Prescription and Nonprescription Cannabinoids: A Dual-Path Regulatory Framework

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Scientific understanding of the human endocannabinoid system (ECS) has grown to include clinical outcomes data on the benefit of exogenous cannabinoids, specifically *Cannabis sativa L.*—the plant's component cannabinoids, terpenes, and synthetic counterparts.[1] As research mounts and the medical community begins to view cannabis as a legitimate therapy, there has been a shift toward an emerging standard of care (SOC).[2] A dual-path federal regulatory framework is needed to support this SOC in order to ensure patient safety, product quality, and market access.

All humans have an ECS, comprised of receptors throughout the body that together uniquely support homeostasis.[3,4] *Cannabis sativa L.* is a hardy plant species comprising numerous cannabis cultivars and chemovars, each with wide-ranging concentrations of delta-9-tetrahydrocannabinol (THC; the psychoactive component of cannabis); cannabinoids such as cannabidiol (CBD), cannabigerol (CBG), and cannabinol (CBN); as well as terpenes such as myrcene and linalool.[1] Evolving clinical evidence on the impact of cannabinoids, flavonoids, and terpenes on ECS receptors and body systems can serve as a common denominator for local, state, and international laws regarding access to prescription and nonprescription products containing natural or synthetic analog cannabinoids.

Emerging Standard of Care for Cannabis

In recent years, literature on the therapeutic benefits associated with cannabis and cannabinoids has grown, reaching 568 systematic reviews and 2282 primary studies between 1999 and 2016, according to a comprehensive review conducted by the Committee on the Health Effects of Marijuna.[5] As research studies become more rigorous and access to cannabis increases, there has been a shift toward an emerging SOC across many medical conditions.[2] The combined list of qualifying medical conditions among 38 US states and territories with medical marijuana programs now exceeds 75, not including hospice care and terminal illness qualifications. Such qualifying acute and chronic conditions include amyotrophic lateral sclerosis, ulcerative colitis, multiple sclerosis, fibromyalgia, post-traumatic stress disorder, chemotherapy-induced nausea and vomiting, severe and intractable pain, parkinsonism, rheumatoid arthritis, epilepsy, seizures, psoriatic arthritis, obsessive-compulsive disorder, and opioid use disorder, as well as rarer qualifying conditions such as Tourette syndrome, Huntington's disease, lupus, and muscular dystrophy.[6] Importantly, many cannabis components such as CBD, CBG, CBN, and terpenes, have demonstrated beneficial clinical and preclinical activity across many of these same conditions.[1] Importantly, shifts toward an SOC for medical cannabis are being driven by off-label use of prescription cannabinoids, especially by physicians in states without medical marijuana programs. Additionally, clinical trials suggest efficacy of off-label use of these agents for conditions ranging from severe chronic obstructive sleep apnea to chronic neuropathic pain, and adjuvant treatment of chronic pain in patients receiving opioid therapy.[7-9]

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>
> —*Rob Dhoble*

Although strides are being made regarding the consistency of care and patient safety in the prescription market, the wide variety and availability of nonprescription cannabinoid products is left largely unregulated. To date, the FDA has not established labeling requirements or ingredient analysis standards for nonprescription cannabinoids, but instead has focused on enforcement actions related to unsubstantiated medical claims and quality issues of manufacturers of these products.[10]

Limitations of Current Pharmacotherapy

Cannabis medicine may fill the gaps in the efficacy and tolerability of many FDA-approved treatments for chronic conditions as well as the lack of safe and effective treatments for many rare diseases.[11-13] Nearly one-third of patients recently surveyed said they stopped taking a prescription medication without consulting a health care practitioner, most commonly because of side effects (29%) or they felt the drug was not working (15%).[14]

Additionally, the current health care landscape is limited by the cost of health insurance, high deductibles, and the high cost of prescription medications.[15] As a result, many Americans postpone or delay needed medical treatment, with 1 in 5 having to liquidate their savings to pay a medical bill.[15] In fact, 31% of surveyed adults

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reported that they or a family member have relied on home remedies or over-the-counter (OTC) drugs instead of seeing a doctor, and approximately 18% reported not filling a prescription due to cost, thus taking an OTC product instead.[16]

Only 3 cannabinoid products are FDA-approved in the United States—cannabidiol (Epidiolex), dronabinol (Marinol, Syndros), and nabilone (Cesamet)—and these agents are narrowly labeled.[17-20] Although there are more than 10 new prescription cannabinoids in clinical development, most of these compounds are likely many years from potential FDA approval, and many are expected to have indications representing relatively small treatment populations, such as fragile X syndrome, intraocular hypertension, and cystic fibrosis.[11-13]

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>
> ***—Mark Green, MD, former FDA Panel Member of the Peripheral and Central Neurological Drugs Advisory Committee***

Thus, the health care marketplace urgently requires a dual-path approach to ensure affordability and market access to quality prescription and nonprescription cannabinoids for use under the direction of medical professionals, with nonprescription cannabinoids comprising "self-care."

