The State of the Current Medical Cannabis Market

Canada and 11 US States have legalized adult-use marijuana, and 19 other States have legalized medical cannabis. However, many wonder about the future of cannabis for medical purposes. If the same products are available for both medical and recreational consumers, why should a patient seeking a medical solution go through the paperwork and expense to obtain and renew a Medical Card? Two recent medical cannabis conferences[i] and multiple discussions with healthcare providers have shown there are 5 factors limiting the current utilization and stalling the future growth of cannabis for medical and/or wellness purposes.

1. **Physicians have been cut out of the supply-chain, feel alienated, and are concerned about their patients' well-being.** Due to a lack of large-scale, clinical trials producers have assumed that physicians have limited interested in learning about medical cannabis. However, as gatekeeper of their patients' healthcare, physicians and other healthcare professionals need to be able to address their patients' logistical and medical inquiries based on the most current data – even if incomplete.
2. **There is no patient benefit for obtaining/renewing a medical card if adult-use/recreational use is widespread.** There are currently few programs in place to motivate a patient to keep a medical card if recreational marijuana is also available. As such, using medical cannabis to treat their conditions become unduly complex with patients seeing little benefit in registering for a card. This undermines the integrity of cannabis as a medical solution.
3. **The public is being flooded with unreliable and misleading information.** Misleading labelling, inconsistencies in testing for contaminants, and a hyped safety profile has led to poor quality and risky products. Poor regulatory oversight will result in potential for harm, delegitimizing the industry, as well as increased scrutiny from government agencies.
4. **There are no uniformly recognized standards for dosing, labelling, and consistency regarding bioavailability.** Lack of standardization confuses users and limits the ability of producers and healthcare providers to viable medical solutions.
5. **The Cannabis Industry suffers from institutional short-sightedness.** The recreational market offers short-term financial benefits and higher margins, and with the industry engaged in multiple mergers and acquisitions, capital is being diverted from healthcare.

Below, I will explore these shortcomings and offer solutions for growing the influence of medical cannabis.

1. **Attending physicians have been largely cut out of the system.** In Canada and throughout the 29 US States where medical marijuana products have been approved, governments have specified which medical conditions qualify a patient to become a registered Medical Marijuana (MMJ) card holder. In most of these areas, a licensed physician will review the

medical records of an applicant and then make the determination about whether or not the patient has a legitimate condition that qualifies them for medical cannabis.

Unfortunately, there is no requirement that a patient's attending physician sign-off on their cannabis use. As such, it is entirely up to a patient to inform their physician that they have acquired a medical marijuana card and have an interest in trying cannabis to treat their condition and/or symptoms. In two recent studies of chronic pain and cancer patients[ii], 48% of cancer patients and 49% of pain patients, began using cannabis without first informing their treating physicians (e.g., oncologists, pain management specialists). In the complementary studies amongst oncologists and pain management specialists, physicians each estimated that they have an average of 22 (amongst Oncologists) to 48 patients (amongst Pain Management Specialists) in their practices who have come to them admitting to using cannabis without first informing them.

Patients concealing their use from their physicians say the primary reason is a belief that using cannabis will have no/little impact on their current/other treatments (57% of cancer patients and 46% of pain patients). This is followed by a belief that their physicians will disapprove of their cannabis use (36% of cancer and 57% of pain patients). Yet, when patients have asked, oncologists and pain management specialists say they have advised *few* patients to stop using cannabis (15% of oncologists' and 17% of pain specialists' patients).

The industry, itself, further perpetuates this separation between patient and physician. The clearest evidence of this is the near total lack of communication (either formal or informal) between the dispensary and the patients' attending physicians. Any information about strains or forms of ingestion tried, side effects experienced, improvement or worsening of symptoms, or any other clinically valuable insights discussed between patient and "cannabis counselors" is solely left to the patient to communicate back to their physician(s).

