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Twenty-First Century Illicit Drugs and Their Discontents: Why the FDA Could Not Approve Raw Cannabis as a "Safe," "Effective," and "Uniform" Drug

Paul J. Larkin

The raw, agricultural form of cannabis is not capable of being approved for use by the Food and Drug Administration (FDA)—regardless of whether Congress or the U.S. Attorney General reschedules it downward from Schedule I. Rescheduling cannabis would not allow the drug to be distributed under federal law unless the FDA finds that it is a safe, effective, and uniform drug. The FDA could not do so under existing law, and the Attorney General cannot waive the Food, Drug, and Cosmetic Act's requirements. Congress could do so by statute—but any such law would put at risk the health of users and nonusers in order to satisfy the desires of a minority for a transient high.

In a May 2023 article published online in the *Journal of the American Medical Association Network Open*, the authors conducted a survey among medical cannabis users in Australia between December 2018 and May 2022 to determine if they reported improvements over time in their quality of life from their cannabis use.[1] The authors concluded that "[p]atients using medical cannabis reported improvements in health-related quality of life, which were mostly sustained over time," but they cautioned that "[a]dverse events were rarely serious but common, highlighting the need for caution with prescribing medical cannabis."[2]

The study illustrates some of the problems with contemporary debates over the legalization of cannabis. Replete with tables, charts, graphs, and statistical analyses, and published in the distinguished *Journal of the American Medical Association*, the Australian study appears to offer support for the proposition that cannabis is a legitimate medical treatment. The study certainly will be used for that purpose in public policy debates over the proper legal treatment of that drug, both in Australia and the United States. The problem is that, when critically analyzed, the study does not come

close to proof that raw cannabis is a safe, effective, and uniformly made drug—the proof required by federal law for a new drug to be distributed in interstate commerce.

A central weakness in the study's value is its reliance on the subjective evaluation of cannabis' effects on individuals as proof of cannabis' value on their quality of life.[3] Drugs used for the treatment of diseases or injuries are not ordinary consumer goods like cell phones, motor vehicles, or stereo systems. That is, drugs are not widgets that we entrust to the judgment of the market, goods that may be sold without prior government approval and that succeed or fail based on consumer decisions about their value. Nor do we decide whether a drug should be legalized by polling users to learn whether they believe that it is "Awesome!" or "Gnarly!" This nation has taken a different course. Ever since 1938, when the federal Food, Drug, and Cosmetic Act (FDCA) became law,[4] it has been a federal crime to distribute a drug[5] in interstate commerce unless and until the Commissioner of Food and Drugs[6] finds that the drug is safe, effective, and uniformly made.[7] Prior authorization under a rigorous medical and legal standard is the rule of the road.[8]

Reports like the one noted above—studies that uncomfortably resemble the analyses that modern corporations likely prepare for new varieties of candies[9] (substitute "chocolate" for "cannabis" in the above study, and see if it makes a difference in the outcome)—do not prove that a drug is safe and effective at treating a disease, its cause, or its sequalae; at best, they tell whether users "like" the drug. That finding might be interesting, but it is not tantamount to legal proof that the drug should be approved for medical use.

That is only one shortcoming of the Australian study. There are more:

- The authors admitted the limitations of their study. There was no control group, so the authors could not determine whether adverse reactions were due to the subjects' underlying medical conditions, the cannabis they used, or both.[10]

- Responses were voluntary, which poses the risk that only favorable reactions would be reported (perhaps to enable subjects to continue to receive cannabis).[11]

- "[N]o official prescribing guidelines exist in Australia" for cannabis as a treatment.[12] Instead, "the target dose is determined on a case-by-case basis."[13]

- Cannabis "[p]roduct types and cannabinoid content varied over time in accordance with the treating physician's clinical judgement."[14]

- With respect to (the admittedly small number of) parties smoking raw cannabis, there was no stated uniformity in the number, depth, and rate of inhalations.[15]

- Nearly half (48 percent) of the subjects were also taking opioid analgesics.[16]

Even disregarding all those qualifications, the poll still does not help decide whether smoking raw cannabis is a legitimate therapeutic modality. Why? More than 70 percent of the subjects were being treated with cannabis for "non-cancer pain" or "anxiety,"[17] subjective symptoms reported by a patient, rather than objective facts such as having recently undergone surgery or having been diagnosed with cancer. As Dr. Peter Bach, a physician and Director of the Center for Health Policy and Outcomes at the Memorial Sloan Kettering Cancer Center, explained, "[E]very intoxicant would pass that sort of test because you don't experience pain as acutely when you are high. If weed is a pain reliever, so is Budweiser."[18] Plus the benefits were found to be relatively minor,[19] and there were also adverse events.[20] Even giving the study the benefit of every doubt, it does not prove that cannabis is a legitimate medical palliative.

My point is not that the study is worthless or that the authors acted in bad faith. It is not, and they did not. The study has limited usefulness when it comes to deciding whether raw cannabis is safe, effective, and uniformly made, which are the requirements that the FDCA imposes before that drug can be distributed across state lines. Just as further research is necessary to determine whether there are medically valuable cannabinoids that can and should be approved for use in treating disease—which the Food and Drug Administration has found in several cases—so, too, there is a need for additional research into whether cannabis products legitimately and properly produced by pharmaceutical companies can provide relief for the ailments noted by the subjects without producing adverse effects.

The gravamen of this *Special Report* is that, under long-standing federal law, the FDA Commissioner could not find that the raw (or agricultural or botanical) form of cannabis is a safe, effective, and uniformly made drug (requirements before anyone may ship that drug in interstate commerce) or that smoking raw cannabis is a legitimate therapeutic modality. The states that have approved smoking raw cannabis as a treatment for either

a few specified ailments—or whatever ones a licensed physician is willing to risk his reputation by endorsing[21]—did not make the findings that the FDCA demands. Without even genuflecting toward the findings that federal law requires before a drug can be approved, those states have washed their hands of the responsibility to protect the public health, whether by shifting the responsibility to (what are certain to be) underfunded state agencies or just passing the buck to physicians willing to recommend cannabis use for anyone who has a double sawbuck and 10 minutes to spare.[22] Those states have simply succumbed to the demands or entreaties made by parties ostensibly seeking to alleviate the suffering of the afflicted or, in reality, simply seeking to get rich off of a beguiling, but habit-forming, drug. The dishonesty of those states' decisions, the fetid justifications that they found acceptable for legalizing cannabis, is a testament to the proposition that hypocrisy is the tribute that vice pays to virtue. The parts below explain why.

The Complementary Roles of Federal and State Drug Regulation

Federal and state law serve complementary roles in the use of drugs to treat disease. State law governs the hands-on treatment of individual patients by state-licensed physicians, while federal law regulates what drugs may be distributed in interstate commerce.[23] Under the FDCA, the responsibility to approve the distribution of a "drug" in interstate commerce rests with the Commissioner of Food and Drugs. Along with his or her principal lieutenants and staff, the commissioner must review all "new drugs"[24] to determine whether they are "safe," "effective," and uniformly made for their intended treatment purposes.[25] The nation has accepted that assignment of responsibilities for more than 80 years. Whether the drug is an antibiotic, antiviral, antifungal, antineoplastic, or antiwhatever, no state has refused to respect the FDA's judgment that a drug is not safe, effective, and uniformly made by legalizing the sale under state law of any such drug.

With the exception of cannabis.

The Current—and Chaotic—State of American Law and Policy Governing Cannabis

The utility of cannabis as a medical treatment has been the subject of considerable debate within the medical profession. Some physicians believe that cannabis or its cannabinoids (biologically active constituents) have

legitimate therapeutic uses in treating (for example) long-term pain, nausea, appetite suppression, the spasticity caused by multiple sclerosis, and other ailments.[26] By contrast, other physicians (and nonphysician experts) strongly disagree. They see medical cannabis not as a legitimate pharmaceutical but as a mistaken belief in the therapeutic value of caring or as a fraudulent attempt to justify its distribution.[27] They also believe that one cannot yet know the likely long-term harms from cannabis use (particularly today's high-potency cannabis), because the states did not independently investigate cannabis' potential long-term harms before legalizing it, and that they—and we—might regret those decisions.[28]

Federal law, however, is clear. It prohibits the distribution of cannabis for any medical or recreational use[29] but allows it to be cultivated for research purposes.[30] Two acts of Congress are particularly relevant here: the Food, Drug, and Cosmetic Act of 1938 and the Controlled Substances Act of 1970.

The Food, Drug, and Cosmetic Act. The Food, Drug, and Cosmetic Act[31] prohibits the interstate distribution[32] of any "adulterated or misbranded" drug into interstate commerce,[33] as well as the distribution of any "new drug"[34] unless the Commissioner of Food and Drugs[35] has found it to be "safe" and "effective" for its intended use.[36] To enforce those requirements, the FDCA authorizes the government to pursue criminal prosecution and civil remedies, including the seizure of any adulterated drugs.[37]

To obtain the FDA Commissioner's approval, a drug sponsor must submit to the FDA sufficient information to enable the agency to answer those questions in the sponsor's favor, as well as to prove that the drug[38] is appropriately labeled. The sponsor must also establish that its manufacturing process will "preserve the drug's identity, strength, quality, and purity."[39] To do so, a manufacturer must submit what is known in the trade as a New Drug Application, or NDA.[40]

An NDA is a massive and complex document, containing extensive scientific and clinical data such as "full reports" of all years-long clinical trials, relevant nonclinical studies, and all other information that the FDA deems relevant to its evaluation of the drug's safety and effectiveness, as well as a detailed description of the company's manufacturing processes.[41] The NDA must also include the labeling proposed for the drug[42] and "an explanation of why its benefits exceed its risks under the labeling's conditions for use.[43] The FDA may approve an NDA only if it finds that the drug is "safe for use" under "the conditions of use prescribed, recommended, or suggested" in the proposed label.[44] To make that finding, the drug's probable therapeutic benefits must outweigh any risk of harm.[45]

Safety and effectiveness testing generally proceeds in three phases.[46]

- Phase I encompasses initial clinical testing on a small number of people to assess safety;[47] tolerability; pharmacodynamics (viz., the effect of a drug on the body); pharmacokinetics (viz., the movement of a drug through a body); and (only preliminarily) potential therapeutic benefits of the proposed new drug.[48]

- Phase II testing is critical because it is designed to determine and measure a safety and efficacy profile for humans far better than the results of Phase I does.[49] Accordingly, medical and scientific experts play a critical role at this stage.[50]

- Phase III testing—which is more expensive and time consuming than prior stages and ordinarily takes 1.5 years to complete and analyze the data—seeks to confirm or refute the therapeutic effects of a drug on a particular disease shown in Phase II.[51]

An NDA must also include "an explanation of why the drug's benefits exceed the risks under the labeling's conditions.[52] To make that finding, the drug's probable therapeutic benefits must outweigh any risk of harm.[53] Finally, after approval, a drug sponsor must report to the FDA any newly identified adverse events or treatment risks.[54]

Atop all that, a drug sponsor must also prove in its NDA that it follows good manufacturing practices, guaranteeing that the drug production manufacturing process will turn out approved, safe products.[55] The sponsor also must establish that its drug will remain stable in whatever containers it proposes to use.[56] In addition, the FDA may approve a new drug only if the agency finds that the drug is "safe for use" under "the conditions of use prescribed, recommended, or suggested" in the proposed label[57] and that the labeling is satisfactory to ensure safe dispensing, application, and use of a drug.[58]

The FDA has never approved the raw cannabis plant as a treatment for any ailment,[59] but it has approved the use of certain biologically active cannabis compounds, known as cannabinoids (or phytocannabinoids).[60] The FDA has approved the synthetic delta-9-THC analogues dronabinol (Marinol) and nabilone (Cesamet) for treatment of chemotherapy-induced nausea and emesis, as well as appetite stimulation in cachexic patients suffering from cancer or HIV/AIDS wasting syndrome.[61] The FDA has also approved Epidiolex,

a purified form of cannabidiol (CBD), for use in treating Dravet's Syndrome and Lennox–Gastaut Syndrome, severely debilitating forms of childhood-onset epilepsy.[62]

The Controlled Substances Act of 1970. The other relevant law is the Controlled Substances Act of 1970 (CSA).[63] The CSA directly incorporates the definition of the term "drug" found in the Food, Drug, and Cosmetic Act,[64] and it defines the term "controlled substance" (with certain exceptions) as "a drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V of part B of this title."[65]

A licensed physician may prescribe, and pharmaceutical companies and retail stores may distribute, any drug listed in Schedules II through V, which are subject to (decreasingly) strict regulations for public safety purposes. By contrast, drugs listed in Schedule I, such as cannabis, are illegal to manufacture, distribute, or possess because they have no accepted medical use and are dangerous.[66] Schedule I drugs can be distributed for research purposes, but only under rules promulgated by the U.S. Department of Justice limiting distribution to legitimate investigators.[67]

By contrast, the CSA places Schedule I drugs outside the boundaries of legitimate medical practice, classifying them as contraband even if a state-licensed physician would prescribe them for a specific patient.[68] Any physician prescribing cannabis can be prosecuted for prescribing a controlled substance outside of legitimate medical practice, and the same potentially severe penalties apply alike to physicians and ordinary street dealers.[69] When it passed the CSA in 1970, Congress placed cannabis into Schedule I.

There has been no material change in cannabis status under federal law since then. Congress empowered the U.S. Attorney General, in consultation with the Secretary of Health and Human Services, to reclassify cannabis,[70] but no attorney general has yet done so.[71] Since 1970, Congress has revised the FDCA and CSA on numerous occasions,[72] and it has nibbled around the edges of the reclassification and legalization issues.[73] Nonetheless, despite numerous entreaties to modify the CSA's classification of cannabis,[74] Congress has not fundamentally reconsidered whether the nation should legalize its use. The CSA's scheduling system, and cannabis designation as a Schedule I controlled substance, remains in place.[75] In addition, because the CSA must be read consistently with the FDCA,[76] even if Congress completely removed cannabis from the CSA, the drug could not be distributed in interstate commerce without the FDA Commissioner's approval.[77] Together, those laws forbid the interstate and intrastate distribution of cannabis for any nonscientific investigatory purpose.

State Cannabis Regulation. Nonetheless, since 1996, numerous states have decided to liberalize their own state laws governing cannabis. At present, 42 separate jurisdictions—37 states, four territories, and the District of Columbia—have revised their laws to allow cannabis or its products[78] to be used for medical purposes, while 18 states, two territories, and the District of Columbia permit cannabis to be used recreationally.[79] To be sure, some states have rejected bills that would have legalized cannabis for medical or recreational use, but a majority of states now allow it to be used under state law for one purpose or another. The oddity is that, because states cannot exempt their residents from the reach of federal law, the states that have legalized cannabis use are effectively—and openly—encouraging them to commit federal crimes, which leaves residents in the lurch if they follow through.[80]

Why have the states decided to legalize cannabis under state law? Is it because the FDA deems cannabis a "safe" and "effective" drug under the FDCA, but the Justice Department has refused to give effect to that finding because the distribution of cannabis is a felony under a different federal law, the CSA? No. The federal government's health care agencies, including the FDA, have consistently found that cannabis is not a safe and effective drug: On the contrary, it carries substantial risks, and smoking it is not a legitimate medical treatment modality. Although there has been a decades-long and still-ongoing debate over the medical effectiveness of cannabis and its compounds to treat disease or alleviate its symptoms, there is considerable scientific support for the agencies' conclusion that agricultural cannabis is not a safe, effective, and uniform drug.

The FDCA and the FDA's Rules Require that a New Drug Be Proven "Safe," "Effective," and "Uniform" to Be Distributed In Interstate Commerce

Raw cannabis cannot satisfy the FDCA's safety, effectiveness, and uniformity requirements. That is true for a host of reasons, as the next subparts will explain.

At the outset, it is important to note that the age of the cannabis plant does not prove that it is "safe." One argument advanced in favor of cannabis' safety is that cannabis was used for medical purposes for centuries without scientific proof of its safety and efficacy.[81] That is true but irrelevant. "Prior to the twentieth century, drug manufacturers could hawk any potion, claim treatment of any ailment, and hail efficacy or potency on a bottle's label, all in the name of increasing sales."[82] Only in

that century did American society reject a *laissez faire* approach to drug regulation. The Pure Food and Drug Act of 1906 required the contents of drugs to be disclosed,[83] and the FDCA prohibited the commercialization of drugs until the FDA had found them to be safe, effective, and uniform.[84] Accordingly, the historical treatment of cannabis in the 17th, 18th, or 19th centuries, whether in America or the rest of the world, is of no importance. What truly matters is how this nation treats cannabis today.

Another argument commonly advanced to prove cannabis' safety is that, unlike opioids or alcohol, cannabis cannot depress the respiratory system, so overuse cannot prove fatal. That argument is true *but only insofar as it goes*. The number of cannabinoid receptors in the base of the brain, which controls automatic breathing (such as when we are asleep) is too few in number to shut down the brainstem's regulation of nonconscious respiration.[85] But cannabis use *and driving* can prove fatal to the driver as well as others, as discussed below.[86] In fact, the available evidence shows an increase in cannabis-related crashes and fatalities in states that have legalized cannabis. Plus, there are other potential harms from smoking cannabis as a treatment or palliative. They are discussed below.

The Potential Harms to Cannabis Users

The Risk of Adulteration. As Dr. Nora Volkow, the Director of the National Institute on Drug Abuse, told Congress in 2020, "in general, adequate and well-controlled studies are lacking" to test the cannabis sold in states with legalized medical-use or recreational-use régimes.[87] A result is that "individuals across the country are using cannabis strains and extracts that have not undergone the rigorous clinical trials required to show that they are safe and effective for medical use, and are not regulated for consistency or quality."[88] Commercially sold cannabis can be adulterated, and consumption of such cannabis poses several risks, risks that become particularly hazardous when that use is heavy, long-term, or begins in adolescence.

Much of the cannabis sold in states with medical or recreational cannabis programs has not undergone rigorous testing to ensure that is does not contain dangerous toxins. In fact, commercial cannabis can contain a "hodgepodge" of dangerous contaminants.[89] Among them are microbials (e.g., *E. coli*, fungi, mold), toxins (e.g., aflatoxins), hazardous chemical solvents remaining from the extraction process (e.g., butane, hexane, propane), pesticides (e.g., organophosphates), heavy metals (e.g., arsenic, cadmium, lead, mercury), and other harmful (e.g., formaldehyde) or distasteful (e.g., insects) substances.[90]

To be sure, randomized testing is now required by some jurisdictions, and where that is done regularly, consistently, and honestly, that practice should reduce the risk of adulteration to some extent.[91] But that risk will not vanish. Why? Despite legalization, there still is a thriving illicit cannabis market.[92] The universally acknowledged widespread existence of that industry;[93] the preference that many users have for buying lower-cost cannabis (because illicit sellers do not pay taxes or comply with health and safety regulations); and the desire many users have to make their purchases in private (because buying from public, state-licensed cannabis dispensaries could "out" them as users) means that the cannabis used by the public will continue to possess a range of adulterants ranging from the unsavory to the toxic.[94] California is a good example, because its illicit market is larger than its legitimate one and shows no signs of disappearing.

The Risk of Addiction and Dependence.[95] Cannabis is not an ordinary consumer good because it can lead to dependence and addiction by users (as well as injury (or worse) to third parties). Like any other substance that produces an intoxicating effect (even if only during its initial use)—like alcohol, tobacco, or heroin—cannabis generates a pleasurable "high" that people enjoy. "Unfortunately, for some people the 'rush' that marijuana produces is more a curse than a blessing."[96] The reason is that heavy or long-term use can lead a person to develop a tolerance to THC, requiring ever greater quantities of the chemical to experience the same euphoria.[97] That increasing-quantity user carries potential downsides. Among them are damage to a user's mental or physical functioning;[98] physical dependence on THC, which leads to the unpleasant experience of suffering withdrawal symptoms when use is discontinued; or to addiction, in which using cannabis becomes the fulcrum of one's life.[99]

Here, as often occurs elsewhere in science, including with respect to cannabis, there is no certainty that any one individual will or will not suffer mental deterioration, physical dependence, or addiction from heavy, long-term cannabis use. Nor is there any test that can alert someone to the certainty that cannabis use will shorten or degrade his life. It is a matter of probabilities. There are, however, some useful "rules of thumb," according to two drug policy experts, Wayne Hall and Rosalie Pacula, that are helpful in this regard.[100] There is a 10 percent risk for people who have ever used cannabis. That risk increases to between 20 percent and 33 percent for people who use the drug more often. The risk jumps to 50 percent—which is tantamount to a coin flip—for people who use cannabis daily. Given the labile nature of the adolescent brain, the risk is greater still for people who begin heavy or long-term use during their minority.[101] As NIDA Director

Volkow put it, "as compared with persons who begin to use marijuana in adulthood, those who begin to use in adolescence are approximately 2 to 4 times as likely to have symptoms of cannabis dependence within 2 years after first use."[102] Physical dependence is therefore a serious problem.

The Risk of Mental Illness. It has been known for centuries that cannabis use can cause acute, short-term hallucinations.[103] A different question is whether overuse can cause long-term psychosis. For example, a well-known 1987 study of the relationship between cannabis use and more than 45,000 Swedish military conscripts found an association between long-term use and schizophrenia—namely, frequent cannabis smokers were six times more likely to have schizophrenia than non-smokers—but did not find a causal relationship.[104] A 2012 report by the United Kingdom Schizophrenia Commission came to the same conclusion,[105] as did a 2020 report by NIDA,[106] which is reflected in congressional testimony given by Dr. Volkow that year.[107]

Other researchers disagree. Some of them have concluded that factors, such as alcohol, cigarette, or non-cannabis drug use, confound the association between cannabis and psychosis, which prevents a causal relationship from being shown.[108] Nonetheless, numerous reports, based on clinical studies or meta-analyses of the literature, have found a serious risk between long-term use or heavy use of high-potency cannabis and Cannabis Use Disorder (CUD)—namely, the inability to cease using cannabis despite its adverse psychosocial effects on a user's life[109]—and schizophrenia.[110] Many of those studies have come not only in this century, but also in the past decade, particularly in the past three to four years.[111]

This is not to say that any and all cannabis use triggers schizophrenia. That is not true. There is a consensus that experimental or small-scale cannabis use will not inevitably cause someone to suffer from schizophrenia. Nevertheless, a causal relationship between cannabis use and psychosis is "biologically plausible," and there also is a material risk that use can speed along individuals toward that outcome if they are genetically predisposed to that illness.[112] Factors such as the amount, potency, age of first use, and genetic disposition are critical. As one researcher concluded, "[w]hile only a minority of cannabis users develop a psychotic disorder, users who consume daily types of cannabis" with a 10 percent or greater THC content "are over 5 times more likely to suffer from a psychotic disorder than never users."[113] That is a particular risk for people who begin heavy, long-term use during adolescence.[114] Dr. Volkow's point is that we should be concerned about the risk that cannabis will accelerate the development of mental illness in people who, unfortunately, are already on that sad trajectory or use high-potency THC products for an extended period.

That is a serious public policy problem. If any other consumer good posed the same risk, members of the public and elected officials would daily express their outrage that the nation allows such a product to be sold, and congressional chairs would haul the FDA Commissioner to Capitol Hill for hearings and demand that he or she outlaw that good, immediately and forever.[115] Indeed, if umbrage could be harnessed as energy, we would need no fossil or green fuels for a week or more after that hearing (at least until some other "crisis" captivated the public).

An important reason for reconsidering the relationship between heavy or long-term cannabis use and schizophrenia is the 15-fold increase in the THC content of cannabis products today over the weed smoked in the 1960s.[116] The past 60 years have witnessed "ganjapreneurs" develop sophisticated indoor and hydroponic cultivation techniques, as well as the cross-breeding of cannabis strains, which have increased cannabis' potency tremendously. Cannabis had a THC content of approximately 1 percent to 3 or 4 percent during the Summer of Love (1967), but the THC content in commercial cannabis products today approaches 100 percent pure THC. The increase is like switching from near beer to grain alcohol. No one could responsibly believe that the potency increase is immaterial. Distributers certainly do not; for them, it is an attractive selling point.

That increase has enormous clinical significance. As a general matter, "[s]mall changes in a drug product or substance can result in large changes of performance."[117] The same likely is true when the potency of a drug, like THC in cannabis, is increased, as several researchers have concluded.[118] Today's hyperpotent cannabis might exacerbate the effect that THC might have on people genetically predisposed to schizophrenia, as some observers have noted.[119] That risk requires us to re-evaluate earlier studies on this aspect of cannabis legalization.

Variances in Labeling and Packaging. The FDCA prohibits mislabeling a drug.[120] Commercially sold cannabis is subject to inaccuracies and inconsistencies in how dispensaries label their wares.[121] More troubling still is the manufacture of edibles to resemble candies that children commonly consume.[122] (That problem is discussed further below.[123]) Even if that form is not, technically speaking, a "mislabeling" of the product, its design is to attract, induce, or fool children into believing that cannabis "Gummy Bears" are ordinary candy, despite overwhelming evidence that cannabis use can seriously harm them.

Potential Harms to Particular User Populations

The Potential Harms to Adolescents.[124] Law can deem someone to be an adult at age 18,[125] but law cannot govern biology. Starting before birth, the brain matures into a person's mid-20s as it prunes existing neural pathways and creates new ones.[126] In fact, the prefrontal lobe region, the area responsible for reasoning, judgment, decision-making, and other higher mental functions, is the last region to undergo neuromaturational development.[127] Use of disabling substances like cannabis can have an adverse long-term impact on the labile brain.[128] We have been aware of that risk for some time, as well as the adverse psychosocial outcomes that can follow impaired neural development.[129]

Recently, however, a host of researchers has concluded that early onset and long-term regular cannabis use, or heavy use of high-potency cannabis, enhances the risk of resulting schizophrenia more than we once thought. According to those reports, either practice could damage the juvenile brain in ways that would not happen to adults and lead either to long-term psychosocial problems or render those users more susceptible than never- or experimental-users to the potential that cannabis has to accelerate the onset of schizophrenia.[130] For all those reasons, it is no surprise that government agencies like the FDA and NIDA, and numerous respected private organizations, including the American Academy of Pediatrics, agree that juveniles should not use cannabis.[131]

Not only cannabis' ingredients but also its delivery system can prove troublesome for minors where it might not for adults. Consider edibles—cannabis-infused food products or drinks often packaged to resemble ordinary items, such as brownies, chocolates, cookies, candies, lozenges, and sodas.[132] Some edibles have been labeled as "Pot Tarts," "Buddahfinger," "Munchy Way," or Keef Kat," while others resemble "Gummy Bears."[133] The labeling can confuse children. Plus, two features of edibles make them particularly attractive: They can be infused with sugar, which makes them desirable for juveniles with a sweet tooth, and their consumption does not generate the tell-tale aroma of burnt cannabis, thereby enabling users to lower their risk of detection and arrest.[134] Finally, the risk of cannabis abuse by minors is also troublesome with respect to "vaping"—i.e., use of an Electronic Nicotine Delivery System devices (ENDS, also known as e-cigarettes or "vapes"). The devices aerosolize a solution held in a cartridge to enable users to limit damage from smoking by inhaling addictive nicotine without the carcinogenic tars. ENDSs can aerosolize a high-potency liquid THC- and nicotine-filled cartridge, thereby giving juveniles a two-fer: receipt of both

drugs without the characteristic odor of burnt carbon. Not surprisingly, cannabis vaping is becoming common among minors.[135]

The Potential Harms to Unborn or Nursing Children.[136] Children and adolescents are not the only youngsters that might be adversely affected by cannabis use. Use of cannabis by pregnant women is on the rise. THC crosses the placenta,[137] so children in utero and nursing unwillingly consume it.[138] There is no conclusive proof that maternal cannabis use during pregnancy or nursing will or will not harm a child within or outside the womb.[139] Some studies found a serious risk that THC might damage its involuntary recipient, for example, by impairing a child's "higher-order executive functioning" during the "school-age years."[140] Other studies have found no material association between in utero cannabis use and a host of maladies, such as fetal mortality and malformation.[141] The evidence therefore points both ways.[142]

That uncertainty, however, does not end the inquiry; it raises the question of how we should proceed in the face of uncertainty. As noted by the U.S. Substance Abuse and Mental Health Services Agency, "[n]o amount of marijuana has been proven safe to use during pregnancy or while breastfeeding,"[143] let alone the hyper-potent cannabis now available.[144] The question is how we should proceed in the face of uncertain risks. At a minimum, the FDA should require warning labels specifically focused on the risks to pregnant and nursing women.[145] Other options are available, too, such as making it a crime to distribute cannabis to a woman in either category.[146]

The Potential Harms to Non-User Third Parties

Cannabis-Impaired Driving.[147] Any discussion of the potential harms of cannabis to third parties should begin with the risk that cannabis users will drive under its influence, crash their vehicles, and maim or kill innocent passengers, pedestrians, or other drivers. Drug-impaired driving has not yet received the attention it deserves, let alone what we devote to alcohol-impaired driving.[148] But all that it might take is the fatality of a well-known party (e.g., a professional athlete) or highly positioned victim (e.g., family member of a Senator) to generate intense scrutiny of this issue.[149] Were that (unfortunately) to occur, a powerful case can be made that drug-impaired driving is as serious a public policy problem as alcohol-impaired driving. Indeed, in the Obama Administration, Office of National Drug Control Policy Director Gil Kerlikowski made that finding in 2010.[150]

THC clearly impedes safe driving,[151] even though some users mistakenly believe that it does not erode (or even enhances) their skills.[152] That risk

is not a trivial one.[153] There is an increasing number of people who drive after cannabis use;[154] the effect of cannabis on one's driving skills does not necessarily dissipate quickly;[155] and the danger is greatly increased if someone consumes a cannabis-alcohol cocktail (a not-infrequent occurrence),[156] because each drug augments the impairing effect of the other one.[157]

To be sure, the FDA would not deny approval to a drug simply because someone might illegally drive under its influence; opioids and benzodiazepines also have a disabling effect, but they can be lawfully prescribed. But the agency might demand that any business that packages or sells cannabis must note in the label and directions for use that no one should drive within a few hours of consuming cannabis, and that cannabis-impaired driving is illegal in every state.[158] The FDA also could recommend that no one drive after consuming cannabis for at least a certain number of hours.[159] Finally, the FDA could recommend that Congress invoke its Article I Spending Clause or Commerce Clause authority to adopt one or more measures to address it.[160]

Cannabis-Induced Violence. We have known for some time that alcohol is perhaps the drug most commonly used by people who commit crimes.[161] There is a considerable body of expert authority for the alcohol–crime nexus. Indeed, it would be reasonable to treat alcohol as a "criminogenic" drug—namely, a drug that leads to lawbreaking and violence by drowning judgment while someone is inebriated. At a minimum, alcohol can catalyze a person's inherent violent tendencies.[162] One psychiatrist colorfully described that phenomenon by saying that "[t]he conscience" is "that part of the mind which is soluble in alcohol."[163]

Does cannabis have the same criminogenic effect? Or do its users instead become passive and laid back, people who laugh, eat, and say "dude" a lot? The now-campy 1936 film *Reefer Madness* depicted cannabis use as being even more violence-inducing than alcohol. It portrayed cannabis-using adults as uncontrollably sex-crazed, homicidal maniacs. That over-the-top depiction of cannabis use allowed the drug's advocates to lampoon their critics as being silly, out-of-touch, uncool ninnies. That has been an effective strategy for decades.

