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Challenges in Regulating the North American *Cannabis* and Hemp-derived Product Market

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Abstract

Prior to the introduction of the *Cannabis Act* of 2018, recreational use and misuse of *Cannabis* was a public health concern in Canada. The United States (US) and other countries have met similar challenges in regulating the *Cannabis* and hemp markets under a patchwork of laws. Having been an illicit substance, the recreational *Cannabis* market has carried negative connotations without much consideration to well-established medical marijuana programs in North America. The intention of the *Cannabis Act* was to provide a comprehensive framework of regulations to protect public health and safety, reduce youth access, improve quality in the supply chain, and deter the illicit market and criminal activities. The market potential for hemp, which is defined as *Cannabis* containing 0.3% △-9-tetrahydrocannabinol (△-9-THC) or less, prompted the US Congress and Trump Administration to pass the US Agriculture Improvement Act at the end of 2018. This act, which followed on the heels of Canada's *Cannabis Act*, took hemp out of the Drug Enforcement Administration's hands, provided for crop insurance programs, incentivized farming opportunities, and reduced regulatory risk for retailers of finished products containing hemp-based cannabidiol (CBD). While the introduction of these two landmark Acts in North America has coincided with a boom in the demand for CBD products and propelled a significant increase in the supply chain for hemp flower, there are challenges for the regulating authorities in both countries. Canada regulates CBD differently than the US because cannabinoids, including CBD, are included on the prescription drug list in Canada and therefore can only be associated with health claims as components of medications that have been granted a Drug Identification Number. While some states permit CBD in food products, the US Food and Drug Administration (FDA), which governs interstate commerce, has remained steadfast that such products are not yet legal at this time. The US Federal Trade Commission has used its authority to target manufacturers of CBD-containing food products that do not possess competent and reliable scientific evidence to substantiate marketing claims. Health Canada and US FDA are also facing the unenviable task of implementing an enforcement strategy. Fifteen hundred dietary supplement and food products are already available for sale in the US through e-commerce, and a thriving illicit market threatens to serve the demands of consumers in both countries. Canada has a great opportunity to lead by ensuring consumer confidence, demonstrating quality in cross-border supply chains, and upholding the tenets of the *Cannabis Act*. If FDA permits CBD in finished products through new regulations, it will foster an even playing field for all finished product CBD manufacturers and retailers. The international *Cannabis*/hemp trade should be an important topic of conversation in future amendments of the Canada-United States-Mexico Agreement (CUSMA) on North American Free Trade. Active enforcement strategies in the aftermath of new regulations from all North American trading partners, will be paramount to long-term market viability for the *Cannabis* market.

Keywords: *Cannabis* • Medical marijuana • Cannabidiol • CBD • Industrial hemp • *Cannabis* act • 2018 farm bill • Dietary supplements • *Cannabis* health products

Introduction

Over the past five centuries, cannabis and cannabis-derived products have elicited quite polar reactions, emotional reactions, political debate, and changing public perceptions over industrial, recreational, medical, and even prescription drug use. Governments at the national, state and local levels have argued for and against its outright prohibition and criminalization. Figure 1 highlights some of the more significant changes that have occurred from the time the cannabis plant was first introduced into North America until today. Over the years, cannabis went through a series of criminalization and decriminalization in Canada and in states of its southern neighbor. Medical opinions, social climates, and political landscapes have changed radically over the years to the point where cannabis is casting off the negative connotations of its illicit drug past, replaced by a more mainstream, medically-beneficial user persona unique to this botanical. The archetype for this modern paradigm shift in thought and farming renaissance in cannabis is Canadian in origin. There is no better example for illustrating how cannabis is sparking an economic industry and transforming the global marketplace while balancing consumer access and ensuring safety in the supply chain than Canada's recently enacted *Cannabis Act* of 2018 [1].

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Canada's Regulatory Framework for Cannabis Products

Under the *Cannabis Act* of 2018, there are three streams by which cannabis products can legally be sold: 1) Recreational cannabis, 2) Medical cannabis and 3) Prescription cannabis Health Products [2]. Recreational cannabis is the focus of the *Cannabis* industry in Canada and was the driving force behind passage of the *Cannabis Act* in Oct 2018 and its global significance. The critical requirement of the *Cannabis Act* was creating the framework and controls the regulations would implement to provide the critical requirement of the Cannabis Act was creating the framework and controls to be implemented through regulations to provide access to safe cannabis products, reduce youth access to safe cannabis products to users, reduce youth access, eliminate the black market and eliminate public health hazards as well as criminal elements

Cannabis Events - Canada

1533: King Henry VIII of England made a law that all farmers grow industrial hemp or face penalties.