Most current producers and distributors seem to think that physicians will only accept data from validated clinical trials in order to openly accept cannabis into their treatment armamentarium. When asked what barriers prevent their wide use of cannabis, 69% of physicians say a lack of clinical trials is a moderate to significant barrier[ii]. However, 76% of these physicians say that the cannabis industry should spend more time educating physicians about the risks, benefits and logistics of medical cannabis. While wide-scale clinical research is not currently possible given the classification of cannabis by the FDA and an overall lack of capital required for large-scale trials, there is other data that physicians can (and will) use to help guide those patients seeking a MMJ solution.

Non-trial data shown to significantly influence physicians' prescribing of traditional pharmaceuticals includes:

- **Health Economics and Outcomes Research (HEOR).** Unlike physicians outside of the USA, the current US healthcare system places the community-based physician in the role of businessperson. As such, they often have to make economic decisions about the types and breadth of services offered to their patients. Furthermore, corporate and government hospital systems are

extremely cost-conscious, and data showing the impact of cannabis on reducing traditional medical costs (e.g., ED visits, hospitalizations, admissions, etc.) would have a significant impact. Risks and increase costs due to untested CBD could also be calculated.

- **Quality of Life (QoL) Data.** Chronic medical conditions are complex, and treatments often involve daily medication and other adjustments (e.g., dietary changes, physical therapy, etc.). These treatment plans are complicated by medication side-effects and on-going symptoms that make adherence to prescribed treatments difficult. A study conducted by the NIH[iii] suggested that greater treatment satisfaction was associated with better compliance, improved persistence, and with lower regimen complexity/treatment burden. Studies that can show patients' using cannabis for medical purposes experience fewer side effects, lessened symptom severity/frequency, and an overall better outlook on their treatment will significantly encourage use of cannabis.
- **Testimonials from Key Opinion Leaders (KOLs).** Physicians are best educated through discussions with their colleagues and experts in specific medical practices. In addition, most medical organization (e.g., ASCO, AAFP, etc.) have regional and national meetings where physicians can meet with KOLs and hear the latest medical trends. Widespread use of KOLs as advocates for specific treatments has been a mainstay in traditional pharmaceuticals for decades. Engaging KOLs to discuss the current data and benefits and risks of cannabis will provide a credible means to educate physicians and ease their concerns about safety and legal jeopardy.

2. **There is little to no benefit to the patients for staying on a medical card.** With the rise of adult-use laws in Canada and in 11 States, medical patients in these areas have little incentive to register and renew their medical cannabis card. One factor is the lack of guidance from their attending physician(s) as noted above. Because doctors are largely removed from details of acquisition and use of cannabis, they have little insight into the available strains and forms of ingestion. Thus, providing patients with thoughtful recommendations is difficult, if not impossible for the physician.

   Further, patients have long shown to be poor at self-reporting health issues and medication usage to their physicians. Self-reported answers may be exaggerated, and respondents may be too embarrassed to reveal private details. There are also instances when the patient provides data they believe their physician wants to hear, thus, 1) confirming the physician's biases; 2) making themselves look good; or, 3) making themselves appear more distressed in order to receive promised services.

   Without a dispensary communicating directly with a patient's physician, the attending doctor must rely on unreliable patient recall. In traditional pharmaceutical markets, clear communication paths between physician, patients, and pharmacists have been established. As issues arise the pharmacist has the authority to speak to a physician on behalf of the patient and make the physician aware of issues and problems. Thus, allowing the physicians

to alter the treatment plan to address factors that may potentially interfere with effective resolution of the patient's condition/symptoms.

Acquiring and renewing a medical cannabis card is expensive and requires a significant time obligation. Although the laws differ from state to state and in Canada, acquiring a medical card often involves:

- Obtaining copies of medical records to confirm an approved condition (fee may be required by the doctor).
- Paying a non-refundable application fee ($33-$66)
- Paying for a doctor's appointment ($25-$200)
- Cost of the card ($60-$200)
- Renewing card at 6-months or 12 months ($25-$200)
- Experimenting with strains to find one that works sufficiently (7-11 strains tried, on average), and
- A significant amount of time experimenting with strains/forms of ingestion in finding a satisfactory solution (6-10 weeks, on average).