Here's an example of that strategy in practice. In 2019, Alex Berenson, a former *New York Times* journalist, published a book entitled *Tell Your Children* (the original title of the film *Reefer Madness*) and subtitled *The Truth About Marijuana, Mental Illness, and Violence*, that addressed the troubling relationship between those three subjects. Along with a host of other information, Berenson reviewed five published studies between 2010 and 2018 on the issue. As he explained, skeptics were wrong to believe

that cannabis use and psychosis were both attributable to an underlying genetic disorder.[164] The "genes linked to schizophrenia" might "generally contribute to risky behaviors such as drug use," but those genes "did not cause marijuana smoking."[165] At the same time, "[t]he reverse was also true." That is, "[c]annabis raised the risk of schizophrenia both in people who already had higher than usual genetic odds of developing the disease"—the siblings of schizophrenics are the classic example—"and those at normal risk."[166]

The response to his book, by and large, was scathing, if not condemnatory.[167] Critics said that Berenson posited that anyone who experiments with cannabis will immediately and permanently become a Mr. Hyde– or Hannibal Lecter–like homicidal maniac (which Berenson disavowed saying). Reviewers largely derided his cautionary description of a serious drug policy-criminal justice problem as if he had done precisely what he eschewed doing.

That approach does not represent the views of scientific professionals today. Recent studies have concluded that there is a need to reconsider the relationship between cannabis use or abuse and violence, whether toward third-party strangers or intimate partners. The relationship between the two is uncertain. Several studies, many published only in the past decade, have disagreed over the issue whether there is even an association (not a cause-effect relationship) between cannabis use and violence. There also appears to be a widespread agreement, however, that the subject needs further investigation.[168] When that is done, Berenson's critics ultimately might be able to say "I told you so"—or they might owe him an apology. Only time will tell.

Cannabis Has Not Been Proven to Be "Effective"

Is cannabis an effective treatment for some diseases or injuries? An argument in favor of legalizing medical-use cannabis is that it, or certain cannabinoids, treat the sequalae of various diseases, particularly non-cancer or neuropathic pain. There is a considerable body of literature making that claim.[169] A goodly number of physicians have published books or articles endorsing that position.[170] And a considerable number of individuals attest to its beneficial effects.[171]

Even when considered as an analgesic, however, let alone as a treatment for disease, cannabis is not an "effective" drug simply because a large number of people would describe its euphoric feeling as "Awesome!" Rigorous scientific proof is essential. To establish a drug's effectiveness, a

drug's sponsor must offer "substantial evidence" of the drug's efficacy at treating the cause or sequalae of a certain disease or injury, which must be in the form of "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."[172] Neighborhood "budtenders" do not qualify.

The people who do—the experts at the federal agencies devoted to public health—have consistently found that raw cannabis is not an effective medical treatment. The FDA,[173] the Office of the U.S. Surgeon General,[174] the National Institute on Drug Abuse,[175] the Substance Abuse and Mental Health Services Administration,[176] and the Department of Health and Human Services (HHS)[177]—those agencies have consistently found that botanical cannabis has not been proven to be a safe and effective drug. Even the Biden Administration reiterated that conclusion in a letter it sent to Congress in April 2022.[178]

In a 2017 report entitled *The Health Effects of Cannabis and Cannabinoids*, the National Academy found that, among other things, there is substantial evidence that cannabis can alleviate *chronic pain* (pain lasting beyond three months) *of moderate severity*.[179] (Aside from the general limitations of smokable cannabis as a medicine and studies about its potential analgesic effect,[180] cannabis is insufficiently potent to substitute for opioids as the analgesic of choice for *acute* or *severe pain* stemming from motor vehicle crashes, surgery, gunshot wounds, terminal cancer, or other causes.[181]) There are, however, multiple problems with treating raw cannabis as an analgesic for chronic moderate pain.[182] Plus, several post-2017 studies and reports challenge the National Academy's belief that raw cannabis is an effective treatment for people who suffer from chronic pain.[183] Finally, the National Academy did not distinguish the analgesic effect of cannabis from that of alcohol, and the latter, as noted above, is not a legitimate therapeutic drug.[184]

Cannabis Is Not a Uniformly Made Product

Proof that a drug is safe for use and effective at treating a disease or its symptoms or sequalae is not all that a pharmaceutical company must establish. A sponsor must also establish that the drug is pure to enable physicians to prescribe medications with confidence that their patients will receive the same therapeutical benefits from every pill or injectable solution in every batch. To prove that its drug is pure and uniform, a sponsor must establish that it follows good manufacturing practices.[185] Here, again, raw cannabis falls short.[186]

The Varying Features of Raw Cannabis. Commercially manufactured prescription and over-the-counter medicines contain "pure and stable" chemicals, which enables the FDA and physicians to know "precisely what their patients are taking."[187] Batch testing ensures that the amoxicillin, amantadine, amphotericin, and azacytidine manufactured today are the same as the ones produced yesterday and will be synthesized tomorrow. "The quality, safety, and efficacy of starting materials are basic prerequisites in the pharmaceutical industry,"[188] and "[t]he pharmaceutical industry requires consistency in the active ingredients of source material."[189] Consistency is not just a virtue; it is a legal requirement.

One that cannabis cannot meet. As two experts have noted:

> Though some herbal remedies do appear to be safe and effective, the opposite is closer to the truth. Cannabis is a good example. The number of parameters on which cannabis can vary is enormous from strain, growing conditions, harvesting methods and handling to storage and processing of the raw material to combining them with a wide variety of foods and other excipients in manufacturing to methods of administration (eating, smoking, "vaping," applying to mucous membranes). At every step, from planting through consumption, myriad influences can alter dose, absorption rate, interactions among constituents, exposure to toxins, and a host of other factors that can result in underdosing, overdosing and various types and levels of acute and chronic poisoning, not excepting an increase in the probability of lung cancer.[190]

Variance in Content. To start with, unlike the series of drugs noted above, which are produced by reputable pharmaceutical companies, cannabis, like other botanicals, is not a "standardized good." That is, cannabis is not a single chemical compound or a product with precise and uniform ingredients, formulations, and potency in every batch.[191] In fact, "[t]he number of species in the *Cannabis* genus has long been controversial."[192] Some believe that there is but one, highly polymorphic species (called *Cannabis sativa L.*); some believe that there are three species (*Cannabis sativa L.*, *Cannabis indicia*, and *Cannabis ruderalis*), with the first two of primary interest; while others see cannabis as polytypic (having many species and subspecies).[193] Moreover, due to selective breeding—initially done to increase fiber content for use as hemp, but now done to increase THC content for a bigger "kick"—cannabis comes in "hundreds of strains" with different chemical compositions.[194]

Even within each species, seeds differ between and among wild and cultivated versions of the plant.[195] Because of factors like "genetics, environment,

growth conditions, and harvesting stage,"[196] the cannabis plant itself is "a chemically complex and highly variable" product[197]—said more colorfully, "a complex chemical slush"[198]—containing hundreds of different chemicals.[199] The variety is "enormous."[200] Because of selective breeding and cross-breeding, there are hundreds of strains of cannabis, with different chemical compositions. The chemical composition of a cannabis plant can vary along a host of parameters: strain, growing conditions, harvesting methods, handling, storage, and processing of the raw material; its use in a wide variety of foods or liquids; the addition of different excipients via nonpsychoactive components of, for example, a brownie; manufacturing process; and method of administration (ingestion, inhalation, application to mucous membranes, or "vaping").[201] The amount of different macronutrients (carbohydrates, fats, and proteins) matters.[202] The stress on a plant also can affect its content. "[A]ny kind of stress tends to increase product potency somewhat, though usually at the cost of decreasing the total yield."[203]

Moreover, a cannabis plant from a particular strain still is not a single chemical compound or a product with precise and uniform ingredients, formulations, and potency. The chemical composition of a cannabis product sold at a dispensary can vary along a host of parameters, such as breeding, region, cultivation conditions, harvesting stage, storage time, and the like.[204] That difference can matter to patients. As two pro-cannabis physicians have noted, "the cannabinoid production varies from plant to plant, and ten drops of one batch might be therapeutic, but ten drops of the next batch might have a much higher content of THC and sicken the patient."[205] The lack of certainty and uniformity in the chemical make-up of different varieties of cannabis is a critical shortcoming under the standards demanded by contemporary medicine and law because neither the FDA nor a treating physician could know precisely what substances a patient would use.[206]

The ways in which individuals use cannabis also vary. Cannabis and its products are sold as the botanical flower (and its components), hash, hash oil, ointments, and edibles, whether solid (e.g., brownies or "Gummy Bear" look-alikes) or liquid (e.g., soft drinks or sauces). Those forms vary in their composition and potency.[207] THC exists in assorted formulations for different methods of use: inhalation, ingestion, sublingual, intranasal, transdermal, and sublingual or rectal transference.[208] Those differences matter.[209] For example, THC reaches the brain far more quickly (and in a greater quantity) when a user inhales it rather than ingests or absorbs it, which explains why many users prefer to smoke a doobie rather than consume THC as a pill, in food, or in another manner.[210] "Dabbing"—heating a cannabis extract and inhaling the

fumes—also generates effects perceived as stronger and longer lasting than smoking.[211] Moreover, many users titrate the amount inhaled to achieve their desired state of euphoria.[212]

Accordingly, there is no standard number of occasions when someone will smoke marijuana, no standard number of total inhalations, and no standard depth or length of any one inhalation. The foregoing likely explains why major medical entities—such as the American Medical Association, the U.S. National Institutes of Health, and the Royal College of Physicians—recommend research into non-smoking cannabis delivery systems and why the FDA has never approved any drug in a smokable form.[213]

Variance in THC Potency. There is considerable variation in the psychoactive component of cannabis—delta^9-tetrahydrocannabinol, or THC.[214] A variety of factors affects the THC content of a particular batch of cannabis, such as interplant differences, the part of a particular plant used (flowers contain more THC than stems), the environment in which cannabis is grown, the plant's age, the season of the year, and so forth.[215] Potency has increased markedly over the past decades due to considerations such as the strain, region, cultivation processes, processing stage, storage time, and other considerations.[216] The THC component of cannabis has increased remarkably over time as growers have sought to enhance their profits by creating a better, more attractive, psychotropic product. Cannabis had a THC content of no more than 3 percent to 4 percent from the 1960s through the 1980s. Today, the THC content can be 12 percent to 20 percent in the plant form or in hashish (dried cannabis resin and crushed plants). As one report concluded, "Due to the wide range of approaches to cannabis resin production (including the cannabis plant material used and the method of extraction), THC concentrations can vary widely, from <1% to 30%."[217] Hash oil, an oil-based extract of hashish, has a greater THC content, in the range of 15 percent to 65 percent, while other extracts can have a 90-plus percent THC content.[218] The range of THC in cannabis products makes it difficult for a physician to know exactly how much of that compound will reach a patient.[219]

Those differences are important. As Dr. Volkow has noted, "increase in THC content raises concerns that the consequences of marijuana use may be worse now than in the past."[220] If "[t]he average person will get quite stoned on marijuana containing 1.1% THC,"[221] use of 90-plus percent THC might have a logarithmically greater effect on a user, particularly one who is inexperienced or does not limit his or her intake.[222] That is why Dr. Volkow has questioned "the current relevance" of findings in now-dated studies on cannabis' effects, especially ones that assessed long-term outcomes.[223]

In addition, higher-content THC cannabis might adversely affect some people, but not others. As this author has written before:

> The potential toxicity of a drug is an essential feature of the early stages of a drug trial because no drug can be deemed safe if the minimum lethal dose and the potential adverse long-term effects are unknown. Concern with toxicity remains a critical issue throughout the remaining phases of a pharmaceutical trial. A drug that materially reduces the size of tumors is not safe if it is toxic to the liver and kidneys. A drug that provides short-term relief from respiratory distress is not safe if it causes long-term heart failure in everyone who uses it. Yes, there are tradeoffs involved in treatment. Some patients suffering from a fatal, incurable disease might be willing to sacrifice the quality of their remaining days for a larger number of them (or vice versa). But a physician cannot responsibly offer a patient a legitimate choice if there are no known data indicating what the short-term and long-term effects of a potent drug might be. As for cannabis sold for recreational use, where no physician is involved and the only advice comes from a financially self-interested "ganjapreneur" or "budtender," the consumer cannot expect to receive a neutral, disinterested product analysis or recommendation for use.[224]

Moreover, the psychoactive effect of THC varies according to an individual's "set" (user expectation) and the "setting" (environment) in which the use occurs.[225] Given their variance from person to person and occasion to occasion, a physician could not be confident when predicting the effect of THC use on an individual patient. The result is that neither the FDA nor a recommending physician would know the potency of the cannabis that a patient would use or the setting in which use would take place, leaving the agency and treating physician in the dark about its use.

Variance in CBD Potency. Another common cannabinoid besides THC is cannabidiol, or CBD. We are still learning about the potential psychodynamic properties of CBD, but what we know is encouraging. CBD has no known toxicities, and it does not appear to produce an effect that is euphoric, intoxicating, cognition-impairing, addictive, or psychosis precipitating. In fact, because CBD and THC might have possibly antagonistic pharmacological effects, CBD might serve to offset or moderate potential adverse results from using THC, such as anxiety, cognitive impairment, amotivational syndrome, dependence or addiction, and psychosis.[226] Unfortunately, growers, seeking to create a product offering the ultimate "rush," have increased the level of THC in their products and have reduced the CBD level over the past two decades, from a THC:CBD ratio of 2:1 to a ratio of 80:1 or higher.[227]

The result is that different stores, or even the same one, might sell cannabis with different potencies even if the THC content of all its products were the same.[228]

Variances in Cultivation, Collection, and Manufacturing Practices. Good manufacturing practices are critical to ensure uniformity in any drug or drug product.[229] The cannabis industry is no exception.

As Brian Thomas and Mahmoud ElSohly explained in their book *The Analytical Chemistry of Cannabis*, the need for good practices begins at the start of the cannabis plant life cycle. Growers should specify and rigorously control the seeds or clones used, and they should scrupulously record the conditions of their planting, growth, and harvesting in "a detailed protocol or batch production record."[230] Important for growers of cannabis for medical use is "the use of hygienic procedures to minimize microbial load," such as bacteria or fungi.[231] "Good manufacturing practices" are also "a critical activity" because "quality control" is "required to ensure the suitability of medicinal products."[232] The FDA and World Health Organization both have guidelines for good growing or manufacturing practices to be followed in the creation of herbal medicines.[233]

Good laboratory testing practices are equally important because laboratories are where a traditional drug is manufactured and where a cannabis plant is turned into a product.[234] The FDA also has several guidelines for what is known as "release testing,"[235] the validation of pre- and post-formulation analytical testing methods to measure factors such as drug purity[236] and stability;[237] degradation; clarity; pH; variance in content, weight, and volume; and container-seal efficacy.[238] Good cultivation and manufacturing practices, along with recommended pre- and post-formulation testing, helps to ensure that tomorrow's product will be just as useful as yesterday's and today's. Every business should use them to ensure that the public receives a pure, uniform, and stable drug.[239] Unfortunately, not all do.[240]

* * * * *

For all the foregoing reasons, neither the FDA nor a physician can know precisely what substances will be found in a particular grower's batch or a dispensary's stock of cannabis; how much THC and CBD someone would receive by smoking raw cannabis; or, given the different circumstances under which it might be used, how it will affect a specific patient. The FDA therefore could not approve the plant form of cannabis as a therapeutically useful drug. In fact, the presence of toxic substances would render a drug

adulterated and subject to administrative seizure by the FDA, as well as civil action or criminal prosecution by the U.S. Department of Justice for interstate distribution. And a physician could not know precisely how smoking cannabis would affect his or her patient.

Yes, the FDA has approved certain drugs produced by legitimate pharmaceutical companies from raw cannabis, and "[t]here are clearly several possible therapeutic indications for cannabis-based medicines."[241] Nonetheless, "for many of them the evidence for clinical effectiveness of the drug is still inadequate by modern standards."[242] As University of Pennsylvania Medical School Professor David Casarett succinctly put it, "A joint is hardly a medicine."[243] It has been said that ignorance is bliss, but it sure ain't where medicine is concerned.

Going Forward

What lessons can be learned from our experience with medical-use and recreational-use cannabis? There are several.

Proposition 1. The present state of American law and policy governing the importation, cultivation, distribution, and possession of cannabis, whether for medical or recreational use, is utterly incoherent. As Dr. Peter Grinspoon accurately and colorfully put it in his 2023 book *Seeing Through the Smoke*, "You don't have to be stoned to be dazed and confused by the current discord in our society around cannabis."[244] On that point, there is a consensus.

Proposition 2. Only Congress can remedy this problem. The states can revise their own drug laws to exempt whatever drugs they wish to legalize, because the Constitution does not require states to have a criminal code.[245] But states cannot nullify federal law, whether it be the CSA or the FDCA, and Congress cannot order state and local law police officers to enforce federal law.[246] The Supremacy Clause of Article VI makes federal law supreme as long as Congress has acted within its delegated authority,[247] with the consequence that state-law defenses to the prosecution of an alleged CSA or FDCA violation have no force and effect.[248] Here, too, there is no serious disagreement.

Proposition 3. Congress has not yet taken up the cross of resolving how federal law should treat cannabis. Knowing that they will make enemies however they vote, Members of Congress have pursued two paths. One is to pray (to keep my metaphors straight) that "this cup [will] pass from me,"[249] perhaps by hoping one or more federal agencies will resolve the issue. Last year, President Joe Biden, a fervent believer in the Progressive

theory of the superiority of expert administrative agency governance rather than congressional lawmaking, nudged two agencies down that path. In October 2022, he directed HHS Secretary Xavier Becerra and U.S. Attorney General Merrick Garland to reconsider the scheduling of cannabis.[250] The Attorney General possesses that authority under the CSA,[251] in consultation with the HHS Secretary, but none of Garland's predecessors has invoked it to reschedule cannabis. What he and Becerra will decide to do remains to be seen.

Proposition 4. The states' legalization of medical-use and recreational-use cannabis without examining or reexamining the potential harms from high-potency forms of that drug should be seen as the scandal that it is. In the rush to obtain a new source of revenue and to satisfy a vocal constituency clamoring for a substance that has (at best) only the same painkilling properties as bourbon, the states have chosen to disregard the 80-plus-year judgment that American society has made to forbid large-scale commercialization of a potentially dangerous drug until after it has been proved safe and effective by its sponsors. Maybe a few of those legislators thought that they were offering a respite from pain or other consequences of the maladies that the aged and ill can suffer. Nevertheless, even if "[c]aring without science is well intentioned kindness," it is "not medicine."[252] This author has previously written that the claim, made both by cannabis' sellers and physicians, that smoking a joint can cure what ails you "falls along the spectrum somewhere between risible and fraudulent."[253]

> Medical marijuana is a sham that we have been selling to minors over the last twenty-five years. It is bad enough for adults to lie to serve their own venal purposes. It is worse for adults to teach their children by example that lying is an appropriate way to get what one wants. It is worst of all to incorporate those lies into our law. Yet, that is what we have done throughout the period of state medical marijuana schemes. (Yes, I used the word "scheme" intentionally, with all of the nefarious connotations that it implies). Minors have grown up believing that smoking marijuana is not harmful for two reasons. One explanation is simple: they have parents, relatives, siblings, or friends who smoked marijuana and did not die. Even presidential candidates have used marijuana and not only lived to tell the tale but also won election (and re-election). The other reason is more complicated, but unfortunately, more pernicious. Minors know that the states allow it to be sold, that the federal government has two agencies—the FDA and the DEA—whose mission is to protect the public against the use of dangerous drugs, and that the federal government has not shut down state medical marijuana dispensaries on the ground that they are

> run by unscrupulous charlatans threatening the public health with their product. State legalization efforts have been free riding on the public's belief that, notwithstanding the oft-repeated statements by numerous federal agencies that the federal government has not approved marijuana for any legitimate therapeutic use, the federal government would not stand idly by while millions of people use a drug that could damage their health or well-being. So, minors use marijuana, and some will wind up doing so for a lengthy period, resulting for some in serious damage to their bodies, minds, careers, and lives. Dishonesty by adults leads to poor choices by some minors, which leads to poor lives for some soon-to-be adults. That is a serious adverse consequence of empowering the states, under the flag of federalism, to make nationwide scientific decisions about the safety of particular drugs.[254]

Proposition 5. If Congress decides to legalize cannabis, reliance on the expertise, judgment, and good faith of the FDA is critical. Unfortunately, much of the debate over the efficacy of medical cannabis, as well as its recreational sibling, has been biased for one side or the other. As Carnegie-Mellon University Professor Jonathan Caulkins, an expert on cannabis, wrote in 2016, "Unfortunately, there is very little in the way of intellectually honest marijuana policy analysis."[255] Congressional debates over cannabis are likely to break down into partisan yelling matches. Even the "Tastes Great! Less Filling!" squabbles during commercial breaks for professional football games would be more enlightening than what we can expect from Congress. What we need is the judgment of an impartial, unbiased, scientifically educated group devoted to protection of the public health.

That is why we need to turn to the FDA for its honest scientific judgment. For more than eight decades, this nation has trusted that agency to decide whether a particular substance is a drug and, if it is, whether, in whatever form that is offered to the public, with or without a physician's prescription, it is safe, effective, and uniform. The states that have legalized cannabis for medical use have simply thumbed their nose at the FDCA and taken the law into their own hands without even nodding towards the principle that only drugs with those characteristics should be sold to the public. Were Congress or Attorney General Garland to reclassify cannabis out of Schedule I so that a physician can legally prescribe it, the CSA would no longer forbid its distribution under all circumstances. The FDCA would remain in play, however, because Congress entrusted the FDA Commissioner, not the attorney general, with the responsibility to review new drugs for their safety, efficacy, and uniformity.[256]

Proposition 6. Ultimately, the issue should *not* be seen as whether there is scientific proof that cannabis use *causes* the harms discussed above, such as physical dependance or addiction, adverse psychosocial effects in minors, an increase in maimings and deaths caused by drug-impaired driving, and so forth. Instead, the issue should be whether the *risk* of adverse effects of legalizing cannabis use justifies approving its use as a safe, effective, and uniform medication.

For 80-plus years, the burden of proof on those issues has rested with a drug sponsor; it must satisfy the FDA that its drug can be approved. At present, the potential harms that smoking raw cannabis poses for various populations have not been shown to be insufficient to permit its approval. Nor has it been shown to potentially save lives despite its adverse effects, as would be the question in the case of drugs used for cancer chemotherapy. The question is how much risk American society is willing to accept in this regard, not whether there is some potential benefit and no downside. As several scholars have explained:

> The shift and change in the legal and illegal cannabis market, particularly in relation to high potency cannabis and its potential risks, have not been reflected in the public discourse around the harms of cannabis. From a research perspective, the epidemiological, experimental, and genetic evidence has resulted in a clear shift in the argument from 'whether there is a causal relationship between cannabis and psychosis' to the magnitude of the relationship. The potential harms of high potency cannabis use, especially during development and particularly in those with a family history of psychosis, need to be clearly explained to the public to address the imbalance in the narrative that cannabis is a harmless drug. The decisions about what to do with that information is then for both the public and policymakers to consider."[257]

Proposition 7. On a subject where we most need the dispassionate, science-based judgment of FDA officials, there is a serious question whether the FDA would be allowed to offer a purely medical and scientific judgment on the safety, efficacy, and uniformity of cannabis, rather than be told what to find by senior political appointees or even the President. A drug's proponents bear the burden of proving safety, effectiveness, and uniformity, and in many instances much of the relevant science is unknown or what is known is inconclusive.[258] To date, what we know demonstrates that the FDA could not approve smoking cannabis as a treatment for any medical condition.

Ordinarily, that would end the discussion. At one time, Presidents did not distort or coopt science for their own partisan political purposes, and

scientists did not play partisan politics for their own personal advancement. Sadly, that day is now in the rearview mirror. Politics has infected medicine, science, and law. A recent series of Supreme Court decisions[259] makes it clear that the Biden Administration has no respect for rules of law that it does not like, particularly when those rules keep the President from satisfying his base or establishing his legacy. To achieve those ends, the Administration is not reluctant to claim that science supports its actions, regardless of what the science might actually be.[260] *Fiat politica, ruat caelum*.[261]

We can hope that career FDA officials would not give in to politics, but there is no certainty of that. Even if they do, however, theirs is not the last word on this subject, and recent evidence strongly suggests that theirs will not be the last word unless it is what the Biden Administration wants to hear.[262] Xavier Becerra, Secretary of Health and Human Services, has authority over the FDA Commissioner, and he, a lawyer and former Member of Congress, is neither a physician nor a scientist. Plus, President Joe Biden has the final say, and he, too, has no scientific education, training, or experience. Leaving science-based judgments in the hands of politicians trolling for votes is not a promising way to proceed.

Conclusion

The possibility that cannabinoids might serve as a legitimate therapeutic treatment for the ill or injured justifies research into their potentially therapeutic value. But the raw, agricultural form of cannabis is not capable of being approved for use by the FDA, regardless of whether Congress or the U.S. Attorney General reschedules it downward from Schedule I. Rescheduling cannabis out of Schedule I would not allow the drug to be distributed under federal law unless the FDA finds that it is a safe, effective, and uniform drug.

As explained above, the FDA could not do so under existing law, for a host of reasons that make eminent public health sense, and the Attorney General cannot waive the FDCA's requirements. Congress could do so by statute, but any such law would put at risk the health of users and nonusers. Whether society embraces or rejects the Millsian dislike of state-made paternalistic judgments ostensibly done for the betterment of individuals, there is no good reason to abandon the approach that the nation adopted 80-plus years ago when the FDCA became law or to force on unwilling third parties the risk of injury or death to satisfy the desires of a minority for a transient high.