A Dual-Path Approach to Federal Policy

To better ensure access to quality cannabinoids that may benefit underserved medical populations, we should consider priorities for a dual-path federal regulatory framework including:

- Prescription Cannabinoid Path 1:
  - Accelerated FDA priority review and approval of qualifying cannabinoid New Drug Applications, and supplemental applications, due to expanding medical science supporting the need for safe products that selectively engage the ECS
  - Medicaid, Medicare, Military, and Veterans Administration (VA) reimbursement coverage of on- and off-label use of FDA-approved prescription cannabinoids, especially when prescribed by ECS-trained medical professionals who are able to individualize treatment based on medical condition, adjunctive therapies, and patient needs. Off-label use of FDA-approved prescription cannabinoids provides clinicians with "first-choice" products that are federally monitored for manufacturing consistency, each with rigorously defined profiles in pharmacokinetics, bioavailability, adverse events, drug interactions, and dose responsiveness
  - Federal and state incentives to educate medical professionals on the dynamics of the ECS, to better understand and support the role of cannabinoids and cannabis as part of individualized, condition-specific treatment regimens
- Nonprescription Cannabinoid Path 2: A "brief summary" requirement for health professional and consumer awareness, uniformly depicted on product packaging and within product advertising, to summarize the presence or absence of:
  1) Independent laboratory-assessed listing of product ingredients including CBD, THC, and other cannabinoids; linalool, myrcene, and other terpenes; inert ingredients; and the absence of contaminants
  2) Identification of ingredients as being botanical, synthetic, or biosynthetic
  3) Current Good Manufacturing Practice FDA compliance in manufacturing and packaging, including package expiration
  4) Bioavailability data regarding how dose/serving size relates to absorption and blood levels

Ideally, these dual-path approaches would align with a Drug Enforcement Administration (DEA) re-scheduling of THC-containing cannabis as either a Schedule II or III controlled substance, coinciding with the scheduling class of synthetic THC analogs dronabinol (III) and nabilone (II). Such DEA re-scheduling would increase opportunities for clinical research of THC-containing cannabis among the greater medical community.

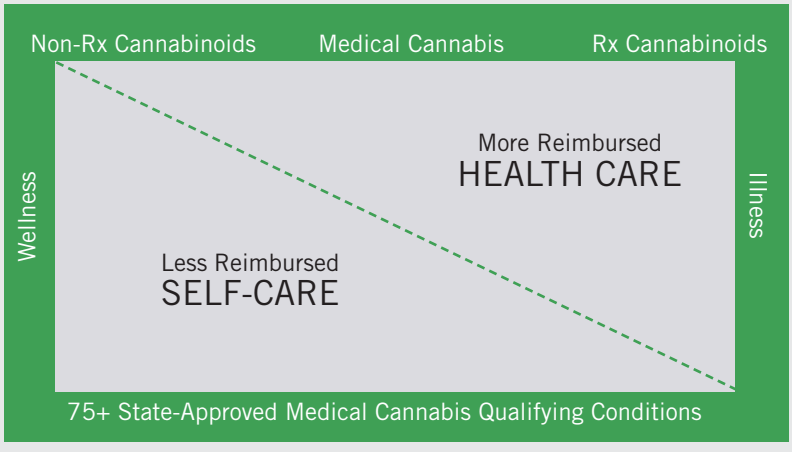

Figure. Self-care to health care cannabinoid ecosystem.

Activating a Dual Path Forward

The FDA is part of the U.S. Department of Health and Human Services (HSS), which is part of the executive branch of the federal government. Executive branch leadership is needed to establish a new framework that bridges relevant gaps existing between the FDA, DEA, U.S. Department of Agriculture, VA, and HSS.

The dual-path framework proposed here would ensure expanded access to both prescription and nonprescription cannabinoid

products, with federal quality standards for each. For example, such a framework could allow some CBD and other cannabinoids (eg, CBG and CBN) to exist as nonprescription products comprised of generally recognized as safe (GRAS) ingredients. Additionally, more rigorously studied prescription cannabinoid agents would be considered worthy of public- and private-sector medical insurance reimbursement. Such a framework may require a new kind of cannabinoid label, which would require legislation to amend the Dietary Supplement Health and Education Act.

What is important is that we recognize the need for new ways to advance both research and regulatory science and encourage them."

—Peter Pitts, Former FDA Associate Commissioner

"There needs to be product consistency and accurate labelling, which has been plaguing the field," Mark Green, MD, former FDA Panel Member of the Peripheral and Central Neurological Drugs Advisory Committee, told *American Journal of Endocannabinoid Medicine.* "Properly designed studies with appropriate controls are needed. All of this is needed in order to go beyond 'proof of concept studies' to approvable products," added Dr. Green who is Director of Headache and Pain Medicine at the Icahn School of Medicine at Mount Sinai in New York.

Former FDA Associate Commissioner Peter Pitts, spoke to *American Journal of Endocannabinoid Medicine* about the legal and policy considerations surrounding prescription and nonprescription cannabinoid products. "It's not about whether more and more robust research into cannabinoids awaits more comprehensive FDA regulation, it's how to ensure that both advance together—with all due speed—in order to best serve the public health," said Mr. Pitts, who is President of the Center for Medicine in the Public Interest. "At present there are more questions than answers. This is always the case with innovative therapies. What is important is that we recognize the need for new ways to advance both research and regulatory science and encourage them," said Mr. Pitts.

The following are instances where we need federal nonprescription cannabinoid regulatory standards:

- When prescription cannabinoids are unavailable to ECS-trained medical professionals and/or are not reimbursed for ECS-related medical conditions
- When ECS-related medical conditions have no corresponding FDA-approved prescription cannabinoid indication
- When prescription cannabinoid ingredients result in potential warnings or precautions, such as for product ingredients representing patient allergies
- When having both prescription and nonprescription cannabinoid product standards will increase treatment options for conditions in which the ECS is the clinical target, and will promote reproducibility of results across the practice of medicine

An Opportunity for Self-Regulation

There is a benefit to adopting nonprescription cannabinoid quality standards for research reported within this journal. By only publishing research conducted with products incorporating quality assurance standards, findings from clinical research studies or case reports can be more easily compared. It is further suggested that the *American Journal of Endocannabinoid Medicine* require that advertisers include a "brief summary" labeling requirement for nonprescription cannabinoid products to increase brand transparency and product quality for clinicians.

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