In some states, patients are allowed to grow cannabis plants if holding a medical card. However, most states only have programs in place to provide medical patients with discounts not available to the recreational patient. Most of these discounts relate to the taxes placed on cannabis products, with medical users having a lower tax rate. Yet, many states do not provide discounts until after a certain amount has been purchased (>4-8 ounces). In Canada, the tax rate (e.g., "sin tax") is between 5-15%, depending on province or territory.

Using the estimates provided above, a medical patient can expect to spend between $100-$500 to acquire a card. In another patient study[ii], medical cannabis users estimate spending $144 per month on average *after* finding a strain that works for them. With an average cost of 1 ounce of marijuana equaling $263 and taxed at a 23.5% rate[iv], these patients will consume 6.5 ounces per year, on average. This amount falls beneath the level required by many states to be eligible for a discount.

Finally, there are few devices available for inhaling cannabis vapor or smoke that has been especially designed for patients with special needs. Patients with inflammatory arthritis, neurologic disorders, and muscle spasm (all of whom are prime candidates for medical cannabis benefits) often do not have the hand grip or dexterity to manipulate a typical pen-shaped device. Patients with glaucoma, cataracts, and blindness are unable to see the lights and other visual cues indicating that the device has been properly loaded and is ready for use. Patients with tremors and palsy have problems measuring liquids, applying creams, and manipulating pills. Yet, the industry has taken few steps to develop devices to aid these patients with their administration of cannabis.

3. **The public is being flooded with unreliable and misleading information.** In 2018, the USA legalized small-scale expansion of hemp cultivation for limited purposes. One of these allowable purposes is for the extraction and distribution of hemp-based CBD (as long as it does not contain more than 0.3% THC). This law, as enforced by the United States Food & Drug Administration (USDA), classifies hemp-based CBD as a food additive which differs significantly from a medication. Medicinal drugs are considered unsafe until proven safe, whereas food supplements are considered safe until proven otherwise. Unfortunately, as a food supplement, most states do not require the same level of control, scrutiny and testing as they do for medicinal cannabis.

   It is well known that cannabis plants obtained from uncontrolled sources may be contaminated with various harmful substances. Contaminants include chemicals that were intentionally added in order to increase yield, weight, or potency (e.g., pesticides, metal particles, synthetic cannabinoids) but also agents that entered the plant unintentionally (e.g., heavy metals, molds and bacteria, aflatoxins). For example, pesticides are frequently present in cannabis sold by Dutch coffee shops but were also found in cannabis offered under state law in California and Canada. If any of these contaminants were present in hemp used for CBD extraction, they would likely end up in a concentrated form in the final oil. One contaminant specifically relevant to cannabis (CBD or THC) oils is the residual presence of toxic solvents used during the extraction procedure.

   In a study of 46 different cannabis oil samples collected from patients and analyzed for cannabinoid content[v], 21 of the 46 products (46% of all samples) had label information on CBD/THC content. Results showed that 7 samples contained *no* cannabinoids (CBD or THC) at all. Additionally, as many as 26/46 samples (57%) had a THC content > 1%, with one sample peaking at 57.5%. In 18/46 samples (39%) the oil contained virtually only THC (with CBD < 0.1%). Finally, 7/46 samples (15%) contained > 25% of its cannabinoid content in the form of acidic cannabinoids, indicating poor control over the decarboxylation process.

   This poor control and high degree of contamination flies in the face of the press which claims that "Marijuana is Safe". A Google search of the phrase *marijuana is safe*, resulted in 189,000 hits, and a search of *marijuana is totally safe* results in 1,800 results. Yet, researchers have identified clear risks of using cannabis in any form.