Endnotes

1. Thomas R. Arkell et al., *Assessment of Medical Cannabis and Health-Related Quality of Life*, 6 JAMA Network Open 2312522, May 9, 2019, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2804653. Australia legalized medical-use cannabis in 2016. *Id*. at 2.
2. *Id*. at 1; *see id*. at 11.
3. The authors say that subjective reports are the best available evidence. *See id*. at 2 ("The term *medical cannabis* encompasses a vast array of products ([e.g.], dried flower, oils, edibles) containing multiple bioactive constituents including, but not limited to, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Because patients are using these products to manage such a wide range of health conditions—in addition to the paucity of evidence from randomized clinical trials—clinical evidence incorporating patient-reported outcomes is becoming increasingly recognized as a vital source of safety and efficacy data. Validated health-related quality of life measures can help provide important, global insights into associations between medical cannabis treatment and daily functioning, physical mobility, and mental health among patients with various and disparate conditions.") (footnotes omitted). That might be the case, but "global insights" regarding "associations" between "medical cannabis treatment" and life's activities—however "important" such insights might be for sociological studies—are not the same type of rigorous testing and proof that federal law requires before a drug may be distributed via interstate commerce. *See infra* text accompanying notes 39–58.
4. Pub. L. No. 75–717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301–392 (2018)).
5. With certain exceptions for "dietary supplements," a "drug" is defined as "(A) articles recognized in the official United States Pharmacopœia, official Homeopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." 21 U.S.C. § 321(g)(1).
6. *See* 21 U.S.C. § 393(d)(1)(2).
7. Technically, the FDCA only limits the distribution of any "new drug," which the act defines as follows: 21 U.S.C. ¶ 321(p) ("The term 'new drug means—(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or (2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."). Despite having existed as an agricultural product for thousands of years, cannabis is a new drug under that definition, as the FDA has found. *See, e.g., Cannabis Policies for the New Decade: Hearing Before the House Commerce Comm. Subcomm. on Health*, 116th Cong. 1–4 (2020) [hereinafter *House Cannabis Hearing*] (statement of Douglas C. Throckmorton, Dep. Dir. For Reg'y Programs, U.S. Food & Drug Adm'n), https://docs.house.gov/meetings/IF/IF14/20200115/110381/HHRG-116-IF14-Wstate-ThrockmortonD-20200115.pdf [https://perma.cc/Y2PF-X36D]; Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency's regulation of products containing cannabis and cannabis-derived compounds (Dec. 20, 2018), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-signing-agriculture-improvement-act-and-agencys [https://perma.cc/RP9Y-CBDP]; Warning Letters and Test Results for Cannabidiol-Related Products: 2015–2019 (Nov. 26, 2019; last accessed Jan. 14, 2020), https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products [https://perma.cc/55EV-KMLC] (warning letters issued to companies selling unapproved new drugs containing cannabidiol, a non-psychoactive substance in marijuana that the FDA has not approved for use in any drug for any purpose).
8. There is another relevant statute not discussed in this *Special Report*. The Marihuana Tax Act of 1937, ch. 553, 50 Stat. 551 (1937) (repealed 1970), effectively outlawed the sale of cannabis, although it did not literally do so. *See* Paul J. Larkin, Jr., *Reconsidering Federal Marijuana Regulation*, 18 Oh. St. J. Crim. L. 99, 101–02 (2020) [hereafter Larkin, *Reconsidering Marijuana*]. Congress made that prohibition clear in Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91–513, 84 Stat. 1242 (codified as amended at 21 U.S.C. §§ 801–904 (2018)), known as the Controlled Substances Act of 1970 (CSA). The CSA incorporated the FDCA's definition of a "drug" and placed all drugs then known into one of five "schedules" based on their utility, danger, and substitutability. The act placed cannabis in Schedule I, the category of drugs that cannot be used for any purpose. Congress authorized the U.S. Attorney General to reclassify marijuana if, after consulting with the Secretary of Health and Human Services, he found it appropriate. 28 U.S.C. § 811(a)–(c) (2018). (In turn, the Attorney General has delegated that authority to the Administrator of Drug Enforcement, 21 C.F.R. § 0.100(b) (2018)). No attorney general has done so. *See* 21 C.F.R. § 1308.11(d)(31) (2022), and the Biden Administration reaffirmed that decision in 2022. *See* Letter from Peter Hyun, Acting Ass't Att'y Gen'l, to Senators Elizabeth Warren & Cory A. Booker (Apr. 12, 2022) (rejecting the Senators' request to move cannabis out of Schedule I; "Cannabis is a Schedule I controlled substance under the Controlled Substances Act (CSA). This is—in part—due to HHS's determination that cannabis has not been proven in scientific studies to be a safe and effective treatment for any disease or condition."). Attorney General Merrick Garland, however, is reconsidering the subject.
9. *See* Brian T. Allen, *The Emperor of American Chocolate*, Nat'l Rev., July 8, 2023, https://www.nationalreview.com/2023/07/the-emperor-of-american-chocolate/.

10. Arkell et al., *supra* note 1, at 11 ("This study suggests a favorable association between medical cannabis treatment and quality of life among patients with a diverse range of conditions. However, clinical evidence for cannabinoid efficacy remains limited, and further high-quality trials are required. While we cannot exclude the possibility that adverse events may have been caused in whole or part by the disease state and concomitant medications, the relatively high incidence of adverse events still affirms the need for caution with THC prescribing and careful identification of patients with contraindications.").
11. *Id*. at 10 ("This study is limited by the use of a retrospective case series design without a control, which restricts what conclusions can be drawn around treatment efficacy, and limits generalizability to other clinical populations.... Furthermore, patients were not required to complete the questionnaires described here, and so these data may be biased upwards if patients experiencing a positive effect of medical cannabis were more likely to respond. Finally, the clinical care model used by Emerald Clinics may have also contributed to perceived improvements in quality of life.").
12. *Id*. at 2.
13. *Id*.
14. *Id*. at 1.
15. *Id*. at 4 ("Most of these prescriptions were for orally administered products including oils (n = 14 779 [90.1%]) and capsules (n = 631 [3.8%]). There were only a small number of prescriptions for dried flower for inhalation either alone (n = 244 [1.5%]) or in combination with an oil (n = 168 [1.0%]).").
16. *Id*. at 5 tbl. 1.
17. *Id*. at 4 ("Chronic non-cancer pain was the most common indication for treatment (68.6% [2160 of 3148]), followed by cancer pain (6.0% [190 of 3148]), insomnia (4.8% [152 of 3148]), and anxiety (4.2% [132 of 3148]).", 8 ("Commensurate with the Therapeutic Goods Administration data reflecting broader prescription patterns across Australia, chronic noncancer pain was by far the most common primary diagnosis in this sample population (n = 2160), followed by cancer pain (n = 190), insomnia (n = 152), and anxiety (n = 132).") ("As might be expected given the high incidence of pain conditions, almost half of all patients were using simple and/or opioid analgesics at baseline.").
18. Peter B. Bach, *If Weed Is Medicine, So Is Budweiser*, Wall St. J. (Jan. 17, 2019, 7:23 PM), https://www.wsj.com/articles/if-weed-is-medicine-so-is-budweiser-11547770981 [https://perma.cc/9HDG-JR8E].
19. Arkell et al., *supra* note 1, at 6–7 ("Effect sizes were small-moderate in magnitude, ranging from 0.21 to 0.72. For all domains except for physical functioning and role-physical, balanced products were associated with marginally greater improvements than either CBD-dominant or THC-dominant products. CBD-dominant products were associated with largest improvements on the role-physical domain, while THC-dominant products were associated with largest improvements on the physical functioning domain.").
20. *Id*. at 7 ("A total of 2919 adverse events were reported over the sampling period (eTable 10 in Supplement 1). Most were either mild (n = 1905) or moderate (n = 922); 86 were severe. Two adverse events were considered serious, including 1 incidence of hallucination. In order of frequency, adverse events included sedation and/or sleepiness (13.1% of patients), dry mouth (11.4%), lethargy and/or tiredness (7.4%), dizziness (7.1%), difficulty concentrating (6.4%), nausea (6.3%), diarrhea and/or loose stools (4.9%), feeling high (4.7%), increased appetite (3.7%), headache (3.2%), anxiety and/or panic attack (2.7%), vivid dreams (1.7%), hallucination (1.4%), and impaired coordination (1.3%). The incidence of adverse events did not differ significantly across cannabinoid composition categories.").
21. No physician can "prescribe" cannabis as the treatment for any medical illness, disorder, or problem of any type because federal law makes cannabis contraband, thereby outlawing it for any purpose, medical or recreational. 21 U.S.C. § 812 (2018). Any physician violating that ban can suffer a loss of his medical license, conviction, and imprisonment. *See* Ruan v. United States, 142 S. Ct. 2370 (2022); United States v. Moore, 423 U.S. 77 (1975). A physician or caregiver, however, can "recommend" that a patient consider using marijuana to relieve the symptoms of certain disabling diseases even if the possession or use of marijuana is a crime. The First Amendment Free Speech Clause prohibits the government from adopting a viewpoint-based restriction on the private communications between a physician and a patient of potential medical treatment options. *See* Conant v. McCaffrey, 172 F.R.D. 681, 694–95 (N.D. Cal. 1997) (issuing preliminary injunction), 2000 WL 1281174 (N.D. Cal. Sept. 7, 2002) (issuing permanent injunction), *aff'd*, Conant v. Walters, 309 F.3d 629 (9th Cir. 2002) (upholding permanent injunction). If the reader thinks that the difference between "prescribing" and "recommending" a drug that can be purchased nationwide is like the difference between dusk and twilight, you are not alone.
22. Chris Roberts, *Anyone Can Get Their Medicine: California Has Already Pretty Much Legalized Marijuana. And That's Okay*, SFWeekly (Sept. 14, 2014) https://web.archive.org/web/20221012064704/https://archives.sfweekly.com/sanfrancisco/chem-tales-marijuana-legalization-recreational-use/Content?oid=3154256 ("Anyone Can Get Their Medicine. Not long ago, a friend of mine visited the doctor. Afterward, I asked him for the diagnosis. 'Good news,' he said with a grin. 'I'm still sick.' A clean bill of health would have been a setback. That would mean no more marijuana. I am often asked how to legally obtain some weed in San Francisco; what ailment is required to get a medical marijuana recommendation. This fascinates people to this day, out-of-towners as well as locals. When I am honest, I say, 'About $40 and 10 minutes.'").
23. *See* Linder v. United States, 268 U.S. 5, 18 (1925) (noting that "direct control of medical practice in the States is beyond the power of the Federal Government."); Dent v. West Virginia, 129 U.S. 114 (1889) (upholding over a federal constitutional challenge a state-law licensing requirement to practice medicine); Paul J. Larkin, Jr., *Public Choice Theory and Occupational Licensing*, 39 Harv. J.L. & Pub. Pol'y 209, 278–79 & nn.322–32 (2016) (collecting cases upholding state regulation of the practice of medicine in its various forms); Patricia J. Zettler, *Pharmaceutical Federalism*, 92 Ind. L.J. 845, 849 (2017) (noting the long-standing consensus that the states regulate "medical *practice*"—the in-person, hands-on work of physicians and other health care professionals with their patients—while the federal government regulates the distribution of "medical *products*, including drugs.") (footnote omitted).

24. The term "new drug" means: "(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or [¶] (2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions." 21 U.S.C. § 321(p)(1) & (2); 21 C.F.R. § 310.3(h) (2021). The FDA has consistently affirmed that cannabis is subject to regulation under the FDCA and that it is not a safe, effective, and pure drug for purposes of that law. *See*, *e.g.*, *FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)*, FDA (Oct. 1, 2020), https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd [https://perma.cc/TF56-2GRQ]; *What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-Derived Compounds, Including CBD*, FDA (Mar. 5, 2020), https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis [https://perma.cc/7HGY-KAZ4]; U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, *FDA and Cannabis: Research and Drug Approval Process*, FDA (Feb. 23, 2023) https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process [https://perma.cc/L2QP- YETU].

25. *See infra* notes 33–53.

26. *See*, *e.g.*, Comm. on the Health Effects of Marijuana, Nat'l Acad. of Sci., Eng'g, & Med., The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research 53–54 (2017) [hereinafter Nat'l Acad. Rep.] (listing potential benefits of cannabis use); David Bearman & Maria Pettinato, Cannabis Medicine: A Guide to the Practice of Cannabinoid Medicine (2019); David Casarett, Stoned: A Doctor's Case for Medical Marijuana (2015); Patricia C. Frye & David Smitherman, The Medical Marijuana Guide: Cannabis and Your Health (2018); Bonni Goldstein, Cannabis Revealed: How The World's Most Misunderstood Plant Is Healing Everything From Chronic Pain to Epilepsy (2016); Peter Grinspoon, Seeing Through the Smoke: A Cannabis Specialist Untangles the Truth about Marijuana (2023); Lester Grinspoon & James B. Bakalar, Marihuana: The Forbidden Medicine (1997); Michael H. Moskowitz, Medical Cannabis: A Guide for Patients, Practitioners, and Caregivers (2017); Matthew Roman, The Clinician's Guide to Medical Cannabis (2020); Dustin Sulak, Handbook of Cannabis for Clinicians: Principles and Practices (2021); J. Michael Bostwick, *Clinical Decisions: Medicinal Use of Marijuana—Recommend the Medical Use of Marijuana*, 368 New Eng. J. Med. 866 (2013); Jerome P. Kassirer, *Federal Foolishness and Marijuana*, 336 New Eng. J. Med. 366 (1997).

27. *See*, *e.g.*, Robert L. DuPont, The Selfish Brain: Learning from Addiction 147–54 (2019 ed. 1997); Ed Gogek, Marijuana Debunked: A Handbook for Parents, Pundits and Politicians Who Want to Know the Case Against Legalization (2015); Kevin P. Hill, Marijuana: The Unbiased Truth about the World's Most Popular Weed (2015); Gary M. Reisfield & Robert L. DuPont, *Clinical Decisions: Medicinal Use of Marijuana—Recommend Against the Medical Use of Marijuana*, 368 New Eng. J. Med. 866, 868 (2013); *see also* Bertha K. Madras, *Update of Cannabis and Its Medical Use* (2015), https://perma.cc/SA4P-SRA6 (commissioned monograph to 37th Expert Committee on Drug Dependence, World Health Organization).

28. *See, e.g.*, Archie Bleyer & Brian Barnes, *Opioid Death Rate Acceleration in Jurisdictions Legalizing Marijuana Use*, 178 JAMA Internal Med. 1280, 1280 (2018); Wilson M. Compton et al., *Medical Marijuana Laws and Cannabis Use: Intersections of Health and Policy*, 74 JAMA Psychiatry 559, 559 (2017); Wayne Hall et al., *Public Health Implications of Legalising the Production and Sale of Cannabis for Medicinal and Recreational Use*, 394 Lancet 1580 (2019); Janni Leung et al., *What Have Been the Public Health Impacts of Cannabis Legalisation in the USA? A Review of Evidence on Adverse and Beneficial Effects*, 6 Curr. Addiction Rep. 418 (2019).

29. 21 U.S.C. §§ 841, 843 & 844 (2018). For a discussion of the early history of marijuana and its federal regulation, as well as the more recent state efforts to legalize under state law the medical and recreational use of cannabis, *see*, for example, Bruce Barcott, Weed the People: The Future of Legal Marijuana in America (2015); Richard J. Bonnie & Charles H. Whitebread II, The Marijuana Conviction: A History of Marijuana Prohibition in the United States (Lindesmith Ctr. 1999) (1974); Martin Booth, Cannabis: A History (2005); Emily Dufton, Grass Roots: The Rise and Fall and Rise of Marijuana in America (2017); John Kaplan, Marijuana: The New Prohibition (1970); John F. Galliher & Allyn Walker, *The Puzzle of the Social Origins of the Marihuana Tax Act of 1937*, 24 Soc. Probs. 367 (1977). For a more recent treatment of that drug, see Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: The Troubling Potency of Twenty-First Century Cannabis*, Heritage Found. Legal Memo. No. 133 (2022) [hereafter Larkin, *Twenty-First Century Cannabis Potency*].

30. Cannabis may be cultivated and distributed for legitimate scientific research into its potential therapeutic benefits. *See* U.S. Dep't of Justice, Off. of Legal Counsel, *Licensing Marijuana Cultivation in Compliance with the Single Convention on Narcotic Drugs* (June 6, 2018); U.S. Dep't of Justice, Drug Enforcement Admin., *Controls to Enhance the Cultivation of Marihuana for Research in the United States*, 85 Fed. Reg. 82,333 (Dec. 18, 2020). Critics have often argued that the FDA cannot approve cannabis as a legitimate drug without proof of its potentially beneficial uses, and no one can conduct the necessary research because the DEA has been reluctant to grant such applications. Whatever might have been true in the 1970s, that argument is unpersuasive today. In the second decade of this century, "there was a 149 percent increase in the number of active researchers registered with DEA to perform bona fide research with marihuana, marihuana extracts, and marihuana derivatives (from 237 in November 2014 to 589 in June 2020)." 85 Fed. Reg. at 82,336. As of December 2020, "more researchers are registered to conduct research in the United States on marihuana, marihuana extracts, and marihuana derivatives than on any other schedule I substance." *Id*. Atop that, late in 2022 Congress passed, and President Joe Biden signed, the Medical Marijuana and Cannabidiol Research Expansion Act, Pub. L. No. 117, 215, 136 Stat. 2257 (2022). That legislation should also increase the amount of authorized research.

31. 21 U.S.C. § 201(g)(1) (2018).

32. The FDCA applies only to drugs that have travelled "in" interstate commerce. *See* 21 U.S.C. §§ 321(b), 331 (2018). That element would be satisfied, however, if cannabis, an ingredient, or a cannabis product has travelled in interstate commerce at any time. *See, e.g.*, United States v. Regenerative Scis., LLC, 741 F.3d 1314, 1320–21, 1326 (D.C. Cir. 2014); Baker v. United States, 932 F.2d 813 (9th Cir. 1991); United States v. Dianovin Pharm., Inc., 475 F.2d 100, 102–03 (1st Cir. 1973); United States v. Detroit Vital Foods, Inc., 330 F.2d 78, 82 (6th Cir. 1964); United States v. Premo Pharm. Labs., Inc., 511 F. Supp. 958, 977 n.23 (D.N.J. 1981); *cf*. Scarborough v. United States, 431 U.S. 563 (1977) (applying that analysis in the case of the interstate shipment of a firearm).

33. *See* 21 U.S.C. § 331(a)–(c) (2018) ("The following acts and the causing thereof are prohibited: (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded. (b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce. (c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.").

34. With certain exceptions for "dietary supplements," a "drug" is defined as "(A) articles recognized in the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." 21 U.S.C. § 321(g)(1). A drug contains active ingredients (components that address a medical problem) and inactive ingredients (called "excipients"). Lawrence T. Friedhoff, New Drugs 2–3 (2009). Any application seeking approval of a new drug must include, *inter alia*, summaries of the drug's biochemical processes, biopharmaceutics (results of the blood levels produced by different batches of the drug), the drug's clinical pharmacology, and the clinical efficacy studies. *Id*. at 97–98.

35. *See* 21 U.S.C. § 393(d)(1)(2) ("(1) Appointment [¶] There shall be in the Administration a Commissioner of Food and Drugs (hereinafter in this section referred to as the 'Commissioner') who shall be appointed by the President by and with the advice and consent of the Senate. [¶] (2) General powers [¶] The Secretary, through the Commissioner, shall be responsible for executing this chapter and for—(A) providing overall direction to the Food and Drug Administration and establishing and implementing general policies respecting the management and operation of programs and activities of the Food and Drug Administration; [¶] (B) coordinating and overseeing the operation of all administrative entities within the Administration; [¶] (C) research relating to foods, drugs, cosmetics, devices, and tobacco products in carrying out this chapter; [¶] (D) conducting educational and public information programs relating to the responsibilities of the Food and Drug Administration; and [¶] (E) performing such other functions as the Secretary may prescribe.").

36. *See* 21 U.S.C. § 331(a)–(c) (quoted at *supra* note 33); 21 U.S.C. § 355(a); *see* Mut. Pharm., Inc. v. Bartlett, 570 U.S. 472, 476 (2013).

37. *See* 21 U.S.C. § 332 (authorizing injunctive relief); *id*. § 333 (same, criminal and civil penalties); *id*. § 334(a)(1) (authorizing judicial seizure); *id*. § 334(g)–(h) (authorizing administrative detention of adulterated and misbranded food and tobacco products); *id*. § 335b (authorizing civil penalties); *see generally* 21 C.F.R. § 1.378 (2017) (authorizing administrative detention of adulterated foods).

38. Friedhoff, *supra* note 34, at 2–3. An NDA must include, inter alia, summaries of the drug's biochemical processes, biopharmaceutics (results of the blood levels produced by different batches of the drug), the drug's clinical pharmacology, and the clinical efficacy studies. *Id*. at 97–98.

39. *See* U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, *New Drug Application (NDA)* (Jan. 21, 2022), https://www.fda.gov/drugs/types-applications/new-drug-application-nda (last visited June 12, 2023). To ship a new drug interstate to clinical investigators before the FDA approves the drug, a sponsor must obtain from the FDA an "Investigational New Drug Application." U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, *Investigational New Drug (IND) Application* (NDA) (July 20, 2022) [hereafter *NDA*], https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application (last visited June 12, 2023).

40. *See New Drug Application*, *supra* note 39.

41. 21 U.S.C. § 355(b)(1); 21 C.F.R. §§ 314.50(d)(2) & (5)(iv); *see Mut. Pharmaceutical*, 570 U.S. at 476; U.S. Gov't Accountability Off., *Report to Congressional Requesters, New Drug Development: Science, Business, Regulatory, and Intellectual Property Issues Cited as Hampering Drug Development Efforts* GAO–07–49, at 1 (Nov. 2006) ("On average, drug sponsors can spend over 13 years studying the benefits and risks of a new compound, and several hundred millions of dollars completing these studies before seeking FDA's approval."). An NDA must include, *inter alia*, summaries of the drug's biochemical processes, biopharmaceutics (results of the blood levels produced by different batches of the drug), the drug's clinical pharmacology, and the clinical efficacy studies. *Id*. at 97–98. To prepare a satisfactory NDA, scientific and technical knowledge in various fields is necessary, such as inorganic, organic, analytical, and physical chemistry (including knowledge of liquid, gas, and layer chromatography); biochemistry; physiology; and mass spectrometry; quality control sampling. Friedhoff, *supra* note 34, at 187–91.

42. 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i).

43. 21 C.F.R. § 314.50(d)(5)(viii); *id*. § 314.50(c)(2)(ix).

44. 21 U.S.C. § 355(d).

45. *Mut. Pharmaceutical, Inc*., 570 U.S. at 476.

46. To save time and expense, pharmaceutical companies typically run preclinical computer simulations to screen compounds with a risk of carcinogenicity. Those analyses, however, must be supported by long-term studies, which ordinarily take three to four years to complete, for a drug to be approved. Friedhoff, *supra* note 34, at 24.

47. *See* Friedhoff, *supra* note 34, at 44 ("The main object of Phase I testing is to evaluate the toxicity profile of the product in humans."). The level at which a drug is not shown to be harmful, known as the No Adverse Effect Level (NOAEL), is generally much lower than the minimum lethal dose. *Id*.

48. Mikkael A. Sekeres, Drugs and the FDA: Safety, Efficacy, and the Public Trust x (2022). The first human dose is generally only 10 percent of the NOAEL in the most sensitive animal safety study. Friedhoff, *supra* note 34, at 45. Each new dosage—what is called the Single Ascending Dose Study—doubles the prior amount until unacceptable human toxicity results or the study reaches the level with the maximum expected benefit. *Id*. Minor adverse effects—such as headaches, dizziness, nausea, or upper respiratory symptoms—are common. *Id*. at 46. Step 2 of Stage I is the Multiple-Dose Tolerance Study. It begins with the highest, well-tolerated dose from the Single Ascending Dose Study administered all at once or every few days for two weeks. *Id*. at 47–48.

49. Friedhoff, *supra* note 34, at 54–55.

50. "The proper design of Phase II studies requires detailed knowledge of: (i) the disease state being studied, (ii) concomitant medications that will be used by the study participants including their typical side effects, (iii) the availability of the patient group being contemplated for inclusion in the study, and (iv) many other details affecting study design and implementation." *Id*. at 57.

51. *Id*. at 65, 87; *see* 21 C.F.R. § 312.21 (2018). Double blind studies—ones in which neither the physicians nor their patients know whether the patient is receiving the drug under study or something else, such as a placebo—is common. *See* Sekeres, *supra* note 48, at 51.

52. 21 C.F.R. § 314.50(d)(5)(viii); *id*. § 314.50(c)(2)(ix).

53. *Mut. Pharmaceutical*, 570 U.S. at 476; FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 140 (2000).

54. Friedhoff, *supra* note 34, at 179.

55. *See, e.g.*, 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i); U.S. Dep't of Health & Human Servs., Food & Drug Admin., Cntrs. for Veterinary Medicine, Biologics Evaluation & Research & Drug Evaluation & Research, *Questions and Answers on Current Good Manufacturing Practices for Drugs* (Mar. 2018) (listing questions and answers on specific topics, such as buildings and facilities, equipment, component controls, drug product containers and closures, production and processing controls, holding and distribution, laboratory controls, and records and reports). "[I]t can be dangerous to assume that products are the same if the manufacturing methods have changed." Friedhoff, *supra* note 34, at 50. The FDA may inspect any facility, including manufacturing plants and offices, at any time without any prior notice, to ensure that a company's manufacturing practices remain satisfactory. *Id*. at 115.

56. *Id*. at 88, 90.

57. 21 U.S.C. § 355(d).

58. *See*, *e.g.*, U.S. Dep't of Health & Human Servs., Food & Drug Admin., Cntrs. for Biologics Evaluation & Research & Drug Evaluation & Research, *Cross Labeling Oncology Drugs in Combination Regimens* (Nov. 2022); U.S. Dep't of Health & Human Servs., Food & Drug Admin., Cntr. for Drug Evaluation & Research, *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).

59. U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, *FDA and Cannabis: Research and Drug Approval Process* (Feb. 24, 2023), https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process (last visited June 12, 2023) ("To date, the FDA has not approved a marketing application for cannabis for the treatment of any disease or condition.... [T]he FDA has not approved any other cannabis, cannabis-derived, or cannabidiol (CBD) products currently available on the market.").

60. *Id*.

61. *Id*.; *see* U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, *FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD), Questions and Answers* 3 & 4 (Dec. 6, 2019), https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#approved [https://perma.cc/SB3X-9V2U].

62. *See* U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, *Press Release: FDA Approves First Drug Comprised of an Active Ingredient Derived from Marijuana to Treat Rare, Severe Forms of Epilepsy*, (June 25, 2018), https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms (current as of Mar. 27, 2020; last visited June 12, 2023).

63. The Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91–513, 84 Stat. 1242 (codified as amended at 21 U.S.C. §§ 801–904 (2019)). The Controlled Substances Act was Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970. Title I addressed prevention and treatment of narcotics addiction, and Title III dealt with the import and export of controlled substances. Gonzales v. Raich, 545 U.S. 1, 12 n.19 (2005). The CSA established several different "schedules" or classes of certain types of drugs, denominated "controlled substances." A "controlled substance" is "a drug or other substance, or immediate precursor, included in Schedule I, II, III, IV, or V of part B of this title," except for "distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1954." 21 U.S.C. § 802(6) (2018). The Controlled Substances Act incorporates the definition of a "drug" from the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 201(g)(1) (2018). The CSA assigns drugs to one of five schedules according to their potential benefits and risks. The CSA placed cannabis into Schedule I, drugs that are potentially dangerous, that lack a legitimate medical purpose, and that have available substitutes. *See* 21 U.S.C. §§ 812, 841 (2018). Schedule I drugs cannot be distributed or possessed for any purpose. The CSA applies to the interstate and intrastate distribution of cannabis. *See Gonzales*, 545 U.S. at 15–33.

64. 21 U.S.C. § 201(g)(1) (2018).

65. 21 U.S.C. § 802(6). There are exceptions for "distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1954." *Id*.