1606: Louis Herbert (a French botanist) planted the first hemp crop in North America in what is now known as Nova Scotia.

1800: King George III (George William Frederick of England) offered free land to immigrants who relocate to Canada and cultivate hemp. The Lieutenant Governor of Upper Canada distributed free hemp seed to farmers enabling hemp to become an essential crop for new immigrants for both textile production and food source.

1917: A new machine for the processing of hemp was invented that separated fibre from the woody core of the stalk; however, cotton and petroleum-based textiles came into favour and hemp production floundered.

1923: The Narcotics Act Amendment Bill introduces the Act to Prohibit the Improper Use of Opium and Other Drugs, thereby making cannabis illegal in Canada.

1937: Canadian law enforcement make the first cannabis seizure 1969: The Royal Commission of Inquiry in the Non-Medical Use of Drugs is formed to investigate cannabis use.

1971: The Gastown riot occurs when peaceful pro-cannabis protestors are dispersed by mounted police officers.

1972: The Royal Commission of Inquiry in the Non-Medical Use of Drugs recommends removal of criminal penalties for using or possessing cannabis. The federal government took no steps to decriminalize following the report.

1990: Manitoba Hemp Alliance formed by Martin Moravcik in Manitoba. Group secured a government grant to procure hemp seed and commence hemp trials for hemp variety containing undetectable amounts of THC (less than 0.003% THC).

1996: Terrence Parker is charged with cannabis possession, cultivation and trafficking. He was producing cannabis for medicinal use and thereby appeal to the Canadian Charter of Rights and Freedoms.

1998: Industrial hemp was legalized in Canada marking the birth of the hemp industry.

2000: Ontario Court of Appeal ruled that prohibition of cannabis infringed upon Terrence Parker's right to life, liberty and security of person thereby declaring Canada's cannabis laws unconstitutional.

2001: The Canadian government enacted the first version of the medical marijuana law (the Marihuana for Medical Access Regulations (MMAR) which allowed licensed patients grow their own cannabis or access it from licensed growers.

2011: Following consumers acceptance of hemp, hemp cultivation in Canada increased from 3,781 acres to 38,828 within a decade.

2011: Justice Donald Taliano ruled that the MMAR and the prohibitions against the possession and production of cannabis were not constitutional.

2013: Government implemented the Marijuana for Medical Purposes Regulations (MMPR), which created a commercially licensed industry for the production and distribution of medicinal cannabis. Quality controlled production of medical cannabis is implemented.

2015: Owen Smith was charged with possession of cannabis cookies. In his appeal of the charges, the Supreme Court ruled that restricting access of medicinal cannabis patients to only dried flower violated their constitutional rights. Production of cannabis oils by Licensed Producers was thereafter permitted.

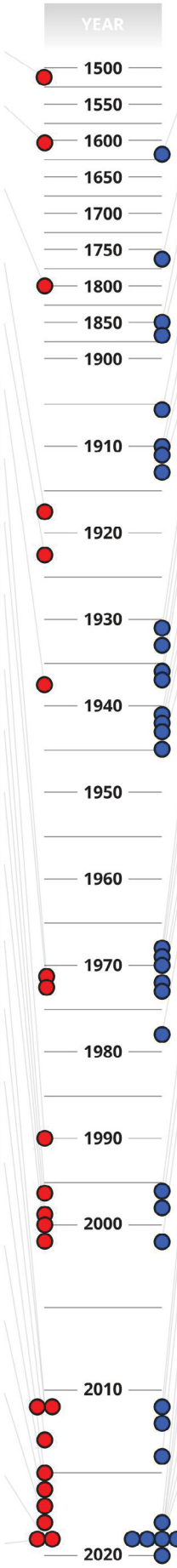
2016: The MMPR was challenged by Neil Allard for suspending the ability of medical patients to product their own cannabis, allowing only for access to cannabis from Licensed Producers. Health Canada responded by replacing the MMPR with the Access to Cannabis for Medical Purposes Regulations (ACMPR).

2017: The Government of Canada proposed the Cannabis Act, to legalize the possession, use, cultivation, and purchase of limited amounts of cannabis by adults 18 years of age and older.