   - Long-term health risks, especially in children, adolescents, and young adults. Research has shown that smoking cannabis in adolescence through the mid-20's leads to changes in the size and interconnectivity of brain tissue and diminished blood flow to parts of the brain[vi]. Further, to-date, there have been no fetal/pregnancy studies or studies of the impact of carcinogenic properties of cannabis when smoked. Children are especially sensitive to contaminants, and with hemp-based CBD often not rigorously tested to assure an absence of these chemicals and metals.
   - Cannabis Hyperemesis Syndrome. Occurring in chronic high-dose users of THC this rare and transient disorder has been receiving a lot of press.
   - Cannabis Use Disorder. Although not as serious as heroin or opioid addition, approximately 2.5% of adults suffer from this form of substance use disorder[vii].

As with food, gambling, or alcohol, abuse can lead to poor decisions and social consequences.

- Exacerbation of existing psychiatric condition. A 2017 study in The American Journal of Psychiatry found that nearly half of 6,788 patients who experienced marijuana-induced psychosis went on to develop schizophrenia or bipolar disorder[viii]. In some people, marijuana can trigger anxiety, panic, paranoia, and confusion. While there is no direct causal evidence of the role of cannabis in these disorders, the correlation is clear.

4. **There are no uniformly recognized standards for dosing, labelling, and consistency regarding bioavailability.** Lack of standardization confuses users and limits the ability of physicians to track the effects of cannabis on a patients' condition and symptoms. Due to multiple factors, there are no current dosage standards for MMJ. As a result, patients and caregivers must "experiment" with dosages in order to find a clinically significant dose. In addition, there are significant issues with dose to dose consistency of cannabis.

   For smokable products, (e.g., flower or vape) a patients' ability to take a consistent dose is highly dependent on lung function (which may vary on a daily basis) and inhalation technique. It is a well-known problem in pulmonary medicine that as many as 50% of patients using a mechanical inhaler show poor technique, thus reducing the effectiveness of their dose. The problem with liquid, oral preparations of MMJ (e.g, tinctures) are just as troubling. A study in the UK[ix] showed that when examining the drop volume from 19 independent manufacturers, when using a traditional medication dropper, the volume varied from 33.8 mL to 63.4 mL per drop. They also found that the angle of the bottle and concentrations of product significantly impacted the drop volume.

   Labeling standards also vary from locale to locale. As noted by the Institute for Safe Medication Practices[x], Canadian and US states require products to be assayed and labeled by the grower (and verified by an accredited third-party lab) for the two major cannabinoids currently of interest, THC and CBD. Only THC and CBD individual quantities must be expressed on the label, but there are up to 113 recognized clinically active cannabinoids which are not often required to be listed. Although the amounts of THC and CBD are clinically relevant for managing patients' symptoms, the way these components are expressed on labels is not standardized (see Figure 1) and can lead to errors.