66. 21 U.S.C. § 841.
67. *See* 21 U.S.C. § 823(a) (2018); 21 C.F.R. §§ 1301.01–1301.93 (2023).
68. *See Ruan*, 142 S. Ct. 2370; *United States v. Moore*, 423 U.S. 122.
69. 21 U.S.C. § 841–44 (2018).
70. 21 U.S.C. § 811(A)(2).
71. Biden Administration Attorney General Merrick Garland could well be the first. *See* text accompanying notes 250–51 *infra*.
72. *See* Paul J. Larkin, Jr., *States' Rights and Federal Wrongs: The Misguided Attempt to Label Marijuana Legalization Efforts as a "States' Rights" Issue*, 16 Geo. J.L. & Pub. Pol'y 495 (2018); Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: An Introduction*, Heritage Found. Legal Memo. No. 210, at 2 & 8 n.11 (2023) (listing examples).
73. Since 2014, Congress has regularly passed appropriations bill riders barring the U.S. Department of Justice from "prevent[ing]" states from "implementing" state medical marijuana programs. *See* Consolidated and Further Continuing Appropriations Act, 2015, Pub. L. No. 113–235, § 538, 128 Stat. 2130, 2217 (2014); Continuing Appropriations Act, 2016, Pub. L. No. 114–53, § 104, 129 Stat. 502, 506 (2015); Further Continuing Appropriations Act, 2016, Pub. L. No. 114–96, 129 Stat. 2193 (2015); Consolidated Appropriations Act, 2016, Pub. L. No. 114–113, § 542, 129 Stat. 2242, 2332–33 (2015); Continuing Appropriations Act, 2017, Pub. L. No. 114–223, 130 Stat. 857, 908–20 (2016); Further Continuing Appropriations Act, 2017, Pub. L. No. 114–254, § 101, 130 Stat. 1005, 1005–06 (2016); H.J. Res. 99, Pub. L. No. 115–30, 131 Stat. 134 (2017); Consolidated Appropriations Act, 2017, Pub. L. No. 115–31, 131 Stat. 135, 228 (2017); Continuing Appropriations Act, 2018, Pub. L. No. 115–56, §§ 103–04, 131 Stat. 1139, 1139–47 (2017); Further Continuing Appropriations Act, 2018, Pub. L. No. 115–90, 131 Stat. 1280 (2017); Further Additional Continuing Appropriations Act, 2018, Pub. L. No. 115–96, 131 Stat. 2044 (2017); Extension of Continuing Appropriations Act, 2018, Pub. L. No. 115–120, 132 Stat. 29 (2018); Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2018, Pub. L. No. 115–141, § 538, 132 Stat. 351, 444–45 (2018); Continuing Appropriations Act, 2019, Pub. L. No. 115–245, §§ 101–103, 312 Stat. 3123, 3123 (2018); H.J. Res. 143, Pub. L. No. 115–298, 132 Stat. 4382 (2018); Further Additional Continuing Appropriations Act, 2019, Pub. L. No. 116–5, § 101, 113 Stat. 10, 10 (2019); Commerce, Justice, Science, and Related Agencies Appropriations Act, 2019, Pub. L. No. 116–6, § 537, 133 Stat. 91, 138 (2019); Continuing Appropriations Act, 2020, Pub. L. No. 116–59, § 101, 113 Stat. 1093, 1093–94 (2019); Further Continuing Appropriations Act, 2020, Pub. L. No. 116–69, § 101, 133 Stat. 1134 (2019); Commerce, Justice, Science, and Related Agencies Appropriations Act, 2020, Pub. L. No. 116–93, § 531, 133 Stat. 2385, 2433 (2019); Further Consolidated Appropriations Act, 2020, Pub. L. No. 116–94, 113 Stat. 2534 (2019). The riders do not altogether bar enforcement of the CSA, but the Justice Department has not decided to take an aggressive enforcement posture. *See* Paul J. Larkin, Jr., *Reflexive Federalism*, 44 Harv. J.L. & Pub. Pol'y 523, 530–31 n.29–33 (2021) [hereafter Larkin, *Reflexive Federalism*]. Congress also enacted the Agricultural Improvement Act of 2018, Pub. L. No. 115–334, 132 Stat. 4490, which redefined marijuana to exclude hemp—that is, cannabis and cannabis-derived products with no more than a 0.3 percent THC content by dry weight.
74. Numerous legislators have introduced bills to declassify cannabis altogether, to shift it from Schedule I to a less restrictive schedule, or to revise the federal regulatory scheme in other ways. *See*, *e.g.*, H.R. 3617, Marijuana Opportunity Reinvestment and Expungement (MORE) Act, 117th Cong. (2022) (passed by the House but not the Senate); S. 4591, Cannabis Administration and Opportunity Act, 117th Cong. (2022). Congress has not yet passed any of these bills.
75. Congress also has implicitly reaffirmed the need for those acts every time it has appropriated funds for the Drug Enforcement Administration and the Department of Justice for their drug law enforcement missions. *E.g.*, 21st Century Department of Justice Appropriations Authorization Act, Pub. L. No. 107–273, Div. B, Tit. IV, § 4002(c)(1), 116 Stat 1758 (2002); *see* TVA v. Hill, 437 U.S. 153, 189–91 (1978) (noting that when passing an appropriations bill, Congress ordinarily assumes that the underlying substantive law will remain unchanged).
76. *See*, *e.g.*, Me. Cmty. Health Options v. United States, 140 S. Ct. 1308, 1323 (2020) (noting that "because repealed by implication are not favored," the "[Supreme] Court will regard each as effective unless Congress' intention to repeal is clear and manifest or the two laws are irreconcilable") (punctuation omitted).
77. *See* Sean M. O'Connor & Erika Lietzan, *The Surprising Reach of FDA Regulation of Cannabis, Even After Descheduling*, 68 Am. U. L. Rev. 823 (2019) (explaining that descheduling cannabis transfers regulatory authority entirely to the FDA).
78. Cannabis can be used in a host of different ways aside from smoking a joint. *See* John Hudak, Marijuana: A Short History 17–18 (2016) (noting that edibles come in "countless forms including cookies, brownies, candies, granola, salad dressing, and even pasta sauce."); Michael Starks, Marijuana Chemistry: Genetics, Processing & Potency 109 (1990) ("For thousands of years Cannabis has been made into a variety of beverages, foodstuffs and, since the sixteenth century, smoking preparations."); Paul J. Larkin, Jr., *Marijuana Edibles and "Gummy Bears,"* 66 Buff. L. Rev. 313, 318–19 (2018) [hereafter Larkin, *Gummy Bears*].
79. *See State Medical Cannabis Laws*, Nat'l Conf. of State Legislatures (Feb. 3, 2022), https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx [https://perma.cc/8FTQ-THGR]. The terms of state cannabis regulations of cannabis differ widely. *See* Drug Policy and the Public Good 245–54 (Thomas Babor et al., eds., 2d ed. 2018); Rosalie Liccardo Pacula et al., *Words Can Be Deceiving: A Review of Variation Among Legally Effective Medical Marijuana Laws in the United States*, 7 J. Drug Pol'y Analysis 1 (2014).
80. *See* U.S. Const. art. VI, cl. 2 ("This Constitution, and the Laws of the United States which shall be made in pursuance thereof; and all treaties made, or which shall be made, under the authority of the United States, shall be the supreme law of the land; and the judges in every state shall be bound thereby, anything in the constitution or laws of any state to the contrary notwithstanding."); *Gonzales*, 545 U.S. at 15–33 (ruling that California's

medical cannabis program is not exempt from the CSA); United States v. Oakland Cannabis Buyers Coop., 532 U.S. 483, 494–95 (2001) (rejecting a medical necessity defense to federal prosecution in a state with a medical marijuana program). Accordingly, state marijuana liberalization initiatives cannot shield anyone from liability under federal criminal law. See, *e.g.*, United States v. Rosenthal, 454 F.3d 943, 948 (9th Cir. 2006) (ruling that the City of Oakland cannot "deputize" someone to distribute cannabis under state law and render him immune from prosecution under federal law); United States v. Stacy, 734 F. Supp. 2d 1074, 1080 (S.D. Cal. 2010) (holding that state medical cannabis laws do not grant a person immunity from prosecution under federal law); People v. Crouse, 388 P.3d 39 (Colo. 2017) (ruling that the federal Controlled Substances Act preempts state constitutional provisions requiring the return to an acquitted defendant of any cannabis seized from him).

81. *See*, *e.g.,* Leslie L. Iversen, The Science of Marijuana v–vi, 116–56 (2d ed. 2008); *id*. at 131 ("Many medical uses have been claimed for cannabis, but in most cases scientific evidence for efficacy is lacking or new and easier-to-use medicines have become available."); Brian F. Thomas & Mahmoud A. ElSohly The Analytical Chemistry of Cannabis 1 (2016).

82. Sekeres, *supra* note 48, at x.

83. Act of June 30, 1906, ch. 3915, 34 Stat. 768; *see* James Harvey Young, Pure Food: Securing the Federal Food and Drugs Act of 1906 (2016) (1989).

84. Ch. 653, 52 Stat. 1040 (1938); *see* Charles Q. Jackson, Food and Drug Legislation in the New Deal (2015) (1970).

85. Iversen, *supra* note 81, at 162–63.

86. *See infra* text accompanying notes 147–57.

87. Statement of Nora Volkow, Dir., Nat'l Inst. on Drug Abuse 7 (Jan. 15, 2020), *in House Cannabis Hearing*, *supra* note 7.

88. *Id*.

89. DuPont, *supra* note 27, at 147–54.

90. *See*, *e.g.*, Casarett, *supra* note 26, at 186–88; Starks, *supra* note 78, at 111–12 (noting that "a wide variety of organic solvents" will extract cannabinoids from the plant, including gasoline, benzene, gasoline, petroleum, chloroform, ether, rubbing alcohol, methanol, and grain alcohol); Thomas & ElSohly, *supra* note 81, at 11, 30, 44–46, 89 (noting that "pesticide residues, metals, and residual solvents" can be found in cannabis); Louis Bengyella et al., *Global Impact of Trace Non-Essential Heavy Metal Contaminants in Industrial Cannabis Bioeconomy*, 41 Toxins Rev., at 4–5 (2022) (noting that "[t]here is a high likelihood" that radioactive cannabis and "[n]on-essential heavy metals" wind up in consumer cannabis); Jenna Hardesty Bishop, *Weeding the Garden of Pesticide Regulation: When the Marijuana Industry Goes Unchecked*, 65 Drake L. Rev. 223, 226 (2016) ("Test samples of marijuana overwhelmingly reveal that growers are choosing to use unapproved and unregulated pesticides, creating a serious public health risk for consumers.") (footnote omitted); Franziska Busse et al., *Lead Poisoning Due to Adulterated Marijuana*, 358 New Eng. J. Med. 1641 (2008); David Christiana, *Vaping-Induced Lung Injury*, New Eng. J. Med., Sept. 6, 2019, https://www.nejm.org/doi/pdf/10.1056/NEJMe1912032?articleTools=true; Tista Ghosh et al., *The Public Health Framework of Legalized Marijuana in Colorado*, 106 Am. J. Pub. Health 21, 23 (2016); Brian M. Graves et al., *Comprehensive Characterization of Mainstream Marijuana and Tobacco Smoke*, 10 Scien. Rep. 7160, 7160 (2020) (noting that there are 2,575 different compounds in cannabis smoke, 536 have been identified, and 100 "are known to cause negative health effects through carcinogenic, mutagenic, teratogenic, or other toxic mechanisms"); David R. Lorenz et al., *Acrolein and Other Toxic Exposures in Relation to Cardiovascular Disease Among Marijuana and Tobacco Smokers in a Longitudinal Cohort of HIV-Positive and Negative Adults*, Lancet eClinical Medicine, Jan. 11, 2021, https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30441-7/fulltext; Todd Subritzky et al., *Issues in the Implementation and Evolution of the Commercial Recreational Cannabis Market in Colorado*, 27 Int'l J. Drug Pol'y 1, 6 (2016); Binnian Wei et al., *Urinary Concentration of PAH and VOC Metabolites in Marijuana Users*, 88 Env't Int'l 1 (2016) (finding in the urine of self-identified cannabis users elevated levels of potentially toxic polycyclic aromatic hydrocarbons and volatile organic compounds).

91. *See*, *e.g.*, Peter Grinspoon, *supra* note 26, at 41.

92. This phenomenon is discussed in detail in Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: The Failure of Cannabis Legalization to Eliminate an Illicit Market*, Heritage Found. Legal Memo. No. 326 (2023) [hereafter Larkin, *Cannabis Illicit Market*].

93. *See* Drug Enf't Admin, 2020 National Drug Threat Assessment DEA–DCT–DIR–008–21, at 51 (Mar. 2021) ("[B]lack market marijuana production continues to grow in California, Colorado, Oregon, Washington, and other states that have legalized marijuana, creating an overall decline in prices for illicit marijuana as well. This further incentivizes drug trafficking organizations operating large-scale grow sites in these states to sell to customers in markets throughout the Midwest and East Coast, where marijuana commands a higher price."); *see also*, *e.g.*, Peter Grinspoon, *supra* note 26, at 42 ("We can all agree that no one has solved the problem of how to minimize the illicit market, except perhaps to avoid taxing the legal market to death, as for example they do in California."); Vanda Felbab-Brown, *Will Cannabis Legalization Reduce Crime in Mexico? Has It in the US?*, Brookings Inst., Apr. 26, 2021, https://www.brookings.edu/blog/order-from-chaos/2021/04/26/will-cannabis-legalization-reduce-crime-in-mexico-has-it-in-the-us/ ("The size of the persisting illegal market can also dwarf legal production. In Colorado, many illegal grows cultivate hundreds or thousands of plants. California's Stanislaus County, for example, imposes a cap of 61 commercial cannabis permits. Yet more than four years after Proposition 64 legalized marijuana, the county is estimated to feature between 1,100 and 1,500 illegal pot grows, even while enforcement has been intense. In the 2019 to first half of 2020 period, the county's sheriff's department destroyed almost 100,000 illegal outdoor and indoor cannabis plants and seized tens of thousands of pounds of processed marijuana. In the state's Siskiyou County, 130,000 illegal cannabis plants, some 26,000 pounds of processed marijuana, and 13 illegal firearms were seized in raids and 123 arrests were made in 2020. In California overall, over 1.1 million cannabis plants and 20.5 tons of processed pot were seized from 455 grow sites last year."); Joseph Detrano, Rutgers Cntr. of Alcohol & Substance Use Studies, *Cannabis Black Market Thrives Despite Legalization* (2023), https://alcoholstudies.rutgers.edu/cannabis-black-market-thrives-despite-legalization/ ("Cannabis' illegal market is anything but dying; in some cases, it's more active than it has been in years.").

94. *See supra* notes 89–90.
95. This problem is discussed in detail in Paul J. Larkin, Jr., *Cannabis Capitalism*, 69 Buff. L. Rev. 215 (2021)
96. *Id.* at 255.
97. *See*, *e.g.*, Carlton K. Erickson, The Science of Addiction 28–30 (2d ed. 2018).
98. *See*, *e.g.*, World Health Org., The Health and Social Effects of Nonmedical Cannabis Use 175–81 (2016) ("The daily use of cannabis over years and decades appears to produce persistent impairments in memory and cognition, especially when cannabis use begins in adolescence."); Iversen, *supra* note 81, at v–vi, 175–81, 185 (inhaling cannabis increases the risk of pulmonary disease, particularly after long-term use); Jerrold S. Meyer & Linda F. Quenzer, Psychopharmacology 416 (2d ed. 2018) ("Heavy cannabis use for a long period of time may lead to impaired executive functioning for at least 2 to 3 weeks following cessation of use.... However, some of the data suggest that heavy, long-time users may continue to show impairment in decision making, planning, and concept formation."); *id.* at 422–25 (discussing potential adverse psychological, neuropsychiatric, and physiological effects from long-term use); *id.* at 424–25 (discussing potential psychosis-causing effect of early-onset, long-term use); Jonathan P. Caulkins et al., Considering Marijuana Legalization: Insights for Vermont and Other Jurisdictions 107 (2015) ("[A] relatively small number of heavy users account for the great bulk of total purchases; many of them have built up a chemical tolerance to the effects of THC and need higher doses than other consumers to achieve the effect they desire."); Marta Di Forti et al., *Proportion of Patients in South London with First-Episode Psychosis Attributable to Use of High Potency Cannabis: A Case-Control Study*, 2 Lancet Psychiatry 233, 236 (2015) ("People who used cannabis or skunk every day were both roughly three times more likely to have a diagnosis of a psychotic disorder than were those who never used cannabis."); Wayne Hall & Nadia Solowij, *Long-Term Cannabis Use and Mental Health*, 171 Br. J. Psychiatry 107 (1997) (finding that 10 percent of recreational users will become physically dependent or addicted); Marie Stefanie Kejser Starzer et al., *Rates and Predictors of Conversion to Schizophrenia or Bipolar Disorder Following Substance-Induced Psychosis*, 175 Am. J. Psychiatry 343, 346 (2018) ("We found that 32.2% of patients with a substance-induced psychosis later converted to either bipolar disorder or schizophrenia. The highest conversion rate (47.4%) was found for cannabis-induced psychosis. Young age was associated with a higher risk of conversion to schizophrenia; the risk was highest for those in the range of 16–25 years. Self-harm after a substance-induced psychosis was significantly linked to a higher risk of converting to both schizophrenia and bipolar disorder.").
99. *See*, *e.g.*, Nat'l Inst. on Drug Abuse, Marijuana 14 (Aug. 2017) ("Marijuana use can lead to the development of problem use, known as a marijuana use disorder, which takes the form of addiction in severe cases. Recent data suggest that 30% of those who use marijuana may have some degree of marijuana use disorder."); Am. Psychiatric Ass'n, Diagnostic and Statistical Manual of Mental Disorders 509–16 (5th ed. 2013) [hereinafter DSM-5] (discussing diagnosis of "Cannabis Use Disorder"); Carlton K. Erickson, The Science of Addiction 175–76 (2d ed. 2018); Wayne Hall & Rosalie Liccardo Pacula, Cannabis Use and Dependence: Public Health and Public Policy 14 (2003); Meyer & Quenzer, Psychopharmacology 420; Cannabis Dependence (Roger A. Roffman & Robert S. Stephens eds., 2006); Anees Bahji et al., *Prevalence of Cannabis Withdrawal Symptoms Among People with Regular or Dependent Use of Cannabinoids: A Systematic Review and Meta-Analysis*, JAMA Network Open, Apr. 2020, at 1, 11; Udo Bonnet & Ulrich W. Preuss, *The Cannabis Withdrawal Syndrome: Current Insights*, 8 Substance Abuse & Rehabilitation 9 (2017); Wilson M. Compton et al., *Marijuana Use and Use Disorders in Adults in the USA, 2002–14: Analysis of Annual Cross-Sectional Surveys*, 3 Lancet Psychiatry 954 (2016); Esme Fuller-Thomson et al., *Is Recovery from Cannabis Dependence Possible? Factors that Help or Hinder Recovery in a National Sample of Canadians with a History of Cannabis Dependence*, Advances in Preventative Med., Apr. 15, 2020, at 1; Wayne Hall, *What Has Research Over the Past Two Decades Revealed About the Adverse Health Effects of Recreational Cannabis Use?*, 110 Addiction 19 (2014); Hall & Solowij, *supra* note 98, at 107; Deborah S. Hasin et al., *Prevalence of Marijuana Use Disorders in the United States Between 2001–2002 and 2012–2013*, 72 JAMA Psychiatry 1235 (2015); Lindsey A. Hines et al., *Association of High-Potency Cannabis Use with Mental Health and Substance Use in Adolescence*, 77 JAMA Psychiatry 1044 (2020). Cannabis withdrawal symptoms include craving, irritability, depression, anxiety, restlessness, weakness, and sleep disruption. *See, e.g.*, William R. Miller et al., Treating Addiction 39, 96 box 6.6, 290 box 18.2 (2011) (describing the symptoms of cannabis withdrawal); Alan J. Budney et al., *Comparison of Cannabis and Tobacco Withdrawal: Severity and Contribution to Relapse*, 35 J. Substance Abuse Treatment 362 (2008); M. Claire Greene & John F. Kelly, *The Prevalence of Cannabis Withdrawal and Its Influence on Adolescents' Treatment Response and Outcomes: A 12-Month Prospective Investigation*, 8 J. Addiction Med. 359, 361–62 tbl.1 (2014).
100. Hall & Pacula, *supra* note 99, at 75–78.
101. *Id.* at 75–78.
102. Nora D. Volkow et al., *Adverse Health Effects of Marijuana Use*, 370 New Eng. J. Med. 2219, 2220 (2014); *id.* at 2220 tbl.1 (noting that negative effects in brain development, educational outcome, cognitive impairment, and life satisfaction are "strongly associated with initial marijuana use early in adolescence"); *see also, e.g.*, World Health Org., The Health and Social Effects of Nonmedical Cannabis Use 15 (2016) ("The daily use of cannabis over years and decades appears to produce persistent impairments in memory and cognition, especially when cannabis use begins in adolescence."); Robin Room et al., Cannabis Policy: Beyond Stalemate 25 (2010) (noting that the risk of dependence is "about one in six for young people who initiate in adolescence"); *id.* at 31–39 (describing studies investigating the risk that adolescent marijuana use could adversely affect learning, result in a greater drop-out rate, be a prelude to other drug use, or lead to schizophrenia or depression); Janni Leung et al., *What Is the Prevalence and Risk of Cannabis Use Disorders Among People Who Use Cannabis? A Systematic Review and Meta-Analysis*, 109 Addictive Behavs. 106479 (2020) (the risk of dependence is 33 percent among young people who engaged in regular (weekly or daily) cannabis use). *See generally* Larkin, *Gummy Bears*, *supra* note 78, at 325–31, 326 nn.30–40 (collecting authorities). Studies have found that a range of 30 percent to 84 percent of juveniles seeking treatment for cannabis dependence have suffered from withdrawal. Greene & Kelly, *The Prevalence of Cannabis Withdrawal*, 361–62 tbl.1, 366.
103. *See* M.W.P. Carney, *Psychosis After Cannabis Use*, 288 Brit. Med. J. 1047 (1983); John A. Talbott & James W. Teague, *Marijuana Psychosis*, 210 JAMA 299 (1969); Samuel T. Wilkinson et al., *Impact of Cannabis Use on the Development of Psychotic Disorders*, 1 Current Addiction Reps. 115, 116 (2014) (footnotes omitted) ("A link between cannabis intoxication and altered behavior including psychosis has long been recognized. In the 19th century,

Moreau (de Tours) characterized transient hallucinations, paranoia, dissociative symptoms, thought disorganization and impairments in attention and memory reminiscent of psychotic symptoms seen in schizophrenia in the context of acute cannabis intoxication. These phenomena have also been documented in numerous case-reports and estimated to occur in about 20%–50% of individuals who use cannabis.").

104. Sven Andreasson et al., *Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts*, 2 Lancet 1483 (1987); *see also* Stanley Zammit et al., *Self Reported Cannabis Use as a Risk Factor for Schizophrenia in Swedish Conscripts of 1969: Historical Cohort Study*, 325 Brit. Med'l J. 1199 (2002) (follow-up study).

105. As the commission reported:

> It has been known for many years that the heavy use of stimulants such as amphetamines and methamphetamine can lead to psychosis and in recent years it has become clear that substances with similar pharmacology such as Khat and "legal highs" can do the same. Most recently concern has focused on cannabis since this is the most widely used illicit drug, and people with psychosis take it more frequently and for longer than the general population.
>
> The critical question is whether the heavy use of cannabis has contributed to the onset and persistence of the psychosis. Here, the evidence has been mounting steadily over the past 10 years and all competent studies have shown that initially healthy people who use cannabis daily are more likely to go on to develop psychosis in the ensuing decades than people who don't… Those with a family history of mental illness, those with a suspicious or psychosis-prone personality, and those who start use in early adolescence, also appear to be at greater risk.
>
> Those people with psychosis who continue to smoke have a worse outcome too, with more persistent symptoms, repeated hospital admissions, and they show more aggression. Drug use not only results in more people with acute psychosis but many of those who are too dependent on cannabis to stop are repeatedly readmitted to acute care units as they relapse.

United Kingdom, The Schizophrenia Comm'n, The Abandoned Illness 55 (2012); *see also id*. at 10 (noting that "[h]eavy abuse of drugs such as amphetamines and cannabis is increasingly considered" to be an "important" trigger for people predisposed toward schizophrenia); *id*. at 20 ("The latest research worldwide shows a strong link between taking drugs, especially cannabis and stimulants such as amphetamines or 'legal highs,' and the onset of psychosis including schizophrenia. Risks increase the younger regular use of the drug starts… [¶] Our respondents confirmed that in many cases problems started with heavy cannabis use, especially of high potency types such as 'skunk,' in adolescence.").

106. *See* Nat'l Inst. on Drug Abuse, Research Report: Cannabis (Marijuana) Research Report 15 (Rev. July 2020) ("Several studies have linked marijuana use to increased risk for psychiatric disorders, including psychosis (schizophrenia), depression, anxiety, and substance use disorders, but whether and to what extent it actually causes these conditions is not always easy to determine. Recent research suggests that smoking high-potency marijuana every day could increase the chances of developing psychosis by nearly five times compared to people who have never used marijuana. The amount of drug used, the age at first use, and genetic vulnerability have all been shown to influence this relationship. The strongest evidence to date concerns links between marijuana use and psychiatric disorders in those with a preexisting genetic or other vulnerability.") (footnotes omitted).

107. As Dr. Volkow explained:

> Regular marijuana use is associated with an increased risk of anxiety and depression, but causality has not been established. Marijuana is also linked with psychoses (including those associated with schizophrenia), especially among people with a preexisting genetic vulnerability, and exacerbates the course of illness in patients with schizophrenia. Heavier marijuana use, greater drug potency, and exposure at a younger age can all negatively affect the disease trajectory (e.g., by advancing the time of a first psychotic episode by 2 to 6 years).
>
> However, it is inherently difficult to establish causality in these types of studies because factors other than marijuana use may be directly associated with the risk of mental illness. In addition, other factors could predispose a person to both marijuana use and mental illness. This makes it difficult to confidently attribute the increased risk of mental illness to marijuana use.

Statement of Nora Volkow, *supra* note 87.

108. *See, e.g.*, Charles Ksir & Carl L. Hart, *Cannabis and Psychosis: A Critical Overview of the Relationship*, 18 Current Psychiatry Reps. 11, 20 (2016) ("The numerous studies that have been conducted based on the tentative assumption that cannabis use might cause an increased risk for psychosis have not provided us with either a better insight into how cannabis actually produces such an effect or with an effective method for reducing the risk of psychosis by reducing cannabis use. We believe this is probably because cannabis does not in itself cause such an increase. Rather, our review of the evidence leads us to conclude that both early use of cannabis and heavy use of cannabis are more likely in individuals with a vulnerability to a variety of other problem behaviors, such as early or heavy use of cigarettes or alcohol, use of other illicit drugs, and poor school performance. In some individuals, the same vulnerability also results in increased risk for psychosis or some other mental disorder.").

109. U.S. Dep't of Health & Human Servs., Ctrs. for Disease Control & Prevention, *Addiction (Marijuana or Cannabis Use Disorder)* (Oct. 19, 2020); DSM-5, 509–16.