2018: The Cannabis Act came into effect. Cannabis flower and oil was legalized for recreational adult use nationwide alongside the medical marijuana use. The new Industrial Hemp Regulations came into effect at the same time.

2019: Health Canada issues "Consultation on Potential Market for Cannabis Health Products that would not Require Practitioner Oversight" document for public comment. Indicating that over-the-counter cannabis health products may be introduced into the Cannabis Act.

2019: The Cannabis Act is amended to include cannabis products in the form of edibles, extract and concentrates and topicals.



Cannabis Events - United States

1619: Virginia Assembly required every colonist to grow hemp. Hemp was allowed to be exchanged as legal tender in Pennsylvania, Virginia, and Maryland.

1776: Colonial Virginian farmers - permitted to use hemp as a cash crop. Farmers could pay taxes to the government in hemp.

1840-60: US domestic production of Kentucky hemp, first grown in 1775, increased from 1840-1860. Peak production of hemp in Kentucky was 1850 (40,000 annual tons). Hemp remained Kentucky's largest cash crop until 1915, when it was replaced by jute, which was free of tariffs.

1865: US domestic production of industrial hemp for textiles subsides and interest in medicinal marijuana products sold in public pharmacies begins.

1906: Requirements for labeling of any cannabis contained in over-the-counter remedies as per the Pure Food and Drug Act.

1910: Mexican immigrants introduced recreational use of marijuana leaf in the US after the Mexican Revolution of 1910.

1911: The era of marijuana/cannabis/hemp prohibition and state regulation began in 1911 with Massachusetts requiring a prescription for sales of Indian hemp.

1913: California, Maine, Wyoming, and Indian ban marijuana.

1931: Texas declares cannabis a narcotic and recommending life sentences for its possession.

1933: By 1933, 29 states criminalized cannabis.

1936: All states had banned non-medical use of cannabis.

1937: US Marihuana Tax Act is enacted and signed into law by President Franklin Roosevelt, prohibiting cannabis at the federal level and halting interstate commerce. This marked the war on cannabis as it outlawed all cannabis at the federal level. It banned cannabis use, production and sales, including industrial hemp.

1941: President Roosevelt signs an executive order to allow for emergency hemp production for industrial uses (e.g. canvas, rope, cordage, oil.)

1942: WW II-era, shortages in textile fiber launches hemp production to supply Navy with rigging materials.

1943: Medical products derived from cannabis were removed from US Formulary and physicians were no longer permitted to prescribe it.

1945: President Roosevelt re-instituted the ban on industrial hemp production.

1968: Cannabis law reform began with Appellate court challenges to the 1937 anti-cannabis laws. President Nixon's Shafer Commission was empowered to review cannabis laws.

1969: The Supreme Court overturned the Marihuana Tax Act in the case Leary v. United States. Gallup's first poll found 12% U.S. citizens in favor of legalizing cannabis.

1970: The Controlled Substances Act is enacted. Cannabis (any amount of THC) is classified as a Schedule I drug and determined to have a high potential for abuse and no accepted medical use. It is prohibited from use for any purpose.

1972: Ann Arbor, Michigan became the first municipality to decriminalize cannabis.

1973: The start of decriminalization in the states began in 1973 with a Texas law amended to declare possession of four ounces or less of marijuana as a misdemeanor.

1978: Nebraska decriminalizes cannabis and no other state would follow for over two decades until 2001. San Francisco residents approved Proposition W to cease the arrest and prosecutive of individuals involved in the cultivation, transfer, or possession of marijuana.

1996: California becomes the first state to legalize medical cannabis with passage of Proposition 215. Today 32 states, and the District of Columbia, have established medical cannabis programs for a variety of medical conditions. (See Table X.)

1998: Industrial hemp legalized in Canada, California moves to legalize industrial hemp in San Francisco.

2001: A second wave of state decriminalization of cannabis begins with Nevada in 2001, followed by 13 additional states, Washington DC, and the US Virgin Islands. Today, sixteen states have decriminalization policies in effect, and an additional ten states have decriminalized that later legalized.

2011: Gallup reported 50% in favor of legalizing cannabis.

2012: Colorado and Washington become the first two states to legalize the recreational use of cannabis, following passage of Amendment 64 and initiative 502, respectively. A total of ten states have moved to legalize cannabis, including Washington, Colorado, Oregon, Alaska, California, Nevada, Maine, Massachusetts, Michigan, and Illinois.