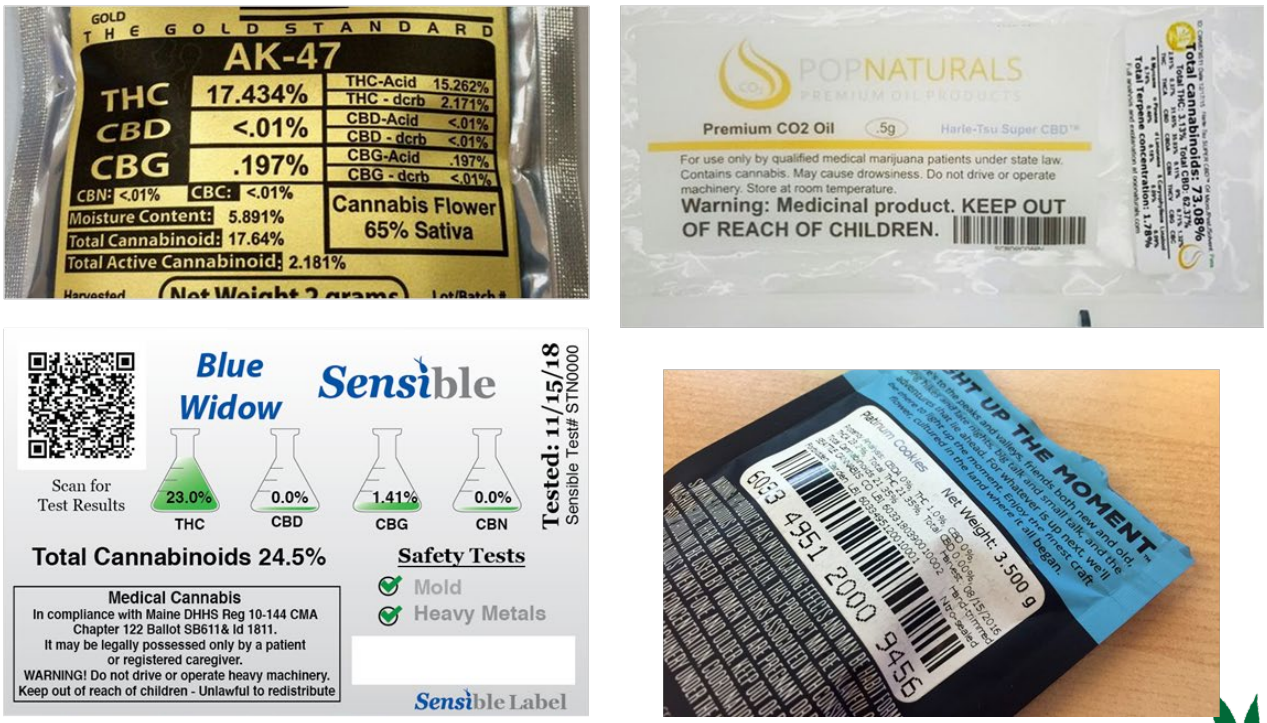
   Many product labels also lack information on important non-cannabinoid ingredients. For example, the labeling of tinctures does not always include the alcohol content, and frequently the term *tincture* is misapplied to products that do not contain alcohol. Transdermal patches often do not include key information such as onset and duration of effect, delivered dose, and cautions about possible systemic effects. It should also be mentioned that there are terpenes present in essential oils of the marijuana plant that give it its fragrance, which are also physiologically active molecules that have been known to have clinical effects—from anxiolytic to anti-inflammatory properties, and more. Product assays will sometimes list plant terpenes, but not all states require this. 120 terpenes have currently been recognized.

Finally, the bioavailability of cannabis is highly variable from form-to-form and batch-to-batch. A recent summary of the bioavailability of cannabis demonstrates this wide variability[xi]. It has been shown that:

- THC has greater bioavailability than CBD, overall
- CBD permeates transdermal surfaces better than THC
- Bioavailability of THC/CBD when taken orally is low (4%-20%), with THC showing less bioavailability
- When taken sublingually, the bioavailability marginally increases over other oral forms, but the time to peak is faster
- Smoking and vaping show the highest variations in bioavailability ranging between 2% and 56%, but resulted in the highest peak plasma levels of THC/CBD

5. **Cannabis Industry suffers from institutional short-sightedness.** So, how is the industry dealing with these short comings in the medical cannabis field? With 11 States and Canada approving adult use of cannabis, there are many producers who are shifting their capital and priorities to the recreational market. From a business perspective, this step appears to make sense. Afterall, adults seeking a "high" are less concerned about the multiple issues with medical cannabis, including:
   - Recreational users have less need for dose consistency as they are not aiming for a specific clinical endpoint,

Figure 1. Example of Cannabis Product Labels



- They have less need for multiple formulations as smoking and vaping are used for a fast high and edibles for a sustained high, and,
- Costs are more flexible (and can be significantly lower) as cannabis is less likely to be used chronically, nor is there as strong a need to "experiment" with various strains and/or forms to find the desired effects.

There is also a strong focus on consolidation within the cannabis industry. Mergers and acquisitions tie up valuable capital which could be used in conducting clinical trials and other healthcare-focused research. For example, recently, Cresco Labs announced what will be the largest acquisition of a public company operating in the American cannabis industry to date, agreeing to buy CannaRoyalty for $825 million. This acquisition was followed by Harvest Health & Recreation's announced $850 million acquisition of Verano Holdings. In Canada, HEXO Corp recently announced the acquisition of Newstrike Brands.