110. *See, e.g.*, Paola Casadio et al., *Cannabis Use in Young People: The Risk for Schizophrenia*, 35 Neurosci. Behavioral Rec. 1779 (2011) (concluding that epidemiological research consistently found that heavy, early cannabis use is associated with late-life schizophrenia outcomes); Cyril D'Souza et al., *Cannabis and Psychosis/Schizophrenia: Human Studies*, 259 Eur. Archives Clin. Neurosci. 413 (2009) (concluding that cannabis increases risk of psychotic outcomes independently of confounding and transient intoxication effects); Suzanne H. Gage et al., *Association Between Cannabis and Psychosis—Epidemiologic Evidence*, 79 Biological Psychiatry 549, 549 (2016) ("Overall, evidence from epidemiologic studies provides strong enough evidence to warrant a public health message that cannabis use can increase the risk of psychotic disorders. However, further studies are required to determine the magnitude of this effect, to determine the effect of different strains of cannabis on risk, and to identify high-risk groups particularly

susceptible to the effects of cannabis on psychosis."); Carsten Hjorthoj et al., *Association Between Cannabis Use Disorder and Schizophrenia Stronger in Young Males Than in Females*, Psychological Med. Online, Mar. 23, 2023, https://pubmed.ncbi.nlm.nih.gov/37140715/; Andrew Johns, *Psychiatric Effects of Cannabis*, 178 Br. J. Psychiatry 116, 116 (2001) ("There is good evidence that taking cannabis leads to acute adverse mental effects in a high proportion of regular users. Many of these effects are dose-related, but adverse symptoms may be aggravated by constitutional factors including youthfulness, personality attributes and vulnerability to serious mental illness.... Cannabis use can lead to a range of short-lived symptoms such as depersonalisation, derealisation, a feeling of loss of control, fear of dying, irrational panic and paranoid ideas."); *id.* at 118 ("A number of studies suggest that heavy cannabis use can lead to an acute functional illness, that is a state resembling the psychosis of acute schizophrenia without the amnesia and confusion of a toxic psychosis," which the authors suggest might be "a precipitated episode of an underlying functional illness."); *id.* at 121 ("Heavy cannabis misuse leads to the risk of psychotic episodes, and aggravates the symptoms and course of schizophrenia."); Neeraj Kancherla et al., *Cannabis Associated Mental Health Effects: A Review*, 13 J. Pharmacy & Bioallied Scis. S943, S944–S945 (2012) (noting various adverse consequences of cannabis use: "*Cannabis* and cannabinoids have been reported to be directly associated with major depressive disorders (MDDs) and worsening the depression crisis.... When individuals are vulnerable to developing a psychotic illness, they use *Cannabis* under CUD due to extreme environmental influence. One in four individuals is dealing with this substance abuse in developed countries. Mostly chronic usage symptoms resemble the signs of schizophrenia. THC has been reported to cause increased psychosis when a higher dose is given, leading them to be in an[d] near the edge situation mentally.... In one study, where over 40,000 people were recruited, the ones who were using *Cannabis* or derived materials had a greater chance of developing BD [viz., bipolar disorder]. With increasing dosage, leading to harmful effects in case of those people often leading to suicidal tendencies.... [S]uicidal behaviours and concurrent usage of *Cannabis* were very strongly associated in individuals as young as 15 years of age. Apart from family issues, heterogeneity of other environmental factors can lead to this kind of behavior development, irrespective of the gender of an individual.... *Cannabis* causes memory loss in individuals with acute usage, just like alcohol with its intoxicated state of mind. However, more permanent damage is caused by chronic usage. There is a marked deficit in learning and then recalling things."); Theresa H.M. Moore et al., *Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systemic Review*, 370 Lancet 319 (2007).

111. *See*, *e.g.*, Peter Allebeck et al., *Does a History of Cannabis Use Influence Onset and Course of Schizophrenia?* 147 Acta Psychiatry Scandinavia 614, 614 (2023) ("Although the relationship between cannabis and psychosis is likely to be highly complex, evidence from experimental and observational studies, including longitudinal studies that minimize reverse causation and robustly address confounding, support a causal effect of cannabis on psychosis.") (footnotes omitted); Mathilde Argote et al., *Association Between Formal Thought Disorder and Cannabis Use—A Systematic Review and Meta-Analysis*, 8 Schizophrenia (Heidelberg) Open art. 78, at 5, Sept. 29, 2022, https://www.nature.com/articles/s41537-022-00286-0 ("The overall effect size of the 19 pooled studies indicated that FTD [Formal Thought Disorder] severity was significantly increased in cannabis-users groups, compared to non-using groups."); *id.* at 7–8 ("Previous studies found that cannabis use was associated with more severe positive symptoms of psychosis, within an epidemiological continuum ranging from the general population to schizophrenia spectrum disorders. Moreover, accumulating pieces of evidence suggest a causal role of cannabis in triggering and aggravating positive symptoms, particularly in schizophrenia spectrum disorders. Since FTD has been suggested to constitute a core symptom of schizophrenia, it was theoretically expected that cannabis use would be associated with exacerbated FTD. The results presented in this meta-analysis tend to support this association, and the effect of cannabis use on FTD seems consistent along the psychosis continuum, regardless of the severity of the psychotic disorder."); Deepak Laura Dellazizzo et al., *Association Between the Use of Cannabis and Physical Violence in Youths: A Meta-Analytical Investigation*, 177 Am. J. Psychiatry 619 (2020); Kirsten H. Dillon et al., *Cannabis Use Disorder, Anger, and Violence in Iraq/Afghanistan-Era Veterans*, 138 J. Psychiatric Rsch. 375 (2021); Benedikt Fisher et al., *Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations*, 107 Am. J. Pub. Health 1193, e3–e5 (2017) (footnotes omitted) ("High THC content in cannabis has been identified as a risk factor for acute and chronic adverse outcomes, including mental health problems and dependance. For example, frequent use of high-potency cannabis ('skunk') has been associated with marked effects on memory, increased paranoia, and greater dependance severity in (especially younger) users in the United Kingdom. In a case-controlled study use of high-THC cannabis was associated with a 3-times-elevated risk of psychotic disorder and, hence, 1 in 4 of incident cases. Use of high-potency wax 'dabs' has been linked to cannabis-induced psychosis among individuals with no psychiatric history."); Julianne C. Flanagan et al., *Association of Cannabis Use with Intimate Partner Violence Among Couples with Substance Misuse*, 29 Am. J. Addiction 323 (2020); Shea-Lee Godin & Sherif Shehata, *Adolescent Cannabis Use and Later Development of Schizophrenia: An Updated Systematic Review of Longitudinal Studies*, 78 J. Clin. Psychology 1331 (2022); Alkomiet Hasan et al., *Cannabis Use and Psychosis—A Review of Reviews*, 270 European Archives of Psychiatry & Clinical Neurosci. 403, 406 (2020) ("In summary, the evaluated publications indicate that cannabis users have a dose-dependent risk of developing a psychosis, but more longitudinal studies with longer observation periods are needed."); Emma C. Johnson et al., *The Relationship Between Cannabis and Schizophrenia: A Genetically Informed Perspective*, 116 Addiction 3227, 3231 (2021) ("[W]e provide evidence that genetic liability for CUD [Cannabis Use Disorder] is robustly associated with SCZ [Schizophrenia], above and beyond tobacco smoking and cannabis ever-use, and we find mixed evidence to support a causal relationship between CUD and SCZ."); Bochao Danae Lin et al., *Nongenetic Factors Associated with Psychotic Experiences Among UK Biobank Participants*, 79 JAMA Psychiatry 857 (2022) (noting that, among 148 correlates of nongenetic factors with psychotic experiences, cannabis use was "among the top correlates"); Rachel Little & Dale D'Mello, *A Cannabinoid Hypothesis of Schizophrenia: Pathways to Psychosis*, 19 Innovations in Clin. Neurosci. 38, 39 (2022) ("Almost 50 percent of individuals who experience an initial episode of cannabis-induced psychosis are diagnosed with schizophrenia 2 to 4 years after their first psychosis experience. The age of onset of schizophrenia is 10 years earlier in individuals that use cannabis habitually, compared to those who are nonusers. This apparent link between cannabis use and onset of schizophrenia is an extension of previously published research on cannabis-induced psychosis.") (footnotes omitted); Ofir Livne et al., *Association of Cannabis Use-Related Predictor Variables and Self-Reported Psychotic Disorders: U.S. Adults, 2001–2002 and 2012–2013*, 179 Am. J. Psychiatry 36, 42 (2022) ("The prevalence of self-reported psychotic disorders in the adult U.S. population significantly increased from 2001–2002 to 2012–2013. Nonmedical cannabis use and cannabis use disorder were consistently associated with self-reported psychotic disorders over time, while frequent and daily/near-daily use were also associated with self-reported psychotic

disorders in the more recent survey."); Arianna Marconi et al., *Meta-Analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis*, 42 Schizophrenia Bull. 1262, 1265 (2016) ("In this meta-analysis of all available published data, we confirm a positive association between the extent of cannabis use and the risk for psychosis. This association was consistent in all the individual studies included, despite differences in the effect size. The pooled analysis reported approximately a 4-fold increase in risk for the heaviest users and a 2-fold increase for the average cannabis user in comparison to nonusers."); R.M. Murray et al., *The Influence of Risk Factors on the Onset and Outcome of Psychosis: What We Learned from the GAP Study*, 225 Schizophrenia Rsch. 63, 65–66 (2020) ("[A]bout one quarter of new cases of psychosis could be attributed to daily use of high potency cannabis. A subsequent study carried out by Di Forti et al. (2019) showed that this proportion had risen to 30%, possibly due to the further increase in the potency of the available cannabis."); Thor Norstrom & Ingeborg Rossow, *Cannabis Use and Violence—Is There a Link?*, 42 Scandinavian J. Pub. Health 358, 358 (2014) ("The elasticity estimate implies that a 10% increase in cannabis use frequency is associated with a 0.4% increase in frequency of violence.") (citation omitted); Rasmi Patel et al., *Association of Cannabis Use with Hospital Admission and Antipsychotic Treatment Failure in First Episode Psychosis: An Observational Study*, 2016 Brit. Med'l J. Open e009888; Dorsa Rafiei & Nathan J. Kolla, *Fact or Fiction Regarding the Relationship Between Cannabis Use and Violent Behavior*, 50 J. Am. Acad. Sci. & L. 44 (2021); Eline B. Rognli et al., *Transition from Substance-Induced Psychosis to Schizophrenia Spectrum Disorder or Bipolar Disorder*, 180 Am. J. Psychiatry 437, 437 (2023) ("In this study of more than 3,000 patients with substance-induced psychosis, the 6-year cumulative rate of transition to schizophrenia spectrum disorder was 27.6%, with the highest rate associated with cannabis-induced psychosis (36.0%).... The transition rate from substance-induced psychosis to bipolar disorder was 4.5%."); Maryam Sorkhou et al., *Does Cannabis Use Predict Aggressive or Violent Behavior in Psychiatric Populations? A Systematic Review*, 48 Am. J. Drug & Alcohol Abuse 631, 631 (2022) ("Although cannabis use is associated with aggression or violence in individuals with PTSD or psychotic-spectrum disorders, causal conclusions cannot be drawn due to methodological limitations observed in the current literature."); *id*. at 638 (finding a "positive relationship between cannabis use and aggression in people with psychotic disorders"); Marco De Toffol et al., *Cannabinoids as Medicines: What the Evidence Says and What It Does Not Say*, in Marijuana and Madness 346, 351 (3d ed. Deepak D'Souza et al. eds., 2023) ("Sophisticated [Mendelian Randomization] studies have confirmed a relationship between cannabis use disorder and schizophrenia, with a significant risk-increasing effect of cannabis use disorder on liability to schizophrenia, above and beyond tobacco smoking.") (citation omitted).

112. THC interacts with the endogenous cannabinoid system, which, in turn, interacts with dopaminergic and neurotransmitter systems implicated in the production of psychotic symptoms. Wayne Hall & Louisa Degenhardt, *Policy Implications of the Evidence on Cannabis Use and Psychosis*, *in* Marijuana and Madness, *supra* note 111, at 51, 52; *see also*, e.g., Allebeck et al., *supra* note 111, at 614; Weiqiu Cheng et al., *The Relationship Between Cannabis Use, Schizophrenia, and Bipolar Disorder: A Genetically Informed Study*, 10 Lancet Psychiatry 441, 447 (2023) ("We found evidence of genetic overlap between each psychotic disorder [schizophrenia and bipolar disorder] and cannabis phenotype pairs at the genome-wide, regional, and locus levels."); Deepak Cyril D'Souza, *Cannabinoids and Psychosis*, 78 Int'l Rev. Neurobiology 2889 (2007).

113. Marta Di Forti, *To Legalize or Not to Legalize, that Is the Question!* 19 World Psychiatry 188, 189 (2020).

114. *See*, *e.g.*, Allebeck et al., *supra* note 111, at 620 ("The use of high potency cannabis has been increasing in recent years and seems to be associated with higher risk of psychosis. Adolescents in the end of the 1960s were exposed to cannabis of lower potency, so the associations found in this study might be lower than what would be found today.") (footnote omitted).

115. *See* Wayne Hall & Louisa Degenhardt, *Policy Implications of the Evidence on Cannabis Use and Psychosis*, *in* Marijuana and Madness, *supra* note 111, at 51, 52 ("If there was [*sic*: were] similar evidence of an association between a pharmaceutical drug and psychosis, regulators would withdraw the drug from the market (if the risk was [*sic*: were] large), or only allow it to be prescribed if accompanied by warnings to patients and prescribers about these risks.").

116. *See*, *e.g.*, Office of the Surgeon Gen., U.S. Surgeon Gen.'s Advisory: Marijuana Use and the Developing Brain (Aug. 29, 2019) ("Marijuana has changed over time. The marijuana available today is much stronger than previous versions. The THC concentration in commonly cultivated marijuana plants has increased three-fold between 1995 and 2014 (4% and 12% respectively). Marijuana available in dispensaries in some states has average concentrations of THC between 17.7% and 23.2%. Concentrated products, commonly known as dabs or waxes, are far more widely available to recreational users today and may contain between 23.7% and 75.9% THC.") (footnotes omitted); World Health Org., The Health and Social Effects of Nonmedical Cannabis Use 12–13 (2016); DSM-5, 511 ("During the past two decades, a steady increase in the potency of seized cannabis has been observed."); Desmond Slade et al., *Is Cannabis Becoming More Potent?*, in Marijuana and Madness (2d ed. David Castle et al. eds., 2012); Alan J. Budney et al., *Cannabis*, *in* Lowinson & Ruiz's Substance Abuse: A Comprehensive Textbook 216 (Pedro Ruiz & Eric Strain eds., 5th ed. 2011) (The potency of marijuana increased by 60 percent from 2000–2010.). This phenomenon is discussed in detail in an earlier publication in this series. *See* Larkin, *Twenty-First Century Cannabis Potency*, *supra* note 29; *see also infra* notes 207-15 and accompanying text..

117. Friedhoff, *supra* note 34, at 50.

118. *See*, e.g., Tom Freeman & Sam Craft, *Is Cannabis Becoming More Potent? in* Marijuana and Madness, *supra* note 111, at 43, 43 ("There is compelling evidence that use of higher potency cannabis products is associated with poorer outcomes related to psychosis. Daily use of high potency cannabis has been found to carry a five-fold increased risk of psychotic disorders in studies conducted in the United Kingdom and a multisite study in Europe and Brazil."); Kat Petrilli et al., *Association of Cannabis Potency with Mental Health and Addiction: A Systematic Review*, 9 Lancet Psychiatry 736, 736 (2022) ("Overall, use of higher potency cannabis, relative to lower potency cannabis, was associated with an increased risk of psychosis and [Cannabis Use Disorder]."); Volkow et al., *supra* note 102, at 2222 (footnotes omitted) ("Regular marijuana use is associated with an increased risk of anxiety and depression, but causality has not been established. Marijuana is also linked with psychoses (including those associated with schizophrenia), especially among people with a preexisting genetic vulnerability, and exacerbates the course of illness in patients with schizophrenia. Heavier marijuana use, greater drug potency, and exposure at a younger age can all negatively affect the disease trajectory (e.g., by advancing the time of a first psychotic

episode by 2 to 6 years)."); *see also*, *e.g.*, Suman Chandra et al., *New Trends in Cannabis Potency in USA and Europe During the Last Decade (2008–2017)*, 269 Eur. Archives Psychiatry Clinical Neurosci. 5 (2019); Robin Murray et al., *Traditional Marijuana, High-Potency Cannabis and Synthetic Cannabinoids: Increasing Risk for Psychosis*, 15 World Psychiatry 195 (2016).

119. *See*, *e.g.*, Allebeck et al., *supra* note 111, at 614 ("Patients with a cannabis history (n = 32), compared to those without (n = 128), had an earlier age at onset, a higher number of hospital admissions and a higher total number of hospital days. There was no significant difference in type of onset and clinical symptom profiles between the groups.... Our findings indicate that the disease burden of schizophrenia is greater in individuals who use cannabis during adolescence."); Di Forti et al., *supra* note 98, at 236 ("[U]se of high-potency cannabis (skunk) confers an increased risk of psychosis compared with traditional low-potency cannabis (hash)."); Marta Di Forti et al., *The Contribution of Cannabis Use to Variation in the Incidence of Psychotic Disorder Across Europe (EU-GEI): A Multicentre Case-Control Study*, 6 Lancet Psychiatry 427, 432 (2019) ("Use of high potency cannabis was a strong predictor of psychotic disorder in Amsterdam, London, and Paris where high potency cannabis was widely available, by contrast with sites such as Palermo where this type was not yet available. In the Netherlands, the THC content reaches up to 67% in Nederhasj and 22% in Nederwiet; in London, skunk like cannabis (average THC of 14%) represents 94% of the street market whereas in countries like Italy, France, and Spain, herbal types of cannabis with THC content of less than 10% were still commonly used. [¶] Thus our findings are consistent with previous epidemiological and experimental evidence suggesting that the use of cannabis with a high concentration of THC has more harmful effects on mental health than does use of weaker forms.") (footnotes omitted); Marta Di Forti et al., *High-Potency Cannabis and the Risk of Psychosis*, 195 British J. Psychiatry 488, 491 (2009) (finding that "the risk of psychosis is much greater among people who are frequent cannabis users, and among those using sinsemilla (skunk) rather than occasional users of traditional hash. It is not surprising that those who use skunk daily seem to be the group with the highest risk of all."); Robin Murray et al., *Traditional Marijuana, High-Potency Cannabis and Synthetic Cannabinoids: Increasing Risk for Psychosis*, 15 World Psychiatry 195, 196 (2016).

120. *See* 21 U.S.C. § 331(a); *supra* note 40.

121. Thomas & ElSohly, *supra* note 81, at 85 ("Particularly concerning are the recent observations that errors or inaccuracies in chemical content and labeling are prevalent in products purchased from medical cannabis markets in the United States."); Ryan Vandrey et al., Research Letter: *Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products*, 313 JAMA 2491, 2491 (2015) ("Edible cannabis products from 3 major metropolitan areas, though unregulated, failed to meet basic label accuracy standards for pharmaceuticals. Greater than 50% of products evaluated had significantly less cannabinoid content than labeled, with some products containing negligible amounts of THC. Such products may not produce the desired medical benefit. [¶] Other products contained significantly more THC than labeled, placing patients at risk of experiencing adverse effects."). Packaging requirements are also important because of the risk that children might come across edible forms of cannabis and mistake it for ordinary food. For that reason, packages should also be tamper-resistant. *See* Peter Grinspoon, *supra* note 26, at 42.

122. *See* Larkin, *Gummy Bears*, *supra* note 78, at 382–83 (reprinting photographs of such edibles); Robert J. MacCoun & Michelle M. Mello, *Half-Baked—The Retail Promotion of Marijuana Edibles*, 372 New Eng. J. Med. 989, 990 (2015) ("Whether through deliberate acquisition or unknowing consumption, these child-friendly edibles increase minors' risk of exposure to and experimentation with marijuana.").

123. *Infra* text accompanying notes 132–34.

124. This subject is discussed in detail in Larkin, *Gummy Bears*, *supra* note 78.

125. *See*, *e.g.*, U.S. Const. amend. XXVI (defining age 18 as the minimum eligible age to vote).

126. *See, e.g.*, Volkow et al., *supra* note 102, at 2220 ("The brain remains in a state of active, experience-guided development from the prenatal period through childhood and adolescence until the age of approximately 21 years.").

127. *See, e.g.*, Matthijs G. Bossong & Raymond J.M. Niesink, *Adolescent Brain Maturation, the Endogenous Cannabinoid System and the Neurobiology of Cannabis-Induced Schizophrenia*, 92 Progress in Neurobiology 370, 373 (2010).

128. *See* George F. Koob et al., Drugs, Addiction, and the Brain 285 (2014) ("The adolescent period represents a critical phase of development, characterized by specific progressive neurobiological maturational processes in the prefrontal cortex that includes myelination and synaptic pruning. This period of maturation also involves the rearrangement of key neurotransmitter systems, such as glutamate, γ-aminobutyric acid, dopamine, and endocannabinoid systems in the frontal cortex. Changes in these systems are believed to support the emergence of adult cognitive processes. Over the course of adolescence and early adulthood, individuals show normative growth in planning, preference for delayed rather than immediate rewards, resistance to peer pressure, and impulse control. Many of the brain regions that are undergoing these developmental changes may be particularly affected by alcohol and marijuana use."); *see also*, *e.g.*, World Health Org., The Health and Social Effects of Nonmedical Cannabis Use 16 (2016) [hereinafter WHO Report] ("Accumulating evidence reveals that regular, heavy cannabis use during adolescence is associated with more severe and persistent negative outcomes than use during adulthood."); Alan J. Budney et al., *Cannabis*, *in* Lowinson and Ruiz's Substance Abuse: A Comprehensive Textbook 227 (Pedro Ruiz & Eric Strain eds., 5th ed. 2011) ("Cross-sectional and longitudinal studies have reported a clear association between chronic cannabis use and impaired psychological functioning. In particular, cannabis has been associated with poorer life satisfaction, increased mental health treatment and hospitalization, higher rates of depression, anxiety disorders, suicide attempts, and conduct disorder.") (endnote omitted); Harold Kalant, *Effects of Cannabis and Cannabinoids in the Human Nervous System*, *in* The Effects of Drug Abuse on the Human Nervous System 387, 394 (Bertha Madras & Michael Kuhar eds., 2014) (noting "the possibility that during brain maturation in adolescence, heavy exposure to cannabis might prevent the growth of axons and the establishment of large numbers of synaptic connections that normally accompany experience and learning") (citations omitted); *id.* ("[T]he results of MRI studies of the brains of late teen-aged males who had used marijuana heavily throughout adolescence" revealed a "smaller brain size and thinner cortex in early heavy users than in age-matched users who did not begin until after 17."); Bertha Madras, *Drug Use and Its*

Consequences, *in* The Effects of Drug Abuse on the Human Nervous System 14–15 (Bertha Madras & Michael Kuhar eds., 2014); Bossong & Niesink, *supra* note 127, at 370 ("THC may adversely affect adolescent experience-dependent maturation of neural circuitries within prefrontal cortical areas.").

129. Consider this 1997 summary: "[I]n agreement with previous studies early onset cannabis use, and particularly frequent use, was associated with clear increases in risks of substance use, juvenile offending, mental health problems, school dropout and unemployment subsequent to age 16. Those reporting using cannabis on 10 or more occasions by age 16 had rates of these outcomes which were between 2.1 and 19.6 times higher than the rates for those who did not use cannabis at age 16. There seems to be little doubt on the basis of this evidence that early onset cannabis use was associated with increased psychosocial risk in later adolescence.... [T]o a substantial extent, linkages between cannabis use and other aspects of psychosocial adjustment arose because those who elected to use cannabis at an early age were a high risk population which, independently of cannabis use, would have been at higher than average risk of later adjustment difficulties. [¶] Nonetheless, even after adjustment for childhood, family and related factors those who reported early cannabis use, and particularly frequent use, were at increased risks of later cannabis abuse/dependence, other substance use, juvenile offending, leaving school without qualifications and unemployment. These findings suggest a possible cause and effect association in which early onset cannabis use increases individual vulnerability to later substance use, antisocial behaviours and unemployment.... Our major conclusions about the social and legal response to cannabis use by young people are three fold. [¶] (1) It would be misleading for social and law enforcement policies to argue too strongly that cannabis use by young people is a factor that leads to seriously increased risks of psychosocial disorder in adolescence. Most of the elevated risk seen among early onset cannabis users is likely to arise from factors that were antecedent to the decision to use cannabis, rather than as a consequence of cannabis use. [¶] (2) Nonetheless, early onset usage is not without risks and those engaging in these behaviours may be more vulnerable to later psychosocial problems as a result of the social context within which cannabis is used and obtained. [¶] (3) Arguments that these difficulties may be addressed by legalizing or decriminalizing cannabis use are open to serious question. While the legalization or decriminalization of cannabis may reduce risks that users will be prosecuted, it is unlikely to change the linkages between cannabis use and the social context in which cannabis is obtained and used." David M. Fergusson & L. John Horwood, *Early Onset Cannabis Use and Psychosocial Adjustment in Young Adults*, 92 Addiction 279, 291-294 (1997) (footnotes omitted).

130. *See*, *e.g.*, Seth Ammerman et al., *The Impact of Marijuana Policies on Youth: Clinical, Research, and Legal Update*, 135 Pediatrics E769, E771 (2015); Bossong & Niesink, *supra* note 127, 372–77; Wayne Hall & Louisa Degenhardt, *Policy Implications of the Evidence on Cannabis Use and Psychosis*, *in* Marijuana and Madness, *supra* note 111, at 51, 51 ("There is consistent longitudinal evidence that young adults who are regular cannabis users have an increased risk of developing psychosis.... [D]aily or near daily users report more psychotic symptoms and are more likely to be diagnosed with a psychotic disorder than individuals who have never used cannabis.... The risk...is higher in people who begin using cannabis in their mid-teens and who regularly use in adulthood, and in young people who have a personal or family history of psychosis."); *id*. at 56 ("The epidemiological evidence for a causal relationship between cannabis and psychosis is consistent and arguably stronger than that for heavy alcohol use and similar to that for amphetamine use and psychotic symptoms."); Wayne Hall et al., *The Effects of Cannabis Use on the Development of Adolescents and Young Adults*, 2 Ann. Rev. Developmental Psychology 461, 463–76 (2020); Di Forti et al., *The Contribution of Cannabis Use*, *supra* note 119, at 432 ("[A]mong the measures of cannabis use tested, the strongest independent predictors of whether any given individual would have a psychotic disorder or not were daily use of cannabis and use of high potency cannabis. The odds of psychotic disorder among daily cannabis users were 3.2 times higher than for never users, whereas the odds among users of high potency cannabis were 1.6 times higher than for never users. Starting to use cannabis by 15 years of age modestly increased the odds for psychotic disorder but not independently of frequency of use or of the potency of the cannabis used. These measures of extent of exposure did not interact with each other, nor did they interact with the sites.... Compared with never users, participants who used high potency cannabis daily had four times higher odds of psychosis in the whole sample, with a five times increase in London and a nine times increase in Amsterdam. We also saw that, in the whole sample, daily use of high potency cannabis was associated with a doubling in the ER [emergency room] for psychotic disorder."); Wayne Hall, *What Has Research Over the Past Two Decades Revealed about the Adverse Health Effects of Recreational Cannabis Use?* 110 Addiction 19, 24–26 (2015); Beng-Choon Ho et al., *Recreational Marijuana Use, Adolescent Cognitive Development, and Schizophrenia Susceptibility*, 3 Biological Psychiatry 222, 230 (2023) ("Nonheavy MJ [cannabis] use, the typical use pattern for most adolescent users, disrupts normal adolescent cognitive maturation. Such deleterious effects from adolescent MJ exposure add to the aberrant adolescent maturation associated with familial [schizophrenia] risk. With increased availability of high-potency forms of MJ in adults, ongoing efforts in restriction and deferment of adolescent MJ access are especially needed."); Oskar Hougaard Jefsen et al., *Cannabis Use Disorder and Subsequent Risk of Psychotic and Nonpsychotic Unipolar Depression and Bipolar Disorder*, JAMA Psychiatry, at E6, May 24, 2023, https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2804862 ("We found significant association between CUD [Cannabis Use Disorder] and both bipolar disorder and unipolar depression, but the risk of bipolar disorder was nominally higher."); Hannah J. Jones et al., *Association of Combined Patterns of Tobacco and Cannabis Use in Adolescents with Psychotic Experiences*, 75 JAMA Psychiatry 240 (2018) (finding a stronger association between cannabis use and psychotic experiences for adolescents than for cigarette use); Katherine H. Karlsgodt, Commentary, *Cannabis Use in Adolescence—Vulnerability to Cognitive and Psychological Effects*, 3 Biological Psychiatry 167, 167 (2023) ("In addition to cognitive changes, cannabis use has been associated with increased rates of psychopathology, including psychosis. Psychosis spectrum disorders typically have onset in late adolescence or early adulthood. Thus, use of cannabis during this particular period may have the potential to impact the developing brain in a way that increases risk for psychosis. This risk, however, is not uniform—it appears that risk increases with earlier use, and the use of high-THC cannabis may increase risk for both cognitive effects and psychosis.") (footnote omitted); *id*. at 168 ("[T]he data from these samples indicate that cognitive changes in those with adolescent cannabis follow, rather than precede, use, and that this may be amplified in those with a family history of schizophrenia. Moreover, despite the growing belief among adolescents that cannabis is a very low risk drug, changes were found not only for heavy users who met the criteria for cannabis use disorder, but also for those with a lower, more typical level of use."); Sarah Kanana Kiburi et al., *Cannabis Use in Adolescence and Risk of Psychosis: Are There Factors that Moderate This Relationship? A Systematic Review and Meta-Analysis*, 42 Substance Abuse 527, 533 (2021) ("The majority of the studies reported that