2014: President Obama signs Farm Bill legalizing research hemp farms. Today there are 41 states with enacted hemp laws for U.S. cultivation. The Rohrabacher-Farr amendment was signed into law, prohibiting the Justice Department from interfering with the implementation of state medical cannabis laws.

2018: President Trump signs 2018 Farm Bill (Agriculture Improvement Act) to re-legalize industrial hemp in the US. The Agriculture Improvement Act also defined hemp products as containing less than 0.3% THC, and removed it from DEA Schedule I. A 2018 Gallup poll indicated 64% US citizens in favor of cannabis legalization.

2019: June 6 -- House Report language, submitted by Mr. Bishop, added a Cannabidiol Regulatory Pathway section to the House Appropriations Bill on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2020.

2019: September 17 -- Senate Markup of the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2020. Senate asked for policy of enforcement discretion for CBD products meeting the legal definition of hemp, establishment for FDA notification process to include safety studies for intended use per product. FDA would also have to ensure that their regulatory decisions on enforcement discretion of CBD do not discourage the development of new drugs.

2019: September 25 -- The House approved the Secure and Fair Enforcement Banking Act, which seeks to improve access to banks for cannabis businesses. It marked the first stand-alone reform bill approved by any chamber of Congress.

2019: Marijuana Opportunity Reinvestment and Expungement (MORE) Act passed the House Judiciary Committee. It represents the first time a federal bill to legalize cannabis had ever passed a Congressional committee.

2019: December 20 -- Further Consolidated Appropriations Act of (P.L. 116-94) was signed into law. The law contained a Joint Explanatory Statement from both House and Senate fr FDA to provide a report regarding the Agency's progress toward obtaining and analyzing data to help determine a policy of enforcement discretion and the process in which cannabidiol, meeting the definition of hemp, will be evaluated for use in FDA-regulated products within 60 days of enactment.

2020: February 2020 -- FDA Commissioner Stephen Hahn provides Congress with the Agency's evaluation of potential regulatory pathways for CBD products and efforts to gather data to support evaluation of a policy of enforcement discretion. FDA stated its ongoing effort to explore lawful marketing of CBD products but reiterated safety risks of products currently on the market (e.g. mislabeled products, and products contaminated with THC, pesticides, heavy metals).

Figure 1. Some of the more significant changes that have occurred from the time the *Cannabis* plant was first introduced into North America until today.

associated with cannabis use. Canada was only the second country ever to federally legalize cannabis after Uruguay [3]. However, the Canadian *Cannabis Regulations* facilitated a world-leading commercial market. The current regulations permit the sale of cannabis flower (dried or fresh), edibles, extracts and topicals. Cannabis for any market must be grown by Licensed Producers while downstream products must be manufactured by Licenced Processors. The general public may also produce their own cannabis but are limited to 4 plants per household. Seeds and plants may be sold by Licenced Nurseries. The regulations establish purchasing limits for individuals for the various products and rules pertaining to limits that can be transported by individuals within Canada. Table 1 summarizes these regulations. The regulations for the retail environment are established by Provincial governments, meaning that privately-owned cannabis retail stores and online sales (government-run only) are permitted in some provinces, but not others. Table 2 details the current retail environments in all Canadian provinces; it summarises the legal oversight, the types of ingredients that can be allowed in different cannabis products. Such other important factors as protection of the young population, requirements for packaging and labelling as well as the type of outlets where different cannabis products can be sold are also highlighted

Medical *Cannabis Regulations* under the *Cannabis Act* were inherited from the Access to cannabis for Medical Purposes Regulations (ACMPR) which came into effect in 2016, replacing the Marihuana for Medical Purposes Regulations (MMPR), which in 2013 had replaced the Marihuana Medical Access Regulations (MMAR). These regulations were all implemented in response to court decisions that ruled in favour of expanding access to cannabis for medicinal purposes [4]. The *Cannabis* Regulations have inherited the spirit of its predecessors, permitting access to safe, quality cannabis products for patients who may use it under the oversight of a healthcare practitioner. Like the ACMPR, the *Cannabis Regulations* permit access to not just dried flower but other products such as oils and capsules, and the regulations permit users to produce their own cannabis. One important distinction to highlight is that Licensed Producers and Processors cannot make any health claims for medical cannabis products.