As noted in Forbes[xii], mergers and acquisitions are nothing new to the cannabis sector. The first merger among publicly traded licensed producers (LPs) was the Canopy Growth acquisition of Bedrocan Cannabis in late 2015. Canopy Growth followed that acquisition in early 2017, buying Mettrum, and it added Hiku Brands in 2018. Aurora Cannabis closed on the acquisitions of both CanniMed Therapeutics and MedReleaf last year—two leading LPs in revenue generation in Canada. Aleafia Health closed on the acquisition of Emblem, and Tilray recently announced the acquisition of Manitoba Harvest. In Canada, the number of companies with licenses exceeds 140, and there are over 50 publicly traded companies. Many of these companies will likely fade away over time.

There have also been two very large strategic investments from players outside of the cannabis industry with Constellation Brands gaining effective control of Canopy Growth and Altria gaining effective control of Cronos Group. In 2018, one of the world's largest pharmaceutical companies, Novartis (valued at $208B[xiii]) has partnered with Tilray in providing their global supply and distribution services.

Many large and small cannabis organizations are also mistaken in the belief that physicians only will accept data from clinical trials. While it is true that, when asked what would encourage them to incorporate cannabis into their treatment armamentarium, physicians will instinctively state "clinical trial data". In our recent study, 69% of oncologists and pain specialists said that the availability of clinical trial data would encourage their recommendations for MMJ. However, due to the pressure of patients asking about cannabis, most physicians say they need information other than clinical data.

- 65% of these physicians say producers should spend more time educating healthcare providers;
- 65% say they need to be assured that their business and/or medical license is not at risk by recommending medical cannabis;
- 62% say that helping professional organizations develop recommendations about labelling, dosing, appropriate use would encourage their use;
- 59% say they are concerned about professional stigma.

It is erroneous to assume that only clinical trial data is acceptable to physicians. Although on the rise, most medical schools do not have courses focused on the human endocannabinoid system. And, while a few producers and non-profit organizations are offering Continuing Medical Education courses, these courses are rarely comprehensive. Even with clinical trials data available, unless the physicians can understand the underlying biochemical mechanisms impacted by cannabis, they cannot effectively integrate it into their armamentarium.

To-date, no producer has developed a Risk Evaluation and Mitigation Strategy (REMS) program. REMS is a drug safety program that the U.S. FDA developed for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. For medical cannabis, given that many organizations are collecting self-reported data from thousands of patients, a REMS program could help reassure physicians that the industry takes safety seriously, and ultimately can be used to show the "true" incidence and severity of risk factors associated with cannabis.

In locations where both adult use and medical cannabis are available, there seems to be little effort made by the cannabis industry to differentiate between medical and recreational brands. This speaks to the credibility (or lack of) given to the industry by healthcare providers and patients. In our survey[ii], a clear majority of physicians say that the names of the strains (e.g., Blue Dream, Sour Diesel – 54%) and the terms for the salespersons (e.g., Budtender – 51%) undercuts and diminishes the seriousness of medical cannabis.

The overarching goal of physicians is to improve the lives of their patients. In helping them achieve this target, the cannabis industry should partner with healthcare organizations to assure that the physician, as gatekeeper of the patient's healthcare, is kept informed regarding the MMJ options provided to patients. Conversely, promotions of cannabis as a medical solution that subvert and/or exclude the patient's healthcare providers will further alienate them, and will allow other industries (i.e., pharma, alcohol, tobacco, etc.) to widen the credibility gap between physicians and the cannabis industry.

The cannabis industry is in a unique position to define MMJ in the minds of patients and healthcare providers. The public mind-set is driving governments and regulatory agencies toward legalization, and this opportunity is closing fast. Once missed, the industry will have no one to blame but themselves.

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