ACU [Adolescent Cannabis Use] was associated with increased risk for psychosis. Overall, the risk of developing psychosis was higher in those reporting adolescent cannabis use compared to non-users (RR 1⁄4 1.71 (95%CI, 1.47–2.00, p<0.00001)."); *id*. at 534 ("Several studies reported that cannabis use was associated with psychosis in a dose-dependent manner with more frequent and/or heavier use having greater odds to result in psychosis compared to less frequent use."); *id*. at 537 ("This systematic review and meta-analysis presents a detailed overview of the association between adolescent cannabis use and risk of psychosis and factors that moderate this association. [¶] Overall, the results show that adolescent cannabis use was associated with increased risk for psychosis. This agrees with a previous review. Only one study found no evidence of increased risk of psychosis following early use of cannabis in high-risk adolescents. This may have been due to the low prevalence of cannabis use in the sample as reported by the authors. [¶] Subsequent analyses carried out to explore whether this association was modified by additional factors found the following factors to influence the association between adolescent cannabis use and psychosis: age of onset of cannabis use, frequency of cannabis use, exposure to childhood trauma, concurrent use of other substances, genetic factors, type of cannabis used, predisposition to psychosis and behavioral difficulties in childhood and urbanicity.") (footnotes omitted); Navdeep Kaur et al., *Variations of Cannabis-Related Adverse Mental Health and Addiction Outcomes Across Adolescence and Adulthood*, Frontiers in Psychiatry 8 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9590692/pdf/fpsyt-13-973988.pdf ("[A]ge of exposure seems likely to modulate cannabis use-related mental health and addiction outcomes. Cannabis' adverse effects on the long-term outcomes tended to be generally worse in adolescents, early cannabis use initiators and cannabis users who consumed for long periods."); Benjamin Murrie et al., *Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-Analysis*, 46 Schizophrenia Bull. 505, 513 (2019) ("The strongest predictor of transition [to schizophrenia] was the type of substance: one-third (34%) of people with cannabis-induced psychosis transitioned to a later diagnosis of schizophrenia, based on estimates from 6 studies and 3040 people. Rates were intermediate for hallucinogens and amphetamines, and below 10% for alcohol and sedative-induced psychoses.... Substance-induced psychoses are common and serious conditions. They are associated with a substantial risk for transition to schizophrenia. The risk of transition to schizophrenia is particularly increased following cannabis-induced psychosis, which should be responded to with assertive attempts at engagement, assessment, and care."); Petrilli, *supra* note 118; Ryan S. Sultan, *Nondisordered Cannabis Use Among US Adolescents*, 6 JAMA Network Open e2311294, at 2, May 3, 2023, https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2804450file:///Users/paullarkin/Downloads/("Cannabis use is associated with deficits in cognitive and executive functioning, including processing speed, sustained attention, working memory, judgment and planning, problem-solving, decision-making, and self-regulation. Adverse mental health outcomes, including increased rates of depression and suicidal behaviors, have also been associated with youth cannabis use. Well-controlled longitudinal epidemiologic studies have demonstrated that adolescent cannabis exposure is associated with a 4-fold increase in adult psychosis diagnoses. Finally, cannabis use among youth is associated with worse academic performance and delinquent behavior.") (footnotes omitted); Volkow et al., *supra* note 102, at 2220 ("The brain remains in a state of active, experience-guided development from the prenatal period through childhood and adolescence until the age of approximately 21 years.... The negative effect of marijuana use on the functional connectivity of the brain is particularly prominent if use starts in adolescence or young adulthood, which may help to explain the finding of an association between frequent use of marijuana from adolescence into adulthood and significant declines in IQ. The impairments in brain connectivity associated with exposure to marijuana in adolescence are consistent with preclinical findings that the cannabinoid system plays a prominent role in synapse formation during brain development.") (footnotes omitted); Michelle L. West & Shadi Sharif, *Cannabis and Psychosis*, 32 Child Adolescent Psychiatric Clinics N. Am. 69, 71 (2023) ("Substance use (ranging from rare use, to casual use, to misuse) is prevalent in early psychosis, both in clinical high risk CHR-p [Clinical High Risk for Psychosis] and in FEP [First Episode Psychosis]. Rates of substance use may vary between 22% and 50% of the young people with FEP, with cannabis as the most prevalent substance misused in these samples. Similarly, research suggests cannabis use is prevalent among young people at CHR-p, with 33% to 54% of youth at CHR-p using cannabis. Although prevalence estimates vary across samples, it is clear that cannabis use is common.") (footnotes omitted); *id*. at 72 ("Cannabis use has been associated with psychosis spectrum symptoms in several ways. First, in terms of incidence, research generally supports that there is a higher incidence of psychosis symptoms in people who use cannabis. In one study, the incidence of psychosis symptoms in adolescent cannabis users was 31%, compared with incidence of 20% in non–cannabis users. Similarly, a systematic review described that most studies have indicated that cannabis consumption may lead to psychotic symptoms. The Diagnostic and Statistical Manual (DSM-5) also includes a diagnosis of cannabis-induced psychotic disorder, in which people experience impairing psychotic symptoms that are directly caused by cannabis and not attributable to another ([e.g.], underlying psychotic) disorder.") (footnotes omitted); *see also supra* notes 109–10, 128–30 (collecting authorities)..

131. *See*, *e.g.*, U.S. Food & Drug Admin., FDA and Marijuana (Feb. 28, 2017) ("The FDA has not approved marijuana as a safe and effective drug for any indication."); Nat'l Inst. on Drug Abuse, Marijuana 17 (Aug. 2017); Am. Acad. Ophthalmology, Complementary Therapy Assessment: Marijuana in the Treatment of Glaucoma 1 (2014); Am. Acad. Pediatrics, *Clinical Report: Counseling Parents and Teens About Marijuana Use in the Era of Legalization of Marijuana*, 139 *Pediatrics* e20164069 (2017); Am. Cancer Soc'y, Medical Use of Marijuana: ACS Position 3 (2013); Am. Med. Ass'n House of Delegates, Report of Reference Committee K 6–7 (2014); Am. Psychiatric Ass'n, Position Statement on Marijuana as Medicine (Dec. 2013); Hall & Pacula, *supra* note 99, at 214–17 (discussing adverse effects on cells and to immunological, reproductive, cardiovascular, respiratory, and gastrointestinal systems, as well as the risk of precipitating psychosis in vulnerable individuals); J.S. Brook et al., *Early Adolescent Marijuana Use: Risks for the Transition to Young Adulthood*, 32 Psychol. Med. 79, 87–88 (2002); *cf*. Am. Epilepsy Soc'y, AES Position on Medical Marijuana (Mar. 21, 2016).

132. Hudak, *supra* note 78, at 20; *id*. at 18 ("The variety now available is a real testament to American entrepreneurship and innovation.").

133. *See* Larkin, *Gummy Bears*, *supra* note 78, at 382–83 (reprinting photographs of edibles); *see also*, *e.g.*, Robert J. MacCoun & Michelle M. Mello, *Half-Baked—The Retail Promotion of Marijuana Edibles*, 372 N. Eng. J. Med. 989, 990 (2015); Jack Healy, *New Scrutiny on Sweets with Ascent of Marijuana*, N.Y. Times, Oct. 30, 2014, at A13, https://www.nytimes.com/2014/10/30/us/new-scrutiny-on-sweets-with-ascent-of-marijuana-in-colorado.html.

134. There is also the risk of unwitting cannabis consumption by children, who stumble across their parents' stash and mistake it for candy. In the words of Dr. Robert Glatter, a New York City emergency room physician, that problem has become "extremely dangerous." Jeff Rossen & Jovanna Billington,

Rossen Reports Update: Edible Marijuana That Looks Like Candy Is Sending Kids to the ER, Today (Sep. 16, 2017, 7:41 AM), https://www.today.com/parents/edible-marijuana-looks-candy-sending-kids-er-t94486 *see also*, *e.g.*, K.J. Dell Antonia, *When Marijuana Looks Like Candy, Not Drugs*, N.Y. Times (Feb. 11, 2014), https://parenting.blogs.nytimes.com/2014/02/11/when-marijuana-looks-like-candy-not-drugs/; Katherine M. Kosa et al., *Consumer Use and Understanding of Labeling of Information on Edible Marijuana Products Sold for Recreational Use in the States of Colorado and Washington*, 43 Int'l J. Drug Pol'y 57, 58 (2017) (noting that a 2016 study found that "annual Regional Poison Center pediatric marijuana cases increased more than fivefold from 2009 to 2015, and edibles were responsible for 52% of the exposures."); MacCoun & Mello, *supra* note 133, at 990 ("Whether through deliberate acquisition or unknowing consumption, these child-friendly edibles increase minors' risk of exposure to and experimentation with marijuana."); Andrew A. Monte et al., *The Implications of Marijuana Legalization in Colorado*, 313 JAMA 241, 242 (2015) ("The most concerning health effects have been among children. The number of children evaluated in the ED [Emergency Department] for unintentional marijuana ingestion at the Children's Hospital of Colorado increased from 0 in the 5 years preceding liberalization to 14 in the 2 years after medical liberalization. This number has increased further since legalization; as of September 2014, 14 children had been admitted to the hospital this year, and 7 of these were admitted to the intensive care unit. The vast majority of intensive care admissions were related to ingestion of edible THC products.").

135. *See, e.g.*, Nat'l Inst. on Drug Abuse, Nat'l Inst. of Health, Vaping of Marijuana on the Rise Among Teens (Dec. 18, 2019) ("Past year vaping of marijuana, which has more than doubled in the past two years, was reported at 20.8% among 12th graders, with 10th graders not far behind at 19.4% and eighth graders at 7.0%. Past month marijuana vaping among 12th graders nearly doubled in a single year to 14% from 7.5%—the second largest one-year jump ever tracked for any substance in the history of the survey."); U.S. Dep't of Health & Human Servs., Off. of the Surgeon Gen., E-cigarette Use Among Youth and Young Adults: A Report of the Surgeon General 6, 14, 57–58, 203, 241 (2016); R. Miech et al., *Vaping Trends Among Adolescents, 2017–2019*, 381 New Eng. J. Med. 1490 (2019); Lucas Drill & Paul J. Larkin, Jr., *Vaping, Marijuana, and Government Regulation*, inFOCUS 14 (Winter 2020), https://www.jewishpolicycenter.org/2020/01/06/vaping-marijuana-and-government-regulation/.

136. This subject is discussed at length in Paul J. Larkin, *Twenty-First Century Illicit Drugs and Their Discontents: The Potential Risks that Cannabis Use by Pregnant and Nursing Women Pose to Their Children*, Heritage Found. Legal Memo No. 319 (Dec. 8, 2022) [hereafter Larkin, *Cannabis and Pregnancy*].

137. *See*, *e.g.*, Giorgia Sebastiani et al., *The Effects of Alcohol and Drugs of Abuse on Maternal Nutritional Profile During Pregnancy*, 10 Nutrients 1008, 1009 (2018) ("Recent estimates of the prevalence of cannabis use among pregnant women in the US range between 3% and 16%. Population-based surveillance data from the National Survey on Drug Use and Health concludes that cannabis use among pregnant women in the US has increased as much as 62% between 2002 and 2014.... There is an increasing trend in prenatal cannabis use, due to the conception [*sic*] of need of cannabis for medical use, cannabis harmlessness, and increased access to the drug."); Kelly C. Young-Wolff et al., *Rates of Prenatal Cannabis Use Among Pregnant Women Before and During the COVID-19 Pandemic*, 326 JAMA, 1745, 1745 (2021); Kelly C. Young-Wolff et al., *Trends in Self-Reported and Biochemically Tested Marijuana Use Among Pregnant Females in California from 2009–2016*, 318 JAMA 2490, 2491 (2017); George Sam Wang, *Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization*, 13 J. Medical Toxicology 99, 99 (2017).

138. *See*, *e.g.*, Am. Academy of Pediatrics, *Marijuana Use During Pregnancy and Breastfeeding: Implications for Neonatal and Childhood Outcomes*, 142 Pediatrics e20181889, at 3 (2018) [hereafter AAP, *Marijuana and Pregnancy/Breastfeeding*] ("Marijuana can affect the normal transport functions and physiologic status of the placenta throughout pregnancy. One study has revealed that short-term exposure to cannabidiol, a nonpsychoactive substance found in marijuana, can enhance the placental barrier permeability to pharmacologic agents and recreational substances, potentially placing the fetus at risk from these agents or drugs.... After maternal ingestion, concentrations of THC in fetal blood are approximately one-third to one-tenth of maternal concentrations.") (endnotes omitted).

139. Larkin, *Cannabis and Pregnancy*, *supra* note 136, at 6 ("There are several reasons why we do not yet know the answers to these questions. The available research relies largely on reports of cannabis use by women, and those reports might underestimate the amount of their use because of their authors' fear of legal repercussions. There also are a series of potentially confounding factors that complicate the interpretation of survey results. Among them are maternal use of alcohol, cigarettes, or illicit drugs other than cannabis; poor maternal nutrition; and limited prenatal care.") (footnotes omitted).

140. *See*, *e.g.*, World Health Org., The Health and Social Effects of Nonmedical Cannabis Use 28 (2016) (noting that "accumulating evidence suggests that prenatal cannabis exposure may interfere with normal development and maturation of the brain. Children exposed to cannabis in utero demonstrate impaired attention, learning and memory, impulsivity and behavioural problems and a higher likelihood of using cannabis when they mature.") (citations omitted).

141. *Id.*

142. *Id.* at 4–6 (collecting studies reaching opposing conclusions).

143. U.S. Dep't of Health & Human Servs., Substance Abuse and Mental Health Servs. Admin., Marijuana and Pregnancy (Sept. 27, 2022), https://www.samhsa.gov/marijuana/marijuana-pregnancy.

144. As the author noted previously:

> A 2022 article in the *American Journal of Obstetrics and Gynecology* concluded that "the available evidence suggests an adverse effect from cannabis exposure on male and female reproductive health, pregnancy and fetal outcomes, and longer-term offspring health and developmental trajectories." Some physicians and researchers have found that cannabis use, whether by a pregnant woman or by someone else living in the same home, poses various different types of risks to a child in utero and after birth. Among these risks are increased placement in a neonatal intensive care unit (NICU); cancer (e.g., neuroblastoma); adverse neurodevelopment (e.g., reduced neuroplasticity—the growth, maturation, and

movement of neurons during life—as well as the genesis and migration of axons and dendrites, axonal pathfinding, and synaptic transmission and pruning); impaired higher-order executive functioning (e.g., impulse control, reduced visual memory, attention) during the school-age years; autism spectrum disorder; lower birth weight (which is associated with an increase in infant morbidity and mortality, as well as long-lasting consequences such as neurosensory impairments, decreased height, and lower IQ and educational achievement); shorter gestation; spontaneous preterm birth; hyperactivity in children; and psychopathology in adolescents.

Larkin, *Twenty-First Century Cannabis Potency*, *supra* note 29, at 5.

145. *Cf.* Tista Ghosh et al., *The Public Health Framework of Legalized Marijuana in Colorado*, 106 Am. J. Pub. Health 21, 24 (2016) ("[The Colorado Department of Public Health and the Environment] department is conducting statewide formative research to help craft media messages geared toward youths, pregnant and breastfeeding women, and Latinos.").

146. *See* Larkin, *Cannabis and Pregnancy*, *supra* note 136.

147. This problem is discussed in Paul J. Larkin, *Driving While Stoned in Virginia*, 59 Am. Crim. L. Rev. Online 1 (2022); Larkin, *Reflexive Federalism*, *supra* note 73, at 554–60; Paul J. Larkin, Jr., *The Problem of "Driving While Stoned" Demands an Aggressive Public Policy Response*, 11 J. Drug Pol'y Analysis 1 (2018); Paul J. Larkin, Jr., *Medical or Recreational Marijuana and Drugged Driving*, 52 Am. Crim. L. Rev. 453 (2015).

148. Society became aware of the problems that alcohol causes drivers shortly after motor vehicle mass production began. *See, e.g.*, Motor Vehicle Act of 1915, Cal. State Laws 1915 § 17, as amended by 1915 Cal Stat. 214 ("No person who is under the influence of intoxicating liquor and no person who is an habitual user of narcotic drugs shall operate or drive a motor or other vehicle on any public highway within this state."); An Act Relative to Automobiles and Motor Cycles, ch. 412, § 4, 1906 Mass. Acts 419, 422 (making the operation of an automobile or motorcycle "while under the influence of intoxicating liquor" a misdemeanor); Eric J. Gouvin, *Drunk Driving and the Alcoholic Offender: A New Approach to an Old Problem*, 12 Am. J.L. & Med. 99, 100 (1986) ("Inebriates and moderate drinkers are the most incapable of all persons to drive motor wagons. The general palsy and diminished power of both the reason and senses are certain to invite disaster in every attempt to guide such wagons.") (quoting a 1904 editorial from the *Quarterly Journal of Inebriety*); Robert B. Voas et al., *Prescription Drugs, Drugged Driving and Per Se Laws*, 19 Inj. Prevention 218, 218 (2014). Since then, due in part to the efforts of people like Candace Lightner, who lost a daughter to a drunk driver and founded Mothers Against Drunk Driving, or MADD, the federal and state governments aggressively implemented multi-step programs to reduce the bloodshed that the Supreme Court once described as a "slaughter" that had "reach[ed] the astounding figures only heard of on the battlefield." Breithaupt v. Abram, 352 U.S. 432, 439 (1957).

149. One theory of public policy change is that it occurs at the confluence of three streams: (1) the Problem Stream (matters that a critical mass of people want to affect, change, or eliminate); (2) the Policies Stream (developed potential responses to or solutions for a problem); and (3) the Politics Stream (changes in the governing majority of (for example) Congress; the occurrence of a galvanizing public event (*e.g.*, 9/11); and so forth). John W. Kingdon, Agendas, Alternatives, and Public Policies (2d ed. 1995).

150. Office of Nat'l Drug Control, National Drug Control Strategy 2010, at 23 (July 2010).

151. "Today there is a wealth of evidence that marijuana is an impairing substance that affects skills necessary for safe driving." Robert L. DuPont et al., *Marijuana-Impaired Driving: A Path Through the Controversies*, *in* Contemporary Health Issues on Marijuana 183, 186 (Kevin A. Sabet & Ken. C. Winters eds., 2018); *see also*, *e.g.*, British Med. Ass'n, Therapeutic Uses of Cannabis 66 (1997); European Monitoring Ctr. For Drugs and Drug Addiction, Drugs Use, Impaired Driving and Traffic Accidents 33–41 (2d ed. 2014); Nat'l Acad. Rep., *supra* note 26, at 227–30; Nat'l Inst. on Drug Abuse, Cannabis (Marijuana) Research Report 7–8 (2020); Nat'l Highway Traffic Safety Admin., Marijuana, Alcohol, and Actual Driving Performance 39–40 (1999); Iversen, *supra* note 81, at 95 (noting that, in laboratory tests and simulator studies, cannabis impaired fine motor skills and manual dexterity as the complexity of tasks increase, impairs a driver's peripheral vision and lateral lane control, and disrupts a driver's short-term (or "working") memory); Stanford Chihuri et al., *Interaction of Marijuana and Alcohol on Fatal Motor Vehicle Crash Risk: A Case-Control Study*, 4 Injury Epidemiology 8 (2017) ("Results of this study indicate that marijuana use is associated with a significantly increased risk of involvement in fatal motor vehicle crashes, as reported in recent epidemiological studies."); Hall et al., *supra* note 130, at 464 ("Overall, the epidemiological and laboratory evidence on the acute effects of cannabis strongly suggests that cannabis users who drive while intoxicated have an increased risk of motor vehicle crashes of 1.5–3 times..., which is lower than the risk for drivers impaired by intoxicating doses of alcohol of 6–15 times. These risks may be larger in younger, less experienced cannabis users and drivers."); Rebecca L. Hartman & Marilyn A. Huestis, *Cannabis Effects on Driving Skills*, 59 Clin. Chemistry 478, 489 (2013) ("Consuming cannabis before driving, with or without alcohol, is a common occurrence that produces substantial morbidity and mortality on the roadway."); Thomas D. Marcotte et al., *Driving Performance and Cannabis Users' Perception of Safety: A Randomized Clinical Trial*, 79 JAMA Psychiatry 201, 206–07 (2022) ("In this study of 191 regular cannabis users randomized to smoke THC or placebo cigarettes ad libitum, we found worse performance in the THC group on a measure of overall driving simulator performance as well as specific driving challenges, including a divided attention task, adding to a growing literature that THC negatively impacts driving ability.... In a placebo-controlled parallel study of regular cannabis users smoking cannabis with different THC content ad libitum, there was statistically significant worsening on driving simulator performance in the THC group compared with the placebo group. The THC content of the cannabis and intensity of prior cannabis use were not associated with driving outcomes; participants self-titrated in a manner that yielded similar reductions in driving performance, despite achieving different THC blood concentrations."); Danielle McCartney et al., *Determining the Magnitude and Duration of Acute Δ9-Tetrahydrocannabinol (Δ9-THC)-Induced Driving and Cognitive Impairment: A Systematic and Meta-Analysis*, 126 Neurosci. & Behav. Revs. 175, 184 (2021) ("Δ9-THC impairs aspects of driving performance and demonstrate that the magnitude and duration of this impairment depends on the dose provided, route of administration and frequency with which cannabis is used."). Ironically, one study of the effect of medical legalization on motor vehicle safety found a $22 premium decline per year following cannabis legalization, particularly in areas close to a cannabis dispensary or that had high DUI rates pre-legalization, perhaps due to a substitution of cannabis for alcohol, the absence of cannabis "bars,"

or a decline in miles driven after use. *See* Cameron M. Ellis, *Medical Cannabis and Automobile Accidents—Evidence from Auto Insurance*, 31 Health Econ. 1878, 1890 (2022). The study did not examine the effect of recreational-use laws. *Id*.

152. *See* Nat'l Highway Traffic Safety Admin., *Drug-Impaired Driving*, https://www.nhtsa.gov/risky-driving/drug-impaired-driving (last visited Apr. 23, 2022) ("Several scientific studies indicate that [any rumor 'that marijuana can't impair you or can make you a safer driver'] is false."); *see also, e.g.*, Colo. Dep't of Transp., FY 2020 Report, The Cannabis Conversation 5 (2020) ("People who consume cannabis more often consider driving under the influence of marijuana to be less dangerous."); Thomas R. Arkell et al., *Driving-Related Behaviours, Attitudes and Perceptions Among Australian Medical Cannabis Users: Results from the CAMS 18-19 Survey*, Accident Analysis & Prevention, Oct. 2, 2020, at 5, https://pubmed.ncbi.nlm.nih.gov/33017729/ [https://perma.cc/F9N7-DCY7] ("The finding that 71.9% of respondents felt that their medical cannabis use does not impair their driving is consistent with previous reports showing that cannabis users tend to perceive DUIC [Driving Under the Influence of Cannabis] as relatively low risk, especially when compared with alcohol."); Camille Gourdet et al., *Countering-Drug Impaired Driving: Addressing the Complexities of Gathering and Presenting Evidence in Drug-Impaired Driving Cases*, RAND 1 (2020) ("The general public…widely holds the misperception that drug-impaired driving is not a risky behavior…which can make the prevention of impaired driving more difficult.") (citations omitted); Marcotte et al., *supra* note 151, at 207 ("A lack of insight regarding driving impairments, particularly at 90 minutes, is of concern, given that users will likely self-evaluate when they feel safe to drive. Although performance was improving at 3.5 hours, recovery was not fully seen until 4.5 hours postsmoking."); Johannes E. Ramaekers, *Driving Under the Influence of Cannabis: An Increasing Public Health Concern*, 319 JAMA 1433, 1434 (2018) ("Regular cannabis users often admit to driving under the influence of cannabis and wrongfully believe that cannabis does not affect their driving performance or that they can compensate for cannabis-associated impairment.") (footnote omitted); *cf*. Jean-Louis Martin, *Cannabis, Alcohol, and Fatal Road Accidents*, PLOS One 11 Nov. 8, 2017, https://doi.org/10.1371/journal.pone.0187320 ("As regards driving under the influence of cannabis, the attributable risk fraction was considerably lower than for alcohol, but significant for all doses taken together, with no apparent dose-effect," but also noting that "[u]nlike alcohol, the level of intoxication from cannabis at the time of the accident is quite difficult to estimate, owing to the strong increase in THC concentration just after consumption followed by a rapid decrease"). Some argue that THC-intoxicated motor vehicle operators, unlike drunk drivers, compensate by driving more slowly and avoid aggressive driving. *See*, *e.g*., Hall et al., *supra* note 130, at 464 ("In laboratory studies, THC produces dose-related impairments in reaction time, information processing, perceptual-motor coordination, motor performance, attention, and tracking behavior.... These effects suggest that cannabis use could cause car crashes if users drive while intoxicated, but studies in driving simulators suggest that cannabis-impaired drivers are aware of their impairment and compensate by slowing down and taking fewer risks.") (citations omitted); Martin, *supra*, at 9–10 (noting that "the demonstrated effects of alcohol intoxication" include "a weakening of the capacities necessary for safe driving and an increase in self-confidence that pushes the driver to over-estimate his or her capacities, in particular, for driving at higher or unsuitable speeds."). Those strategies, however, do not compensate for the delayed reaction time caused by THC. *Id.* ("A number of experimental investigations have shown a decreased capacity of drivers under the influence of cannabis, in particular a decrease in attention, increased reaction time and reduced ability to control direction. Individual variations are considerable, but there is an overall diminution in cognitive and motor functions related to driving. A further dose-dependent effect has been demonstrated in certain aspects of vehicle control, such as steering, keeping distance from the vehicle ahead, driving speed, reaction time and keeping on the right side of the road."); McCartney et al., *supra* note 151, at 184 (noting that "[s]everal measures of driving control" such as "Lateral Control" and "Reaction Time," as well as "driving-related cognitive skills (i.e., Fluid Intelligence, Divided Attention, Tracking Performance, Information Processing, Conflict Control, Reaction Time, Fine Motor Function, [and] Sustained Attention," all "exhibited significant impairment in the initial meta-analyses of 'peak' Δ9-THC effects."). The combination of THC and alcohol aggravates those problems.

153. States that legalized cannabis use, such as Colorado, have seen an increase in the number of drivers involved in fatal motor vehicle crashes. 5 Rocky Mtn. High-Intensity Drug Trafficking Area Strategic Intel. Unit, The Legalization of Marijuana in Colorado: The Impact-Updated 5-17 (2019); Colo. Dep't of Public Safety, Div. of Crim. Just., Off. of Res. & Stat., Impacts of Marijuana Legalization in Colorado: A Report Pursuant to Senate Bill 13-283, at 51 (Oct. 2018); Gourdet et al., *supra* note 152, at 1 ("Recent studies suggest that states that legalized cannabis use have observed temporary increases in traffic fatalities in the years subsequent to the opening of retail stores selling cannabis.").

154. *See*, *e.g*., Nat'l Highway Traffic Safety Adm'n, Results of the 2013-2014 National Roadside Survey of Alcohol and Drug Use by Drivers 2 (2015) (finding that nearly 20 percent of drivers tested positive for potentially impairing legal and illegal drugs other than alcohol); New Zealand Transp. Agency, Risks of Driving When Affected by Cannabis, MDMA (Ecstasy) and Methamphetamine and the Deterrence of Such Behaviour: A Literature Review 10 (2020) ("Of the 11% who had used cannabis in the previous 12 months, 36% of those who drove during that time reported driving under the influence of cannabis."); Joint Legis. Audit & Rev. Comm'n, Report to the Governor and the General Assembly of Virginia: Key Considerations for Marijuana Legalization, Commission Draft 19 (2020) ("evidence shows more Virginians are using marijuana and driving"); Arkell et al., *supra* note 152, at 4 ("[A] substantial proportion of medical cannabis users are driving shortly after using cannabis, with some driving during the time of peak effects when impairment tends to be greatest. More than 19.0% of users reporting driving within one hour of consuming cannabis and 34.6% of all users within 3 hours of use.") (citations omitted). *See generally* Cntrs for Disease Control & Prev., Morbidity and Mortality Weekly Report, Driving Under the Influence of Marijuana and Illicit Drugs (Dec. 20, 2019) ("During 2018, 12 million (4.7%) U.S. residents reported driving under the influence of marijuana in the past 12 months; 2.3 million (0.9%) reported driving under the influence of illicit drugs other than marijuana.").