The *Cannabis Act* also permits the sale of cannabis in the form of an active pharmaceutical ingredient. Phytocannabinoids and synthetic duplicates of phytocannabinoids remain on the Prescription Drug List, with other synthetic cannabinoids being controlled substances under Schedule II of the Controlled Drugs and Substances Act [5]. This means that cannabis Health Products (CHPs) are currently available only as prescription drugs. There are currently two drug products available in Canada, Cesamet (and nabilone generics) and Sativex. In order to market a cannabis Drug, a pharmaceutical company must

Table 1. *Cannabis* regulations in Canada and US.

Federal Jurisdiction				
Location	**Medical**	**Recreational**	**Transportation**	**Cultivation**
Federal – Health Canada	Legal: The current regime for medical *Cannabis* allows access to *Cannabis* for people who have the authorization of their healthcare provider.	Legal: production and sale of *Cannabis* flower, edible *Cannabis*, *Cannabis* extracts and *Cannabis* topicals is legal under the *Cannabis* Act.	Legal: Legal provided obtained from a licensed retailer (must be stored in closed packaging not within the reach of any occupant of the vehicle). When travelling within Canada, may possess up to 30 grams of dried *Cannabis* or its equivalent; must meet the minimum age requirement of the province or territory. Illegal to take any *Cannabis* across Canadian border. Illegal to consume *Cannabis* in/o any motor vehicle.	Legal: 4 plants/household (not per person) obtained from licensed seed or seedlings for personal use only
Provincial or Territorial Jurisdiction				
Location	**Medical**	**Recreational**	**Transportation**	**Cultivation**
Alberta	Legal	Legal (no home storage limit)	Legal (must be stored in closed packaging)	Legal (4 plants/household, sold by public retailers under provincial government oversight, commercial license)
British Columbia	Legal	Legal (1,000 gm home storage limit)	Legal (sealed package)	Legal (4 plants/household, sold by public retailers under provincial government oversight, commercial license)
Manitoba	Legal	Legal (no home storage limit)	Legal (stored in secure compartment)	[1]Illegal (non-medicinal plant growing not permitted at home, commercial license allowed)
New Brunswick	Legal	Legal (no home storage limit)	Legal (no restrictions)	Legal (4 plants/household, commercial license)
Newfoundland and Labrador	Legal	Legal	Legal (sealed packaging)	Legal (4 plants/household, commercial license)
Northwest Territories	Legal	Legal	Legal (unopened or out of reach of passengers)	Legal (4 plants/household, commercial license)
Nova Scotia	Legal	Legal	Legal (closed package)	Legal (4 plants/household, commercial license)
Nunavut	Legal	Legal (159 gm home storage limit)	Legal (not in reach of anyone in vehicle)	Legal (4 plants/household, commercial license)
Ontario	Legal	Legal	Legal (sealed or not available to anyone in vehicle)	Legal (4 plants/household, commercial license). Must not be forbidden by lease agreement or condo rules
Prince Edward Island	Legal	Legal	Legal (secured and inaccessible to anyone in vehicle)	Legal (4 plants/household, commercial license)
Quebec	Legal	Legal (150 gm home storage limit)	Legal (no restrictions)	Illegal (totally prohibited to cultivate *Cannabis* for personal use)
Saskatchewan	Legal	Legal	Legal (allowed in vehicle but not ingested)	Legal (4 plants/household, commercial license)
Yukon	Legal	Legal	Legal (closed container, inaccessible to all passengers)	Legal (4 plants/household, commercial license)

