch Gen Psychiatry*. 2011 Feb; 68(2): 138-147.

<sup>8</sup> Levy E, Pawliuk N, Jooper R, Abadi S, Malla A. Medication- adherent first-episode psychosis patients also relapse: Why? *Canadian J Psychiatry*. 2012 Feb;57(2): 78-84.

<sup>9</sup> Stoner, Susan. [Screening & Assessment of Cannabis Use Disorders. University of Washington Alcohol & Drug Abuse Institute](#). May 2016.

<sup>10</sup> Milin R, Walker S, Duffy A. Assessment and treatment of comorbid psychotic disorders and bipolar disorder. *Clinical Manual of Adolescent Substance Abuse Treatment*. Washington, DC: American Psychiatric Publishing Inc, 2011.

<sup>11</sup> Foti DJ, Kotov R, GueyLT, Bromet EJ. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospital- ization. *Am J Psychiatry*. 2010 Aug;167(8): 987-993.

Scale with no increase in adverse events.<sup>12</sup> Most recently, FDA has approved synthetic cannabis-derived medications for specific indications (examples of medications are Marinol, Syndros, Cesamet and Epidiolex).

The potential mechanism of action of CBD for schizophrenia or other psychiatric disorders is not understood, but it is clear that much more research is needed on this topic. It is particularly difficult to determine its effectiveness, as there is great variability of in the form, dose, and potency and FDA's critical role to ensuring patient safety is necessary. It is our position that if scientific evidence supports the use of cannabis-derived substances to treat specific conditions, the medication should be subject to the approval process of the FDA. We advise that FDA to prioritize studying the adverse effects of cannabis, including the likelihood of addiction.

**We encourage FDA to dedicate funding to research the medicinal potential of cannabis-derived substances. We especially recommend studying appropriate dosing levels and any associated risks, including potential for addiction.**

#### *The Public Health Concerns of Absent Regulation of Cannabis Products*

Even if access to cannabis-derived products is restricted to adults, we cannot underestimate the downstream effect this would have on children and adolescents. Currently, there are no published high quality, randomized, controlled studies demonstrating safe use of botanical cannabis or synthetic, pharmaceutical cannabinoids on children. We are concerned that expanding access to unregulated cannabis products minimizes adolescent perception of cannabis's harmful effects and that by default, ease of access among parents and caretakers means increased access for children and adolescents.

As noted above, the likelihood of developing cannabis use disorder is greatly increased by adolescent use. Emerging evidence suggests a strong association between early cannabis use and deficits in cognition and memory, as well as poor psychiatric outcomes in adulthood.<sup>13</sup> Furthermore, marijuana's deleterious effects on adolescent cognition, behavior, and brain development may have immediate and long-term implications, including increased risk of motor vehicle accidents, sexual victimization, academic failure, lasting decline in intelligence measures, psychopathology, addiction, and psychosocial and occupational impairment.<sup>14</sup> Additionally, younger age of cannabis use is associated with an earlier onset of psychosis

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<sup>12</sup> Kleber, H.D., DuPont, R.L. Physicians and Medical Marijuana: Commentary. *Am J Psychiatry*. 2012 June;169(6): 564-568.

<sup>13</sup> Morin, J. F. G., Afzali, M. H., Bourque, J., Stewart, S. H., Séguin, J. R., O'Leary-Barrett, M., & Conrod, P. J. (2018). A population-based analysis of the relationship between substance use and adolescent cognitive development. *American Journal of Psychiatry*, 176(2), 98-106

<sup>14</sup> American Academy of Child and Adolescent Psychiatry. Policy Statement on Marijuana Legalization (2017). [https://www.aacap.org/AACAP/Policy\\_Statements/2014/aacap\\_marijuana\\_legalization\\_policy.aspx](https://www.aacap.org/AACAP/Policy_Statements/2014/aacap_marijuana_legalization_policy.aspx)

among those at risk<sup>15</sup> and is also associated with increased incidence of anxiety disorders.<sup>16</sup> These findings are of particular concern as symptoms often persist into adulthood, and therefore cannabis use may increase the risk of lifelong symptoms and disability due to mental illness.

In addition to the impact on children, we are also concerned about the public misperception that there is existing government oversight in the manufacturing of these products and its potential for long-term health issues. Since the 2018 passage of the Agricultural Improvement Act, cannabis-derived products have flooded the market in the form of pills, topical lotions, beverages and food products without consistent oversight. The health effects of these products, as well as other compounds in products marketed as cannabidiol or cannabis, are largely unknown. Recent analysis of CBD products commercially available reveals a wide range of concentrations, with only a third accurately labeled for CBD content.<sup>17</sup> Even more concerning is that some of these OTC products contain measurable THC. Despite this, a 2019 Consumer Reports Survey on cannabis-derived products found that 26% of Americans have tried these products at least once, and of those, at least 22% had replaced a prescription or over the counter medications with a cannabis-derived product.<sup>18</sup> This is a concerning trend, particularly for patients who may be pregnant or have a chronic illnesses.

**We recommend that FDA enforce strict regulations that limit marketing to children and adolescents and hold manufacturers accountable for providing the general public, as well as clinicians, the full risks and liabilities associated with cannabis-derived products. It is particularly imperative to disseminate education on these risks to parents, pregnant women, and patients with chronic illnesses.**

The APA stands at the ready to work with FDA to address this important topic. If you have questions, or if we can be of further assistance, please contact Kathy Orellana, Associate Director of Practice Management and Delivery Systems Policy, at [korellana@psych.org](mailto:korellana@psych.org) or 202-559-3911.

Sincerely,



Saul Levin, MD, MPA, FRCP-E  
CEO and Medical Director

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<sup>15</sup> Schimmelmann BG, Conus P, Cotton S, Kupferschmid S, McGorry PD, Lambert M. Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. *Eur Psychiatry*. 2012 Aug;27(6):463-9.

<sup>16</sup> McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, Alati R, Williams GM, Bor W, Najman JM. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. *Arch Gen Psychiatry*. 2010 67(5):440-447.

<sup>17</sup> Bonn-Miller, Marcel et al. (2017). Labeling Accuracy of Cannabidiol Extracts Sold Online. *JAMA*.  
<https://jamanetwork.com/journals/jama/fullarticle/2661569>

<sup>18</sup> January 2019 Consumer Reports national representative survey on CBD Products.  
<https://www.consumerreports.org/cbd/cbd-goes-mainstream/>