155. *See*, *e.g*., European Drug Monitoring Cntr. for Drugs and Drug Addiction, Drug Use, Impaired Driving and Traffic Accidents 36 (2d ed. 2014) ("[M]ost studies found significant negative effects of cannabis on performance up to 10 hours after use."); DuPont et al., *supra* note 27, at 187 ("A study of chronic, daily marijuana users assessed over a three-week period of abstinence showed prolonged impairment of psychomotor function on critical tracking and divided attention tasks necessary for driving safely."); M. Kathryn Dahlgren et al.. *Recreational Cannabis Use Impairs Driving Performance in the Absence of Acute Intoxication*, Drug & Alcohol Dependence, Jan. 14, 2020, at 8, https://pubmed.ncbi.nlm.nih.gov/31952821/ [https://perma.cc/9538-TB2E]; McCartney et al., *supra* note 151, at 176 (citations omitted) ("Recent reports also indicate that the behaviour of cannabis users with respect to

delaying driving is variable; with 13–50% of individuals admitting to driving within 3-hs [3 hours] of cannabis use in recent surveys from the United States, Canada and Australia."); *id.* at 184 ("There appears to be no universal answer to the question of "*how long to wait before driving?*" following cannabis use: consideration of multiple factors is therefore required to determine appropriate delays between Δ9-THC use and the performance of safety-sensitive tasks."); *id.* at 188 ("Findings suggest individuals should wait at least 5-hs [5 hours] following inhaled cannabis use before performing safety-sensitive tasks, although the recovery time required will depend on several factors (in particular, Δ9-THC dose); oral Δ9-THC-induced impairment may also take longer to subside."). Plus, edible cannabis releases THC more slowly than smokable cannabis because it must traverse the gastrointestinal system before reaching the brain. *See* DuPont et al., *supra* note 27, at 185. The delayed onset of cannabis' euphoric feeling could impair driving long after ingestion, when a person believes that it no longer would influence his driving abilities.

156. *See*, *e.g.*, Becky Bui & Jack K. Reed, Colo. Dep't of Pub. Safety, Driving Under the Influence of Drugs and Alcohol: A Report Pursuant to House Bill 17–1315, at 7 (July 2018) (noting that in 2016 alcohol and THC are the most common drug combination in cases with test results); Darrin T. Grondell et al., Wash. Traffic Safety Comm'n, Marijuana Use, Alcohol Use, and Driving in Washington State 1–2 (Apr. 2018) ("Poly-drug drivers (combinations of alcohol and drugs or multiple drugs) is now the most common type of impairment among drivers in fatal crashes."); 5 Rocky Mtn. High-Intensity Drug Trafficking Area Strategic Intel. Unit, The Legalization of Marijuana in Colorado: The Impact-Updated 10 (2019) (depicting that 43 percent of the drivers who tested positive for marijuana also had used alcohol); European Monitoring Centre for Drugs and Drug Addiction, Driving Under the Influence of Drugs, Alcohol and Medicines in Europe—Findings from the DRUID Project 17 (2012) ("[I]n the majority of cases [involving drivers "seriously injured or killed"], illicit drugs were found in combination with other psychoactive substances, mainly alcohol. THC (and/or THC-COOH) seemed to be one of the most prevalent illicit drugs."); Caulkins, et al., *supra* note 98, at 44 (("Marijuana users are much more likely than are nonusers to drink and to abuse alcohol."); Martin, *supra* note 152 ("Among these confounding factors, it is essential that alcohol be taken into account since very often (more than one in two times, according to our data) the consumption of cannabis is accompanied by consumption of alcohol."); Johannes E. Ramaekers, *Driving Under the Influence of Cannabis: An Increasing Public Health Concern*, 319 JAMA 1433 (2018).

157. *See*, *e.g.*, British Med. Ass'n, Therapeutic Uses of Cannabis 71 (1997) (noting the "additive effect" when marijuana and alcohol are combined); Iversen, *supra* note 81, at 96; Percy Bondallaz et al., *Cannabis and Its Effects on Driving Skills*, 268 Forensic Sci. Int'l 92 (2016); Chihuri, *supra* note 151, at 4–5 ("Alcohol and marijuana are each associated with heightened risk of fatal crash involvement. When alcohol and marijuana are used together, there exists a positive synergistic effect on the risk of fatal crash involvement on the additive scale. These results suggest that the combined effects of alcohol and marijuana on fatal crash risk are significantly greater than the sum of their separate effects."); R. Andrew Sewell et al., *The Effect of Cannabis Compared with Alcohol on Driving*, 18 Am. J. Addiction 185 (2009).

158. Because it would be deemed impaired driving.

159. *See*, *e.g.*, McCartney et al., *supra* note 151, at 176. Canada recommends that no one drive after consuming cannabis for six or more hours, but also noted that "[t]he wait time may need to be longer, depending on the user and the properties of the specific cannabis product used." Benedikt Fisher et al., *Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations*, 107 Am. J. Pub. Health 1193, e4 (2017) (Recommendation 8).

160. *See* U.S. Const. art. I, § 3, cls. 1 & 8; South Dakota v. Dole, 483 U.S. 203 (1987) (upholding Congress' authority to condition the receipt of federal highway funds on the state's adoption of a minimum drinking age). There are various steps that Congress could take, such as lowering the Blood Alcohol Standard from 0.08 g/dL to 0.0 g/dL for anyone testing positive for cannabis. *See* Larkin, *Driving While Stoned*, *supra* note 147, at 18–24; Paul J. Larkin, Jr., *Medical or Recreational Marijuana and Drugged Driving*, 52 Am. Crim. L. Rev. 453, 509, 514 (2015).

161. *See*, *e.g.*, David A. Boyum & Mark A. R. Kleiman, *Substance Abuse Policy from a Crime-Control Perspective*, *in* Crime: Public Policies for Crime Control 331, 333 (James Q. Wilson & Joan Petersilia eds., 2002); Ulrika Haggard-Grann et al., *The Role of Alcohol and Drugs in Triggering Criminal Violence—A Case-Crossover Study*, 101 Addiction 100, 105 (2006) ("We found a large increase in the risk of criminal violence among individuals who had been exposed to the short-term effects of alcohol (hazard period of 24 hours before violent act). This corresponds with a strong positive correlation found previously between alcohol and violence in various clinical and laboratory studies.") (footnotes omitted); John Monahan, *A Jurisprudence of Risk Assessment: Forecasting Harm Among Prisoners, Predators, and Patients*, 92 Va. L. Rev. 391, 422 (2006) (finding that 38 percent of parties serving a jail sentence for violent crime were under the influence of alcohol).

162. *See*, *e.g.*, B.J. Bushman et al., *Effects of Alcohol on Human Aggression: An Integrative Research Review*, 107 Psychological Rev. 341 (1990); Jeffrey Fagan, *Interactions Among Drugs, Alcohol, and Violence*, 12 Health Aff. 65, 67–68 (1993) ("The weight of evidence suggests that substance use provides a provocative context for violence, but there is limited evidence that alcohol or drugs directly cause violence.... To assign a causal role to drugs or alcohol requires that we be certain that the behavior would not have occurred if the user had been sober. That is, comorbidity and causation are often confounded. Much alcohol and drug use is overlapping, for example, with mental health problems, a variety of deviant and illegal acts, and poor outcomes in marriage or employment. Nevertheless, we face the paradox that while there is weak evidence of direct effects of alcohol or drugs pharmacologically, there is a high proportion of violent events of all kinds where alcohol is present among assailant, victim, or both parties."); *see also*, *e.g.*, Bureau of Justice Statistics, U.S. Dep't of Justice, Alcohol and Crime: Data from 2002–2008 (July 28, 2010) (noting that 37 percent of state offenders imprisoned for a violent offense in 2004 reported being under the influence of alcohol at the time of the crime); David Boyum & Peter Reuter, An Analytic Assessment of U.S. Drug Policy 28 (AEI Evaluative Studies 2005) ("[M]ore crimes—and in particular, more violent crimes—are committed under the influence of alcohol than under the influence of all illegal drugs combined."); Steven B. Duke & Albert C. Gross, America's Longest War: Rethinking Our Tragic Crusade Against Drugs 38–42 (1993); Sharon M. Boles & Karen Miotto, *Substance Abuse and Violence: A Review of the Literature*, 8 Aggression & Violent Behav. 155, 156–57, 161–63 (2003); *id.* at 161 ("Alcohol is more closely linked to murder, rape, and assault than any other substance" and "has also been found to be a contributing factor in incest, child molestation, spousal abuse, and other family violence."); William F. Wieczorek, *Alcohol, Drugs*

and Murder: A Study of Convicted Homicide Offenders, 18 J. Crim. Just. 217, 218 (1990) ("Studies of violent offenders have found that they are much heavier drinkers than demographically matched samples of the general population."); *id*. at 220 (study found that 56 percent of homicide offenders were under the influence of alcohol or illicit drugs at the time of the crime), 225 (concluding that studies have shown an association between alcohol use and violence, but not necessarily a causal effect).

163. John M. Macdonald, *Alcoholism as a Medicolegal Problem*, 11 Clev.-Marshall L. Rev. 39, 41 (1962).

164. Alex Berenson, Tell Your Children: The Truth About Marijuana, Mental Illness, and Violence 121–22 (2019).

165. *Id*. at 122.

166. *Id*.

167. *See*, *e.g*., Robert Ashford, Letter from Scholars and Clinicians Who Oppose Junk Science About Marijuana, Drug Policy Alliance, Feb. 14, 2019, https://web.archive.org/web/20230606124702/https://drugpolicy.org/resource/letter-scholars-and-clinicians-who-oppose-junk-science-about-marijuana; James Hamblin, *If Legal Marijuana Leads to Murder, What's Up in the Netherlands?*, Atlantic (Jan. 14, 2019), https://www.theatlantic.com/health/archive/2019/01/marijuana-murder-gladwell/579949/; Carl L. Hart & Charles Ksir, *Does Marijuana Use Really Cause Psychotic Disorders?*, Guardian (Jan. 20, 2019), https://www.theguardian.com/commentisfree/2019/jan/20/marijuana-cannabis-health-effects-issues-mental-health-disorders-science; Amanda Chicago Lewis, *Is Alex Berenson Trolling Use with His Anti-Weed Book?*, Rolling Stone (Jan. 12, 2019), https://www.rollingstone.com/culture/culture-features/alex-berenson-marijuana-tell-your-children-trolling-777741/; German Lopez, *What Alex Berenson's New Book Gets Wrong About Marijuana, Psychosis, and Violence*, Vox (Jan. 14, 2019), https://www.vox.com/future-perfect/2019/1/14/18175446/alex-berenson-tell-your-children-marijuana-psychosis-violence; Jacob Sullum, *Does Legalizing Marijuana Cause "Sharp Increases in Murders and Aggravated Assault"?*, Reason (Jan. 9, 2019), https://reason.com/2019/01/09/does-legalizing-marijuana-cause-sharp-in/; Katie Way, *What Fearmongering About Pot Tells You About Mainstream Marijuana Coverage*, Nation (Jan. 28, 2019), https://www.thenation.com/article/archive/alex-berenson-marijuana-legalization-tell-your-children-review/. There were some favorable reviews, but they were in the minority. *See*, *e.g*., Aaron E. Carroll, *It's Time for a New Discussion of Marijuana's Risks*, N.Y. Times, May 7, 2018, https://www.nytimes.com/2018/05/07/upshot/its-time-for-a-new-discussion-of-marijuanasrisks.html?action=click&module=RelatedLinks&pgtype=Article (article subtitled "You may reasonably decide the benefits outweigh the harms, but you should know about those potential harms.") (last accessed Aug. 16, 2023); Paul Davis, Book Review: *"Tell Your Children" by Alex Berenson*, Wash. Times (Jan. 20, 2019), https://www.washingtontimes.com/news/2019/jan/20/book-review-tell-your-children-by-alex-berenson/; Malcolm Gladwell, *Is Marijuana as Safe as We Think?*, New Yorker (Jan. 7, 2019), https://www.newyorker.com/magazine/2019/01/14/is-marijuana-as-safe-as-we-think; Stephanie Mencimer, *This Reporter Took a Deep Look into the Science of Smoking Pot. What He Found Is Scary*, Mother Jones (Jan. 5, 2019), https://www.motherjones.com/politics/2019/01/new-york-times-journalist-alex-berenson-tell-your-children-marijuana-crime-mental-illness-1/.

168. *See*, *e.g*., Giulia Trotta et al., *Cannabis Use and Violence*, *in* Marijuana and Madness, supra note 111, at 279, 280–81 (noting that, on the one hand, "[c]annabis use and violence often co-occur during adolescence and young adulthood, and it is difficult to disentangle the direction of the association," and, on the other hand, "a review of the relevant literature suggests that cannabis users are at increased risk of carrying out interpersonal violence, including severe types of violence such as aggravated assault, sexual aggression, fighting, and robbery."); Dimitri Daldegan-Bueno et al., *Conceptualizing and Considering Cannabis-Related "Harm-to-Others": The Role of Cannabis-Related Violence*, 57 Substance Abuse & Misuse 1488, 1488 (2022) ("Systematic review and other study data show a moderately positive association between cannabis use and perpetration of physical (including intimate-partner) violence, for example involving assault, aggression, and fighting; this risk may be further elevated by intensive use patterns. Such harms may involve injuries/deaths and contribute to the cannabis-related burden of disease."); Laura Dellazizzo et al., *Violence and Cannabis Use: A Focused Review of a Forgotten Aspect in the Era of Liberalizing Cannabis*, 11 Frontiers in Psychiatry art. 567887, at 7–8 (2020) ("Available evidence from meta-analytical studies in youths, intimate partners, and individuals with SMD [Severe Mental Disorders] have shown that there is a global moderate association between cannabis use and violence, which may be stronger in the latter more at-risk population. Though, not only is any type of use of cannabis associated with violence, but preliminary data has highlighted a potential dose-response relationship with larger effects in more frequent users. In this sense, the association between cannabis use and violence is not to be overlooked. [¶] Of interest, positive associations between cannabis use and violence have also emerged in more recent studies following these meta-analyses. For instance, scholars have observed an association between cannabis and violence in intimate partners.... In all, evidence-based research from meta-analyses have indeed shown that cannabis is associated to violence and therefore measures should be taken to mitigate the risk. Nevertheless, there remains [*sic*] questions as to the direction of the association and the potential mechanisms involved, which may be answered with the changes observed following the liberalization of cannabis."); Laura Dellazizzo et al., *Cannabis Use and Violence in Patients with Severe Mental Illness: A Meta-Analytical Investigation*, 274 Psychiatry Rsch. 42 (2019) (concluding that earlier studies found a moderate association between cannabis use and violence in severely mentally ill parties but concluding that additional investigation is warranted); Deepak Cyril D'Souza, *Cannabinoids and Psychosis*, 78 Int'l Rev. Neurobiology 2889, 2889 (2007) ("Also clear is that cannabinoids can also exacerbate psychosis in individuals with an established psychotic disorder, and these exacerbations may last beyond the period of intoxication. Less clear is whether cannabis causes a persistent de novo psychosis. The available evidence meets many but not all the criteria for causality, including dose-response, temporality, direction, specificity, and biological plausibility. On the other hand, the large majority of individuals exposed to cannabinoids do not experience psychosis or develop schizophrenia and the rates of schizophrenia have not increased commensurate with the increase in rates of cannabis use."); Jules R. Dugre et al., *Persistency of Cannabis Use Predicts Violence Following Acute Psychiatric Discharge*, 8 Frontiers of Psychiatry art. 176, at 1 (2017) (finding that recently discharged psychiatric patients who continued to use cannabis were "2.44 times more likely to display violent behaviors"); Maryam Sorkhou et al., *Does Cannabis Use Predict Aggressive or Violent Behavior in Psychiatric Populations? A Systematic Review*, 48 Am. J. Drug & Alcohol Abuse 631, 640 (2022) (footnotes omitted) ("Our findings here suggest that there may be an association between cannabis use and violent or aggressive behaviors in people with psychotic-spectrum disorders and

PTSD. However, methodological limitations, including the use of retrospective or cross-sectional data and heterogeneity across controlled confounders, preclude causal connections between cannabis use and subsequent aggression or violence. Nonetheless, it is important to note that there have been reports of numerous unfavorable outcomes related to cannabis use in mental illness, including worsened symptomology, poorer treatment adherence, and lower life satisfaction."). *Contra*, *e.g.*, Katherine R. Buchholz et al., *Associations Between PTSD and Intimate Partner and Non-Partner Aggression Among Substance Using Veterans*, 64 Addictive Behav. 194, 200–01 (2017) (finding that cannabis use was a "nonsignificant factor" in intimate partner violence by veterans suffering from PTSD); Edward P. Mulvey, *Substance Use and Community Violence: A Test of the Relationship at the Daily Level*, 74 J. Consulting & Clin. Psychology 743, 750 (2006) ("Considering the entire follow-up period,...individuals who drank or used other drugs more often had more involvement in violence. Moreover, at the daily level, it appears that use of alcohol and other drugs often co-occur regularly with violence; violent days are more likely to be substance-using days and substance-using days are more likely to be violent days (although this is less true of marijuana)."); *id.* at 751 ("[T]he key behaviors examined in this study appear to occur in 'bursts.' The time series models provide clear evidence of the serial nature of these policy-relevant behaviors, with substance use on 1 day related to substance use on the next 2 days and violence on 1 day related to violence on the next day. People engage in substance use and violence for periods involving successive days, and the relations among these behaviors appear to predominantly reflect consistency of behavior within series over several days rather than a consistently strong association in which one form of substance use precipitates violence. This implies that we need to develop a fuller understanding of the patterns and effects of these extended periods of substance use for their impact on other aspects of functioning."); E.B. De Sousa Fernandes Perna et al., *Subjective Aggression During Alcohol and Cannabis Intoxication Before and After Aggression Exposure*, 233 Psychopharmacology 3331, 3339 (2016) ("The results in the present study support the hypothesis that acute alcohol intoxication increases feelings of aggression and that acute cannabis intoxication reduces feelings of aggression following aggression exposure."). Here, too, many of the studies were published in the past decade.

169. *See*, *e.g.*, Office of the Surgeon Gen., U.S. Dep't of Health and Human Servs., Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health 1–22 (2016) ("There is a growing body of research suggesting the potential therapeutic value of marijuana's constituent cannabinoid chemicals in numerous health conditions including pain, nausea, epilepsy, obesity, wasting disease, addiction, autoimmune disorders, and other conditions."); Nat'l Acad. Rep., *supra* note 26, at 90 ("Conclusion 4–1: There is substantial evidence that cannabis or cannabinoids is an effective treatment for chronic pain in adults."); Kevin Boehnke et al., *Medical Cannabis Use Is Associated with Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients with Chronic Pain*, 17 J. Pain 739 (2016) (results from an online questionnaire showed that 64 percent of respondents using medical cannabis decreased their opioid use, and 45 percent reported a better quality of life); Ziva D. Cooper et al., *Comparison of the Analgesic Effects of Dronabinol and Smoked Marijuana in Daily Marijuana Smokers*, 38 Neuropsychopharmacology 1984 (2013); Jaseena Elikottil et al., *The Analgesic Potential of Cannabinoids*, 5 J. Opioid Mgmt. 341 (2009); Mary E. Lynch & Fiona Campbell, *Cannabinoids for Treatment of Chronic Non-Cancer Pain: A Systematic Review of Randomized Trials*, 72 Brit. J. Clin. Pharmacology 735, 742 (2011) ("In conclusion this systematic review of 18 recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment for chronic non-cancer (predominantly neuropathic) pain."); Yasmin L. Hurd, *Cannabidiol: Swinging the Marijuana Pendulum from "Weed" to Medication to Treat the Opioid Epidemic*, 40 Trends in Neuroscis. 124 (2017); Russell Noyes, Jr. et al., *Analgesic Effect of Delta-9-Tetrahydrocannabinol*, 15 J. Clinical Pharmacology 139, 143 (1975); Turo J. Nurmikko et al., *Sativex Successfully Treats Neuropathic Pain Characterized by Allodynia: A Randomised, Double-Blind, Placebo-Controlled Clinical Trial*, 133 J. Pain 210 (2007); Martin Pinsger et al., *Benefits of an Add-On Treatment of Synthetic Cannabinomimetic Nabilone on Patients with Chronic Pain—A Randomized Controlled Trial*, 10 European J. Pain S163 (2006); P.J. Robson, *Therapeutic Potential of Cannabinoid Medicines*, 6 Drug Analysis & Testing 24 (2014); Anne Katrin Schlag et al., *The Value of Real World Evidence: The Case of Medical Cannabis*, Frontiers in Psychiatry, 2022, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9669276/pdf/fpsyt-13-1027159.pdf ("Over a million UK patients are self-medicating with illicit cannabis products. The international database evidence suggests that these drugs offer a notable advantage in treatment for many patients in whom current medicines are either ineffective or poorly tolerated. Present findings from RWE [Real World Evidence] globally are highly suggestive of a pattern of evidence which deserves a level of recognition it does not currently receive.... Cannabis has an excellent safety profile and is a historically established medicine[.] Pragmatic long-term studies...can further confirm its safety and effectiveness."); Mark A. Ware et al., *Cannabis Use for Chronic Non-Cancer Pain: Results of a Prospective Survey*, 102 Pain 211, 214 (2003) (discussing survey of patients at a pain management unit: "This survey found that cannabis use among chronic pain patients is not uncommon. Ten percent of the population studied was currently using cannabis for pain relief and another 5% had tried cannabis for pain relief."); Bart Wilsey et al., *Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain*, 14 J. Pain 136 (2013); *see also* Andrew J. Saxon & Kendall C. Browne, *Marijuana Not Ready for Prime Time as an Analgesic*, 36 Gen. Hosp. Psychiatry 4, 5 (2014) ("Numerous small controlled studies have repeatedly demonstrated that certain cannabinoids do reduce acute and chronic pain when compared to placebo in double-blind designs. Most of these trials have use[d] pharmaceutical forms of cannabinoids, either dronabinol (oral THC), nabilone (an oral, synthetic THC analog) or an extract of plant cannabis containing nearly equal proportions of THC and cannabidiol delivered as an oral mucosal spray, although a few have used smoked or vaporized marijuana.").

170. *See supra* note 26. There also are physicians who hold the opposite view. *See*, *e.g.*, DuPont, *supra* note 27, at 147–54; Ed Gogek, Marijuana Debunked 111 (2015) ("Political campaigns sell marijuana laws to the voting public with ads that feature cancer patients using marijuana for nausea. But it's a bait and switch.... The patients using medical marijuana in real life are disproportionately young and male, and few of them have serious illnesses."); Kevin P. Hill, Marijuana: The Unbiased Truth about the World's Most Popular Weed (2015); Reisfield & DuPont, *supra* note 27, at 868.

171. *See, e.g.*, Neeraj Kancherla et al., *Cannabis Associated Mental Health Effects: A Review*, 13 J. Pharmacy & Bioallied Scis. S943, S945 (2012) ("A paradox has been created between the detrimental physical and social implications and the consumers' self-proclaimed medicinal effects for the usage of *Cannabis* and its derivatives.").

172. 21 U.S.C. § 355(d). An FDA guidance document—*see* U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Ctr. for Biologics Evaluation & Rsch. & Cntr. for Drug Evaluation & Rsch., *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) [hereafter FDA Clinical Effectiveness Guidance]—https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-

evidence-effectiveness-human-drug-and-biological-productsprovides the agency's opinion on "the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics." *Id*. at 2. A drug's sponsor must provide "substantial evidence" of the drug's effectiveness—viz., "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. § 355(d). The FDA interprets that provision generally to require "at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness," but "[i]n some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use," while "[i]n other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval—generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds." FDA Clinical Effectiveness Guidance, *supra*, at 3.

173. *See, e.g.*, U.S. Dep't of Health & Human Servs., Food & Drug Admin., *FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)* (Oct. 16, 2019); U.S. Dep't of Health & Human Servs., Food & Drug Admin., *What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-Derived Compounds, Including CBD* (July 17, 2019).

174. *See, e.g.*, U.S. Dep't of Health & Human Servs., Off. of the Surgeon Gen'l, U.S. Surgeon General's Advisory: Marijuana Use and the Developing Brain (Aug. 29, 2019), https://www.hhs.gov/surgeongeneral/reports-and-publications/addiction-and-substance-misuse/advisory-on-marijuana-use-and-developing-brain/index.html; U.S. Dep't of Health & Human Servs., Off. of the Surgeon Gen'l, The Surgeon General's Warning on Marijuana (Aug. 13, 1982), https://www.cdc.gov/mmwr/preview/mmwrhtml/00001143.htm.

175. *See, e.g.*, Nat'l Inst. on Drug Abuse, Marijuana as Medicine (July 2019), https://nida.nih.gov/sites/default/files/marijuanamedicinedrugfacts_july2019_.pdf ("Why isn't the marijuana plant an FDA-approved medicine? The FDA requires carefully conducted studies (clinical trials) in hundreds to thousands of human subjects to determine the benefits and risks of a possible medication. So far, researchers haven't conducted enough large-scale clinical trials that show that the benefits of the marijuana plant (as opposed to its cannabinoid ingredients) outweigh its risks in patients it's meant to treat.").

176. *See, e.g.*, Substance Abuse & Mental Health Servs. Admin. (SAMHSA), Learn About Marijuana Risks (Feb. 27, 2023), https://www.samhsa.gov/marijuana.

177. *See, e.g.*, HHS Sec'y Alex M. Azar II, Remarks on Surgeon General's Marijuana Advisory, Press Conf. (Aug. 29, 2019), https://www.hhs.gov/about/leadership/secretary/speeches/2019-speeches/remarks-on-surgeon-general-marijuana-advisory.html ("Especially as the potency of marijuana has risen dramatically over the past several decades, we don't know everything we might want to know about this drug. But we do know a number of things: It is a dangerous drug. For many, it can be addictive. And it is especially dangerous for adolescents and pregnant women, because of what we know about how it affects the developing brain. We need to be clear: Some states' laws on marijuana may have changed, but the science has not, and federal law has not.") (internal paragraphing omitted); U.S. Dep't of Health & Human Servs., Guidance on Procedures for the Provision of Marijuana for Medical Research (May 21, 1999); U.S. Dep't of Health & Human Servs., Office of Population Affs., Risks of Adolescent Marijuana Use (Apr. 8, 2019).

178. *See* Letter from Peter Hyun, Acting Ass't Att'y Gen'l, to Senators Elizabeth Warren & Cory A. Booker (Apr. 12, 2022) (rejecting the Senators' request to move cannabis out of Schedule I; "Cannabis is a Schedule I controlled substance under the Controlled Substances Act (CSA). This is—in part—due to HHS's determination that cannabis has not been proven in scientific studies to be a safe and effective treatment for any disease or condition.").

179. Nat'l Acad. Rep., *supra* note 26.

180. *See generally* Paul J. Larkin, Jr. & Bertha K. Madras, *Opioids, Overdoses, and Cannabis: Is Marijuana an Effective Therapeutic Response to the Opioid Abuse Epidemic?*, 17 Geo. J.L. & Pub. Pol'y 555, 572–92 (2019) (hereinafter Larkin & Madras, *Cannabis vs. Opioids*).

181. *See, e.g.*, Abhiram R. Bhashyam et al., *Self-Reported Marijuana Use Is Associated with Increased Use of Prescription Opioids Following Traumatic Musculoskeletal Injury*, 100 J. Bone & Joint Surgery 2095, 2096 (2018) ("Prior research provided moderate evidence supporting marijuana use for chronic pain. However, the current literature is inadequate to draw meaningful conclusions as to the effectiveness of marijuana as an acute pain reliever."); Fiona A. Campbell et al., *Are Cannabinoids an Effective and Safe Treatment in the Management of Pain? A Qualitative Systematic Review*, 323 British Med'l J. 1, 16 (2001) ("We found insufficient evidence to support the introduction of cannabinoids into widespread clinical practice for pain management—although the absence of evidence of effect is not the same as the evidence of absence of effect.... Cannabis is clearly unlikely to usurp existing effective treatments for postoperative pain."); Russell Noyes, Jr. et al., *Analgesic Effect of Delta-9-Tetrahydrocannabinol*, 15 J. Clinical Pharmacology 139, 139 (1975) ("Crude preparations of cannabis sativa were recommended for a variety of painful conditions toward the end of the 19th century.... Yet, they proved no match for the potent and rapid acting narcotics and eventually lost favor because their effects were milder and less predictable."); Bart Wilsey et al., *Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain*, 14 J. Pain 146 (2013) ("[T]he analgesic effect of cannabis in treating acute pain would be less than optimal; this is consistent with the recommendation that cannabinoids are not suitable for postoperative pain."); David Raft et al., *Effects of Intravenous Tetrahydrocannabinol on Experimental and Surgical Pain*, 21 Clinical Pharmacology & Therapeutics 26 (1976).