Cannabis and Hemp Regulations in the US, States and Territories				
Federal Jurisdiction				
Location	**Medical**	**Recreational**	**Transportation**	**Cultivation**
US Federal Government (Drug Enforcement Agency, USDA, US FDA, DOJ)	No approval of *Cannabis* for treatment of any disease or condition. FDA has only approved one *Cannabis*-derived and three *Cannabis*-related drug products. FDA approved Epidiolex (CBD extract) in 2018, oral Marinol (dronabinol – synthetic THC) capsules in 1985, oral Syndros (dronabinol) solution in 1985, and Cesamet (nabilone – synthetic, similar to THC) in 1985	No federal approval for recreational *Cannabis* or hemp-derived products. DEA still considers *Cannabis* (> 0.3% THC) to be Schedule I and without medical use.	Federal transportation *Cannabis* and extracts of *Cannabis* (CBD, broad spectrum, full spectrum) is illegal at this time but under enforcement discretion. Congress has asked FDA to look into a regulatory pathway for hemp-derived CBD to be legal in foods, presumably through the dietary supplement pathway.	The Farm Bill of 2013 (Agricultural Act of 2014) defined industrial hemp as distinct from marijuana and authorized institutions or state departments of agriculture with legal hemp cultivation to regulate and conduct research and pilot programs or through state grower licenses. The Farm Bill of 2018 removed hemp as a Schedule I substance as long as it is produced in a manner consistent with the Farm Bill, and by a licensed grower. It also provided hemp farmers with protections under the Federal Crop Insurance Act.
US State or Territory Jurisdiction				
Alabama	**Non-psychoactive CBD Oil**	**Felony (1st offense is a misdemeanor)**	**Not defined**	**Illegal**
Alaska	Legal	Legal	Up to 1 oz. (28 gm)	12 plants in a household (no limit with commercial license)
Arizona	Legal	Illegal	Medical use only	Medical Use only
Arkansas	Legal	Illegal (possession under 3 oz. is misdemeanor)	Medical Use only	Medical Use only
California	Legal	Legal	Up to 1 oz. (28 gm)	Six Plants, or as part of state license for commercial production
Colorado	Legal	Legal	Up to 1 oz. (28 gm)	Six Plants, or as part of state license for commercial production
Connecticut	Legal	Decriminalized (graduated fines for those possessing < 0.5 oz. (14 gm) by those 21 years of age or older, < 21 years have stiffer fines))	Felony (legal for medical use)	Felony
Delaware	Legal	Decriminalized	Medical use only	Medical use only
Florida	Legal	Illegal	Medical use only	Medical use only
Georgia	CBD oil less than 5% THC	Illegal; decriminalized in certain municipalities; (misdemeanor for ≤ 1 oz., felony for possession > 1 oz. Municipal punishments for misdemeanor possession vary.	Medical Use only	Illegal
Hawaii	Legal	Decriminalized (for less than 3 gm)	Not permitted	Medical use only.
Idaho	CBD oil containing 0% THC	Misdemeanor (85 gm/3 oz. or less), Felony for possession of greater than 3 oz but less than 1 lb.	Not defined	Felony
Illinois	Legal	Legal	Up to 1.1 oz. (30 gm)	Five plants in home (medical use) or as part of state license for commercial, recreational purposes
Indiana	CBD oil < 0.3% THC, legal for any use	Misdemeanor	Not defined	Illegal
Iowa	*Cannabis* oil < 3% THC	Illegal	Not defined	Felony
Kansas	CBD oil containing 0% THC, legal for any use	Misdemeanor	Not defined	Illegal
Kentucky	CBD oil	Misdemeanor for less than 8 oz. (230 gm)	Not defined	Misdemeanor (less than 5 plants)
Louisiana	Legal	Illegal	Medical use only	Illegal
Maine	Legal	Legal	Legal to carry up to 2.5 oz. (71 gm)	Up to 3 mature plants, 12 immature plants and unlimited number of seedlings; or commercial grower's license
Maryland	Legal	Decriminalized (10 gm or less)	Medical use only	Illegal
Massachusetts	Legal	Legal	Up to 1 oz. (28 gm)	1 oz. marijuana outside the home, 10 oz inside the home, up to six plants, or commercial grower's license
Michigan	Legal	Legal	Medical and recreational	2.5 oz. marijuana outside the home, 10 oz. and up to 12 plants per households, or commercial grower's license
Minnesota	Legal	Decriminalized in 1976	Medical use only	Medical use only

Mississippi	CBD oil	Decriminalized in 1978 (first offense; 30 gm or less)	Not defined	Illegal
Missouri	Legal	Decriminalized	Not defined	Legal for medical use
Montana	Legal	Illegal	Medical use only	Medical use only
Nebraska	Illegal	Decriminalized (first offense only)	Not defined	Illegal
Nevada	Legal	Legal	Medical and recreational use	Five plants in home for medical use only, or commercial license for recreational use
New Hampshire	Legal	Decriminalized (up to 0.75 oz.)	Medical use only	Medical use only
New Jersey	Legal	Illegal	Medical use only	Medical use only
New Mexico	Legal	Decriminalized	Medical use only	Medical use only
New York	Legal	Decriminalized (CBD-containing foods and nutraceutical products are now banned in NYC.	Medical use only	Misdemeanor
North Carolina	CBD Oil	Decriminalized in 1977 (1.5 oz or less)	Illegal	Illegal
North Dakota	Legal	Decriminalized (civil infraction)	Not defined	Medical use only
Ohio	Legal	Decriminalized (civil infraction)	Not defined	Medical use only
Oklahoma	Legal	Illegal	Not defined	Legal with medicinal license
Oregon	Legal	Legal	Up to 1 oz, more for licensed cultivators	4 plants per household, or commercially licensed growers
Pennsylvania	Legal	Illegal	Medical use only	Medical use only
Rhode Island	Legal	Decriminalized (civil infraction)	Medical use only	Medical use only
South Carolina	*Cannabis* oil (< 0.9% THC)	Misdemeanor	CBD Oil	Illegal
South Dakota	Illegal	Misdemeanor	Not defined	Illegal
Tennessee	*Cannabis* oil (<0.9% THC)	Misdemeanor (< 0.5 oz.; first or second offense only)	CBD oil	9 plants or less (misdeameanor) 10 or more plants (felony)
Texas	CBD (< 0.5% THC and no less than 10% CBD)	Illegal	Not defined	Illegal
Utah	Legal	Misdemeanor (possession up to 1 oz. $1,000 fine; possession over 10 oz. $10,000 fine) Felony for selling any amount)	Not defined	Illegal
Vermont	Legal	Legal (up to 1 oz.)	Legal	Two mature plants, four immature plants, no commercial cultivation allowed
Virginia	*Cannabis* oil (< 5% THC)	Decriminalized	Not defined	Illegal
Washington	Legal	Legal	Legal	Legal with restrictions and commercial licensing
West Virginia	Legal	Misdemeanor	Not defined	Illegal
Wisconsin	CBD oil	Misdemeanor on first offense, felony on subsequent offenses	Up to 12 plants and 3 oz. of leaves/ flowers for qualified patients	Felony
Wyoming	CBD oil	Misdemeanor	Not defined	Illegal
District of Columbia	Legal	Legal	Legal to carry up to 2 oz. (56.7 gm)	Legal to grow up to six plants (only 3 mature at a time) for recreational purposes; no provision for commercial recreational cultivation)
Puerto Rico	Legal	Illegal	Medical use only	Medical use only
US Virgin Islands	Legal	Decriminalized	Medical use only	Medical use only
Guam	legal	Legal	Not defined	Legal for medical *Cannabis* (May only cultivate indoors and cannot be visible to the public and cannot be cultivated in the common areas of any multi-family complex)
The Northern Mariana Islands	Legal	Legal	Can transport up to one ounce of marijuana, 16 oz of marijuana products in solid form, 72 oz of *Cannabis* in liquid form, 5 g of extracts, and 6 immature plants	Legal (no more than six mature and 12 immature plants per household or cultivation location. Tis may be increased based on physician advice)
American Samoa	Illegal	Illegal	Illegal	Illegal

follow the same product development and regulatory path to market as any other prescription drug. Cannabis Drugs were permitted in this fashion prior to the enactment of the *Cannabis Act*. In fact, no novel cannabis drugs have been approved in Canada since the *Cannabis Act* came into effect. With the premarket review of the safety and efficacy of prescription drugs and only specific intended uses permitted, health claims are allowed and required for marketing cannabis Drugs.

Canada has established itself as a world leader in production of hemp food products as well as agricultural hempseed for planting. Canada's hemp industry remains strictly controlled by the federal government with limited access to higher-value cultivars. While Canadian hemp industry shrank in 2018 because of slow-moving CBD regulations, the Canadian hemp industry has served as the model for its southern counterpart. While hemp falls under the purview of the *Cannabis Act,* it is regulated under Canada's Industrial Hemp Regulations (IHR) rather than the *Cannabis Regulations*. Canada has held

Table 2. Comparison of regulations governing retail of *Cannabis* products in Canada.