182. *See generally* Larkin & Madras, *Cannabis vs. Opioids*, *supra* note 180, at 579–80 ("Only a handful of controlled trials of individuals suffering from neuropathic pain have shown pain reduction using smoked marijuana. Results from those studies are inadequate to recommend long-term use of marijuana, for several reasons. The research was conducted over a very short time (days to weeks); the majority of subjects were experienced marijuana users who were also using prescribed but unreported quantities of opioids; and there is no indication that subjects who were using various prescribed opioids were randomized according to dose, type, and frequency. Moreover, the researchers who conducted the tests did not rigorously ask the test subjects about quality-of-life issues, such as their coping skills and objective measures of daily cognitive functioning. Although the therapeutic

efficacy of cannabinoids in reducing chronic pain certainly merits further study, meta-analysis of placebo-controlled studies of the use of whole-plant cannabis or cannabinoids for pain did not find a proven pain-killing effect, and any overall effect for alleviating pain was not statistically significant. Atop that, there is stronger evidence supporting the effectiveness of nonpharmacological therapies, such as exercise, rehabilitation, acupuncture, and non-psychoactive, non-steroidal, anti-inflammatory medications for the treatment of lower back pain, the leading cause of disability worldwide, than for use of plant marijuana as a treatment.") (footnotes omitted).

183. *See* Devan Kansagara et al., Dep't of Veterans Affs., Health Srvcs. Research and Development Serv., Evidence-Based Synthesis Program, Benefits and Harms of Cannabis in Chronic Pain or Post-traumatic Stress Disorder: A Systematic Review 67 (2017) ("We reviewed the literature examining the benefits of cannabis in chronic pain and PTSD populations, as well as literature examining potential harms relevant to these populations. Table 10 summarizes the evidence on the benefits and harms of cannabis use. Overall, we found limited evidence on the potential benefits and harms of cannabis use in chronic pain populations. We found low-strength evidence that cannabis preparations with precisely defined THC-cannabidiol content (most in a 1:1 to 2:1 ratio) may alleviate neuropathic pain but insufficient evidence in populations with other types of pain. The applicability of these findings to current practice may be low, in part because the formulations studied may not be reflective of what most patients are using, and because the consistency and accuracy of labeled content in dispensaries are uncertain. Furthermore, most studies are small, many have methodological flaws, and the long-term effects are unclear given the brief follow-up of most studies. There is insufficient evidence of effects on quality of life or functional status. [¶] Among neuropathic pain studies, we found a discrepancy between continuous and dichotomous pain outcomes. Possible interpretations are that cannabis is simply not consistently effective or that, although cannabis may not have clinically important effects on average, subgroups of patients may experience large effects. We did not find data to clarify which subgroups of patients are more or less likely to benefit."); *id*. at 2, 67–69; Gabrielle Campbell et al., *Effect of Cannabis Used in People with Chronic Non-Cancer Pain Prescribed Opioids: Findings from a 4-year Prospective Cohort Study*, 3 Lancet Pub. Health e341, e348 (2018) (footnotes omitted) ("We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased opioid discontinuation.... We found inconsistencies in our findings between what participants reported and our statistical assessment of associations. Although participants who used cannabis reported that the mean effectiveness of cannabis on pain was 7 out of a possible score of 10, in unadjusted cross-sectional and longitudinal analyses, people who used cannabis in the past month reported greater pain severity and interference than those who had not used cannabis in the past month. In adjusted longitudinal analyses, we found no association between cannabis and pain severity or interference. This finding is inconsistent with previous studies that have found cannabis reduced pain severity. [¶] In our cohort, patients with chronic non-cancer pain who used cannabis reported significantly greater pain severity than those not using cannabis, consistent with surveys of medicinal users who report using cannabis because of a failure of conventional treatments."); Shannon M. Nugent et al., *The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review*, 167 Annals Internal Med. 319 (2017) ("Although cannabis is increasingly available for medical and recreational use, little methodologically rigorous evidence examines its effects in patients with chronic pain. Limited evidence suggests that it may alleviate neuropathic pain, but evidence in other pain populations is insufficient."); *cf*. Li Wang et al., *Medical Cannabis or Cannabinoids for Chronic Non-Cancer and Cancer Related Pain: Systematic Review and Meta-Analysis of Randomised Clinical Trials*, 373 British Med'l J., 2021, https://www.bmj.com/content/374/bmj.n1034.long ("Moderate to high certainty evidence shows that, compared with placebo, non-inhaled medical cannabis or cannabinoids results in a small to very small increase in the proportion of patients living with chronic cancer and non-cancer pain who experience an important improvement in pain relief, physical functioning, and sleep quality, along with several adverse side effects.... Our findings may or may not apply to inhaled forms of medical cannabis, veterans, individuals with substance use disorder or other mental illness, or those involved in litigation or receiving disability benefits.").

184. *See supra* note 18.

185. *See* 21 C.F.R. § 314.50.

186. Even where companies state that they are following accepted practices, the practices themselves might be insufficient. *See* Thomas & ElSohly, *supra* note 81, at 83 ("Medical cannabis products that are obtained from dispensaries or state programs may follow specific international, national, or state requirements relating to growing, formulation, manufacturing, marketing, and distribution. However, in general the standards for these products and their labeling have not been thoroughly researched or harmonized. Cannabis dispensaries in the United States are providing users with products that have not been reviewed or approved by the FDA as mandated by the Compassionate Investigational New Drug Program. These dispensaries are also not legally regulated or licensed by the DEA to distribute cannabis or cannabis derived materials, and the distribution of these substances may not be documented or controlled as is the case with pharmaceutical substances regulated by the FDA or DEA.").

187. DuPont, *supra* note 27, at 148.

188. Thomas & ElSohly, *supra* note 81, at 8.

189. *Id*. at 11.

190. *Id.* at xiii; *id*. at 84.

191. Jonathan P. Caulkins et al., Marijuana Legalization: What Everyone Needs to Know 34 (2d ed. 2016).

192. Starks, *supra* note 78, at 17–19, 45; Thomas & ElSohly, *supra* note 81, at 2.

193. Thomas & ElSohly, *supra* note 81, at 2. *Cannabis sativa L*. has a higher THC and lower CBD content than *Cannabis indicia*. *Cannabis ruderalis* is rarely cultivated for its intoxicating effect. For discussions of the botanical differences between them, see *id*. at 3–4.

194. Starks, *supra* note 78, at 18 ("[T]here are no fertility barriers between the species."); *id*. at 45 ("In the last century, breeding programs have [led] to the development of several hundred distinct varieties."); Thomas & ElSohly, *supra* note 81, at 2–30.

195. Starks, *supra* note 78, at 20; Thomas & ElSohly, *supra* note 81, at 8.

196. Thomas & ElSohly, *supra* note 81, at 8.

197. *Id*.

198. DuPont, *supra* note 27, at 142.

199. There are 545 cannabinoids as of 2016. Thomas & ElSohly, *supra* note 81, at xiii–xiv, 5 tbl. 1.3, 11, 27–37 (noting that cannabis contains more than "cannabinoids" (viz., biologically active ingredients) and other compounds); *id*. at 30 ("The current variation in phytocannabinoid content varies across and within chemotypes has important implications in medicinal cannabis and cannabis-based formulations and dosing. This has become increasingly apparent and can be recognized by the plethora of varieties of cannabis being cultivated, manufactured, and marketed in the medicinal and recreational market.").

200. *Id.* at xiii.

201. *Id*.; see *id*. ("At every step, from planting through consumption, myriad influences can alter dose, absorption rate, interactions among constituents, exposure to toxins, and a host of other factors that can result in underdosing, overdosing, and various types and levels of acute and chronic poisoning, not excepting an increase in the probability of lung cancer."), 11, 30 ("[T]he cannabinoid content and profile changes over time as the plant grows, matures, and ages.... The current variation in phytocannabinoid content across and within chemotypes has important implications in medicinal cannabis and cannabis-based formulations and dosing. This has become increasingly apparent and can be recognized by the plethora of varieties of cannabis being cultivated, manufactured, and marketed as dosing formulations in the medicinal and recreational market.") (footnote omitted), 34 ("[T]he contribution of the various chemical constituents in cannabis to its therapeutic and organoleptic [viz., sensory] effects varies because of several factors, including their differing concentrations (content), chemical properties ([e.g.], stability, volatility), pharmacological actions, ([e.g.], receptor affinities, efficacies), physiochemical parameters ([e.g.], lipophilicity, solubility), pharmacokinetics, and pharmacodynamics)."), 63–64, 84; *see also*, *e.g*., Starks, *supra* note 78, at 111 ("Research has shown that it is not possible to extract more than 50% of the cannabinoids from fresh, undried material.").

202. Starks, *supra* note 78, at 41–42 ("Much of the variation is due to fluctuation in the content of other constituents such as protein, fat, and carbohydrates.").

203. *Id*. at 32.

204. "Formulations provided by dispensaries vary widely in nature and origin of materials, with many cannabis herbal chemotypes processed in different ways. There are myriad solid, and liquid products for various methods of inhalation as smoke or vape, ingestion, and delivery to mucous membranes. Labeling practices vary between states and even dispensaries, often providing the user with limited information on ingredients. Batch production records for raw materials and formulations are generally not available. Varieties of cannabis are often distinguished by popular names that can vary from place to place." Thomas & ElSohly, *supra* note 81, at 83; *id*. at 84 ("This inconsistency has been attributed to the varying origins and age of the plant material and variations in preparation with some notable exceptions ([e.g.], Sativex [an FDA-approved drug manufactured by a reputable pharmaceutical company]), [and] this historical trend appears to be continuing in today's medical cannabis dispensaries."); Starks, *supra* note 78, at 41–42.

205. Frye & Smitherman, *supra* note 26, at 9.

206. Thomas & ElSohly, *supra* note 81, at 44 ("In contrast to the situation in the Netherlands, the differences [in the United States] in chemical content between the products are not often readily discernable from the label, or in some instances even through rigorous quantitative analysis, and the pharmacological and organoleptic effects can be unpredictable. The breadth of product lines in popular markets appears to be more a matter of marketing than of differential therapeutic utility."); *id*. at 85.

207. The THC content can vary from 12 percent to 20 percent in the plant form or in hashish (dried cannabis resin and crushed plants). Hash oil (an oil-based extract of hashish) has a greater THC content and range, from 15 percent to 65 percent. Cannabis oil extracts can be up to 80 percent THC, and crystalline forms of THC can be 99.9 percent pure. *See*, *e.g*., DSM-5 (noting that cannabis potency ranges from 1 percent to 15 percent, hashish from 10 percent to 20 percent); Caulkins et al., *supra* note 191; Wayne Hall & Rosalie Liccardo Pacula, Cannabis Use and Dependence: Public Health and Public Policy 17 (2003); Iversen, *supra* note 81, at 10; Herbert D. Kleber & Robert L. DuPont, *Physicians and Medical Marijuana*, 169 Am. J. Psychiatry 564, 564, 565 (2012) (estimating cannabis potency at as much as 20 percent); Beau Kilmer & Rosalie Liccardo Pacula, *Understanding and Learning from the Diversification of Cannabis Supply Laws*, 112 Addiction 1128, 1131 (2016); Larkin, *Reconsidering Marijuana*, *supra* note 8, at 120; Larkin, *Gummy Bears*, *supra* note 78, at 337–38 & nn.56–62; Joseph M. Pierre, *Risks of Increasingly Potent Cannabis: The Joint Effects of Potency and Frequency*, 16 Current Psychiatry 15, 15 (2017) ("Cannabis preparations such as hashish and hash oil extracts containing THC well above average—from 35% to 90% THC—are now more widely available."); Jeffrey C. Raber et al., *Understanding Dabs: Contamination Concerns of Cannabis Concentrates and Cannabinoid Transfer During the Act of Dabbing*, 40 J. Toxicological Sci. 797 (2015) (finding a range of 53.9 percent to 65.5 percent THC in hash seized from 2004 to 2008); Anna Wilcox, *THC-A Crystalline: The World's Strongest Hash with 99.99% THC*, Herb (Mar. 29, 2017), https://herb.co/2017/03/29/thc-a-crystalline/. Dronabinol (marketed as Marinol) is an FDA-approved pill-form drug of 99 percent THC that is used for chemotherapy-induced nausea. *See* Dronabinol: Pharmacology and Biochemistry, Natl Ctr. Biotechnology Info., https://pubchem.ncbi.nlm.nih.gov/compound/Dronabinol#section=Pharmacology-and-Biochemistry (last accessed Oct. 9, 2022).

208. Thomas & ElSohly, *supra* note 81, at 50.

209. For example, THC is lipophilic (viz., fat soluble) but not water soluble. So, THC-infused tea can contain less THC than a joint. But adding butter or vegetable oil to tea and brewing it for several hours can increase the THC content of the drink. Additionally, the delayed euphoric feeling resulting from ingestion can lead to overconsumption because users believe that they have consumed an insufficient amount to achieve the desired effect. Thomas & ElSohly, *supra* note 81, at 45, 55–56.

210. *See, e.g.*, John Brick & Carlton E. Erickson, Drugs, the Brain, and Behavior: The Pharmacology of Drug Use Disorders 106 (2d ed. 2013); Iversen, *supra* note 81, at 41–47; Starks, *supra* note 78, at 12. Smoking cannabis can result in a 30 percent loss of THC, although the variance of lost THC can be from 2 percent to 56 percent due to "smoking dynamics." Thomas & ElSohly, *supra* note 81, at 53. The peak euphoria produced by edibles might not appear for one to four hours after ingestion (although some psychoactive effects can last longer). Plus, the liver metabolizes and removes some THC. Iversen, *supra* note 81, at 43, 47.
211. *See, e.g.*, Freeman & Craft, *supra* note 118, at 46 (in Deepak D'Souza et al. eds., 2023).
212. *See, e.g.*, Iversen, *supra* note 81, at 149.
213. *Id*. at 149.
214. *See, e.g.*, Freeman & Craft, *supra* note 118, at 46.
215. *See*, *e.g.*, Starks, *supra* note 78, at 43 ("[T]he potency of the plant does not necessarily increase continually as it gets older, but it will often undergo constant variation."); *id* at 82–83 (noting that the environment might inhibit the production of macronutrients necessary for plant growth, but not THC production); *id*. at 89 ("Inevitably, all chemical constituents of marijuana will vary with such factors as genetics, age, sex, and growth conditions."); *id*. at 93 ("To obtain maximum potency, the timing of the harvest is critical. Sometime after the seed has become fully mature, the plant will begin to senesce and die."); *id*. (also noting that there is no scientifically verified and reliable dating mechanism for identifying the optimal harvesting day); ("[T]he specialized cells which synthesize cannabis happen to be more numerous and perhaps more active in the flowering tops than elsewhere."). *See generally id*. at 41–110.
216. *See*, *e.g.*, *id*. at 13–15 (noting that time and light caused THC to deteriorate); Frye & Smitherman, *supra* note 26, at 9; Thomas & ElSohly, *supra* note 81, at xiii–xiv, 30.
217. Freeman & Craft, *supra* note 118, at 45.
218. *See*, *e.g.*, Caulkins et al., *supra* note 98; Beau Kilmer & Rosalie Liccardo Pacula, *Understanding and Learning from the Diversification of Cannabis Supply Laws*, 112 Addiction 1128, 1131 (2016); Larkin, *Gummy Bears*, *supra* note 78, at 337–38 & nn.56–62.
219. *See*, *e.g.*, Casarett, *supra* note 26, at 116 ("Not knowing—by a factor of ten[—]how much of a drug you're going to get makes it almost impossible to find the right dose for the right patient.").
220. Volkow et al., *supra* note 102, at 2222.
221. Starks, *supra* note 78, at 43. An intoxicating dose of THC is quite small, perhaps only 100–200 micrograms. Iversen, *supra* note 81, at 56.
222. Thomas & ElSohly, *supra* note 81, at 97 ("[T]he maximum recommended medical dose of THC (dronabinol) is 20 mg, and in my laboratory several daily cannabis users became sick or vomited after swallowing an 80 mg dose. Yes, this product was labeled as containing 20 doses, but it resembled a brownie, and it was no bigger than a typical serving, there was no clear way of selecting one dose from it, and the THC was not evenly distributed.").
223. Volkow et al., *supra* note 102, at 2222.
224. Paul J. Larkin, *Twenty-First Century Cannabis Potency*, *supra* note 29, at 6.
225. *See*, *e.g.*, Iversen, *supra* note 81, at 82–83; Starks, *supra* note 78, at 38 (noting that factors such as a user's motivational or psychological state, prior experience with cannabis, the time of day, and other drug intake can affect the user's experience).
226. *See*, *e.g.*, Starks, *supra* note 78, at 10–11; Amir Englund et al., *Can We Make Cannabis Safer?*, 4 Lancet Psychiatry 643 (2017); Larkin & Madras, *Cannabis vs. Opioids*, *supra* note 180, at 576 ("[W]e cannot yet say that CBD will reduce or eliminate all adverse effects of THC, but preliminary data indicate that CBD does attenuate specific THC-elicited neuroadaptations.") (footnote omitted); Bertha K. Madras et al., *Dramatic Increase of Dopamine D1–D2 Receptor Heteromers by Tetrahydrocannabinol (THC) in Primate Caudate Nucleus Is Attenuated by Cannabidiol (CBD)*, Neuropsychopharmacology (2016), https://acnp.org/videos/bertha-madras/ [https://perma.cc/RL84-AGVB]; Christian D. Schubart et al., *Cannabis with High Cannabidiol Content Is Associated with Fewer Psychotic Experiences*, 130 Schizophrenia Research 216 (2011).
227. *See* Mahmoud A. ElSohly et al., *Changes in Cannabis Potency Over the Last Two Decades (1995–2014): Analysis of Current Data in the United States*, 79 Biological Psychiatry 613 (2016).
228. The different potency ratios in cannabis are also a reason why the plant could not satisfy the uniformity requirement discussed below.
229. *See* Thomas & ElSohly, *supra* note 81, at 88 ("The manufacturing process is also a critical activity where quality control and best practices are required to ensure the suitability of medical products.").
230. *Id*. at 87.
231. *Id*.
232. *Id*. at 88.
233. *See*, *e.g.*, 21 C.F.R. Pt. 111, §§ 111.1–111.610 (2023); U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Botanical Drug Development: Guidance for Industry (Dec. 2016), https://www.fda.gov/media/93113/download; U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements, 72 Fed. Reg. 34,752 (June 25, 2007); Am. Botanical Council, Sustainable Herbs Program, FDA Good Manufacturing Practices, https://sustainableherbsprogram.org/fda-good-manufacturing-practices/ (last visited June 9, 2023); World Health Org., WHO Guidelines on Good Manufacturing Practices (GMP) for Herbal Medicines (2007).

234. *See* Thomas & ElSohly, *supra* note 81, at 88 (noting that analytical methods must be "validated for specificity, linearity, accuracy, precision, and ruggedness" before being used to assess a product's contents).

235. *Id*. at 90 ("Finished drug products require release testing that may include appearance, identity, assay content uniformity, average weight and weight variation, dissolution, moisture content, and related substances ([e.g.], impurities and degradation products) as per established specifications.").

236. *Id*. at 89–90 ("With a botanical drug product or derived substance, the types of impurities present may range from structurally similar organic components ([e.g.], biosynthetic intermediaries, degradation products) to unexpected byproducts or contaminants, pesticide residues, metals, residual solvents, and water.").

237. *Id*. at 91 ("the purpose of stability testing is 'to provide evidence on how the quality of a drug substance or drug product varies over time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and enables recommended storage conditions, retest periods, and the shelf-life to be established.'"). The FDA has guidelines for such testing. *See* U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Cntr. for Biologics Evaluation & Rsch & Cntr. for Drug Evaluation & Rsch., *Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products* (Nov. 2003), https://www.fda.gov/media/71707/download.

238. *See*, *e.g.,* U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Cntr. for Biologics Evaluation and Rsch & Cntr. for Drug Evaluation & Rsch., Q2(R1) *Validation of Analytical Procedures: Text and Methodology Guidance for Industry* (Sept. 2021), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q2r1-validation-analytical-procedures-text-and-methodology-guidance-industry; U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Guidance Document: Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015), https://www.fda.gov/media/87801/download; U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Guidance for Industry Q3A, Impurities in New Drug Substances (June 2008), https://www.fda.gov/media/71727/download; U.S. Dep't of Health & Human Servs., *Guidance for Industry Q1A(R2)*; U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, *Guidance for Industry Q1B, Photostability Testing of New Drug Substances and Products* (Nov. 1996), https://www.fda.gov/media/71713/download; U.S. Dep't of Health & Human Servs., Food & Drug Adm'n, Cntr. for Drug Evaluation & Rsch., Reviewer Guidance: Validation of Chromatographic Methods (Nov. 1994), https://www.fda.gov/media/75643/download. *See generally* Thomas & ElSohly, *supra* note 81, at 64, 88–94.

239. Thomas & ElSohly, *supra* note 81, at 94 ("In summary, all dosage formulations, including cannabis extracts, pills, lotions, injectables, and consumables, should be shown to be accurately formulated and consistently produced, and to have the delivery characteristics and stability attributes required for safety and efficacy over the lifetime of the product.").

240. *See, e.g.*, Frye & Smitherman, *supra* note 26, at 53 ("While there are some legitimate pesticide-free cannabis growers, for the most part, when cannabis is grown outside of state regulatory guidelines, the plants are typically laden with pesticides."); Moskowitz, *supra* note 26, at 10 (noting that "most testing is up to the vendors," and "studies have shown them to be quite inaccurate," perhaps due to "poor testing, reliance on old testing, the ever-changing nature of harvested cannabis, and/or outright deception").

241. Iversen, *supra* note 81, at 155; *see also*, *e.g.*, Nat'l Acad. Rep., *supra* note 26, at 53–54 (listing such possibilities).

242. Iverson, *supra* note 81, at 155.

243. Casarett, *supra* note 26, at 249; *see, e.g., id.* ("That variability [in the presence and amount of cannabinoids in marijuana], it seems to me, makes it very difficult to call marijuana a 'medicine' in the same way that, say, penicillin is a medicine. For these reasons, I still think of marijuana as more or less equivalent to an herbal remedy. It's essentially plant-based stuff with numerous active and inactive ingredients, only some of which we understand. And those ingredients make an appearance in varying doses and ratios among plants and between crops."); *see also* Charles Krauthammer, *Pot as Medicine*, Wash. Post (Feb. 7, 1997), https://www.washingtonpost.com/archive/opinions/1997/02/07/pot-as-medicine/84704a96-39b8-485e-96e1-08e798569f05/ ("Take any morally dubious proposition—like assisting a suicide—and pretend it is merely help for the terminally ill, and you are well on your way to legitimacy and a large public following. That is how assisted suicide is sold. That is how the legalization of marijuana is sold. Indeed, that is precisely how Proposition 215, legalizing marijuana for medical use, passed last November in California.... Marijuana gives them a buzz, all right. But medical effects? Be serious. The medical effects of marijuana for these conditions are nil. They are, as everyone involved in the enterprise knows—and as many behind Prop 215 intended—a fig leaf for legalization.").

244. Peter Grinspoon, *supra* note 26, at xiii. I agree wholeheartedly with that conclusion. Larkin, *Reflexive Federalism*, *supra* note 73, at 533 ("It is difficult to believe that anyone who voted for the CSA—let alone anyone who voted for the Constitution at the Convention of 1787 or in the Ratification Debates—believed that they were creating a system in which, as a practical matter, the states could hand out licenses to commit federal crimes. Yet, that is the law today. To call it odd does not adequately express the bizarre status of our cannabis policy. A 'potential train wreck' is not too strong a description.") (footnote omitted).

245. Larkin, *Reflexive Federalism*, *supra* note 73, at 568–70 & n.177.

246. *See* Printz v. United States, 521 U.S. 898, 933–34 (1997) (holding unconstitutional the Brady Handgun Violence Prevention Act, Pub. L. No. 103–159, 107 Stat. 1536 (codified as amended at 19 U.S.C. § 922 (2018)), insofar as it directed state law enforcement officers to conduct firearms background checks required by federal law); *see also* Murphy v. NCAA, 138 S. Ct. 1461 (2018) (ruling that Congress cannot order a state to pass a state criminal law); Printz v. United States, 521 U.S. 898 (1997) (ruling that Congress cannot require state law enforcement officers to enforce a federal criminal law); New York v. United States, 505 U.S. 414 (1992) (ruling that Congress cannot order a state to adopt a federal regulatory regime as a matter of state law).

247. U.S. Const. art. VI, cl. 2 ("This Constitution, and the Laws of the United States which shall be made in pursuance thereof; and all Treaties made, or which shall be made, under the authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State notwithstanding.").

248. *See Gonzales*, 545 U.S. 1 (Congress can prohibit individuals from growing cannabis for their own medical use in a state that authorizes such action); United States v. Oakland Cannabis Buyers Coop., 532 U.S. 483, 494–95 (2001) (rejecting a medical necessity defense to federal prosecution in a state that authorizes cannabis to be used for medical purposes).
249. *Matthew* 26:39 (King James).
250. White House, Statement from President Biden on Marijuana Reform, Oct. 6, 2022, https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/06/statement-from-president-biden-on-marijuana-reform/ ("I am asking the Secretary of Health and Human Services and the Attorney General to initiate the administrative process to review expeditiously how marijuana is scheduled under federal law. Federal law currently classifies marijuana in Schedule I of the Controlled Substances Act, the classification meant for the most dangerous substances. This is the same schedule as for heroin and LSD, and even higher than the classification of fentanyl and methamphetamine—the drugs that are driving our overdose epidemic.").
251. 2 U.S.C. § 811(a)(2); text accompanying note 71 *supra*.
252. Reisfield & DuPont, *supra* note 27, at 868 (citation omitted).
253. Larkin, *Reconsidering Marijuana*, *supra* note 8, at 118.
254. Larkin, *Reflexive Federalism*, *supra* note 73, at 594–95 (footnotes omitted).
255. Jonathan P. Caulkins, *The Real Dangers of Marijuana*, Nat'l Affs. 21, 30 (Winter 2016).
256. *See* Sean M. O'Connor & Erika Lietzan, *The Surprising Reach of FDA Regulation of Cannabis, Even After Descheduling*, 68 Am. U. L. Rev. 823 (2019) (explaining that descheduling cannabis transfers regulatory authority to the FDA); *cf.* Thomas & ElSohly, *supra* note 81, at xiv (arguing that the FDA should be more responsible for cannabis regulation than the DEA).
257. Emmet Power et al., *Does Cannabis Use Cause Psychosis?*, in Deepak D'Souza et al., *supra* note 168, at 174.
258. *See* Iversen, *supra* note 81, at 5 ("Often, in analyzing the mass of scientific data, it is difficult to come to clear-cut conclusions."); Sultan, *supra* note 130, at 9 ("Demonstrating a causal link between adolescent cannabis exposure in both the CUD [Cannabis Use Disorder] and NDCU [Nondisordered Cannabis Use] groups and adverse psychosocial outcomes is not possible with the current study. Nevertheless, lines of research in neuroscience demonstrate that recreational cannabis use in adolescents is associated with decreased brain volumes in CB1-rich areas of the brain involved in motivational, emotional, and affective processing. Furthermore, earlier age of onset of cannabis use also is associated with the magnitude of these changes. Prospective longitudinal research with repeated measures could help distinguish explanations for the fairly strong associations observed in this study.") (footnote omitted).
259. *See*, *e.g.*, Biden v. Nebraska, 143 S. Ct. 2355 (2023) (setting aside President Biden's college and graduate student-debt forgiveness program based on a statute empowering the Secretary of Education to provide relief only for servicemembers); West Va. v. EPA, 142 S. Ct. 2587 (2022) (setting aside the EPA's clean power plan rule, which effectively would have shuttered fossil fuel-fired plants, to address "climate change"); Nat'l Fed'n of Indep. Bus. v. OSHA, 142 S. Ct. 661 (2022) (staying an Occupational Safety and Health Administration (OSHA) mandatory COVID-19 vaccination requirement based on a statute allowing OSHA to establish workplace safety rules); Ala. Ass'n of Realtors v. HHS, 141 S. Ct. 2485 (2021) (staying the home eviction moratorium adopted by the Centers for Disease Control and Prevention (CDC) based on a statute authorizing the CDC to assist states with quarantines).
260. Such as in the case of "climate change." *See* Stephen E. Koonin, Unsettled: What Climate Science Tells Us, What It Doesn't and Why It Matters (2021).
261. "Let politics rule, though the heavens might fall."
262. *See* Editors, *Joe Biden's Attempt to Bypass the Senate*, Nat'l Rev., July 24, 2023, https://www.nationalreview.com/2023/07/joe-bidens-attempt-to-bypass-the-senate/ (noting that "the [Biden] administration's attitude towards the rule of law" is "do whatever it wants and dare others to sue.").

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