Key Parameters	Cannabis Products for Non-medical and Medical Purposes	Proposed Category: Cannabis Health Products	Prescription Drugs Containing Cannabis
Legal Oversight	*Cannabis Act*	Would be subject to the evidence-based approach of the Food and Drugs Act while respecting objectives of the *Cannabis* Act	*Cannabis* Act and the Food and Drugs Act
Health Claims	CANNOT make health claims	Would make authorized health claims to treat minor ailments based on evidence	CAN make authorized health claims based on evidence
Ingredients	Subject to restrictions on product composition and ingredients, as set out in the *Cannabis* Regulations	Would include *Cannabis*, and could also include other medicinal and nonmedicinal ingredients supported by evidence	Any *Cannabis* substance and other medicinal and non-medicinal ingredients supported by evidence
Retail Environment: Provincially & territorially authorized retailers	Can sell *Cannabis products*	Would be able to sell CHPs	Available at a pharmacy with a prescription from a practitioner for use by humans or via a veterinarian with a prescription for use in animals
Retail Environment: Federally licensed sellers of *Cannabis* for medical purposes	Can sell *Cannabis* products for human use when authorized by a healthcare practitioner	Would be able to sell CHPs for use by humans or in animals without the need for a prescription	
Protecting Young Persons	Youth can only access *Cannabis* for medical purposes when authorized by a health care practitioner	Oversight by a responsible adult intermediary would be required for youth access (e.g., parent or guardian)	Youth are able to access with a prescription from a practitioner, similar to any other prescription drug
Packaging and Labelling Requirements	Information on: Product contents and their health risks Cannot appeal to Youth No pre-market review or approval.	Would support informed consumer choice and safe and effective use. Cannot appeal to youth Information based on pre-market review	Supports informed consumer choice and safe and effective use information based on pre-market review

a 20-year head start on the US in the experience of growing and processing hemp. Industrial hemp cultivation has been permitted in Canada since 1998 with implementation of the old Industrial Hemp Regulations. After introduction of the *Cannabis Act*, these regulations were revamped and introduced as the new Industrial Hemp Regulations. "Industrial hemp" is defined by the *Cannabis Act* as cannabis that contains 0.3% THC or less in the flowering heads and leaves. As cannabis remains a controlled substance in Canada, regardless of the content of THC, the IHRs provide a means for farmers to legally produce and possess hemp for industrial purposes. A license under the IHR can permit the holder to import or export grain or seed, sell industrial hemp, cultivate industrial hemp, propagate industrial hemp, possess grain or seed for the purpose of cleaning or processing it and to obtain seed by preparing it.

Parts of the hemp plant and derivatives that contain less than 10 µg/g THC are exempt from *Cannabis Act* and the IHR. This includes hemp stalks (bare of leaves and flowers) and their fibres as well as non-viable cannabis seed. As soon as hemp stalks are out of the field, a license is not required. Similarly, as soon as hemp seed is processed into a food and the seed is rendered non-viable, a license is not required to possess it. Possession of grain for the purpose of processing requires that license holders render grain non-viable and have non-viable grain tested for viability. On the other hand, the flowering head and leaves and derivatives of these (i.e. CBD extracts) are controlled under the *Cannabis Act* due to their cannabinoid content. As such, activities such as extraction of CBD from hemp flowers requires a Processing License under the *Cannabis Act*. Industrial Hemp license holders can sell flowering heads and leaves to a processor for extraction under their license. In order to obtain an Industrial Hemp License, an applicant must indicate which activities they plan to conduct under the license and meet the requirements for those activities. Licensed Industrial Hemp cultivators must only grow approved varieties of hemp of which the seeds must be of pedigreed status; meaning registered with The Association of American Seed Control Officials or The Organization for Economic Cooperation and Development Seed Scheme. Licensed Industrial Hemp cultivators who are growing for the purpose of plant breeding must also test for THC levels in their crop starting when the seeds are beginning to mature. Producers growing registered seed varieties for grain, fibre or extraction are not required to test during the growing season. They are required to send a dried representative sample of the flower for testing of THC content and report the results to Health Canada while retaining a portion of the sample for up to one year. Viable hemp seed can only be sold by the farmer to licensed processors, dealers and exporters. Hemp seed is not a registered livestock feed; therefore, a hemp farmer takes on substantial risk if planting a crop without pre-arranging a contract.

In addition to the substantial lead time to glean experience, Canadian hemp farmers have had crop insurance available to them from the inception of the IHR in 1998 – a critical means to expand production. With most of this time predating the boom in CBD popularity, Canadian hemp production focused on supplying seed and fibre products that were primarily exported to the US [6]. Approved Canadian hemp varieties are therefore designed for production of seed and fibre and not high CBD oil production. Table 3 contrasts the number of different cultivars and acres allocated for hemp farming in Canada with Kentucky, a prominent hemp-growing state. Canada lags behind US states in terms of cultivars providing high CBD content. The industry is now scrambling to gain approval of high CBD producing cultivars to enable the Canadian farmers to compete alongside US hemp farmers who commenced industrial production in recent years with approved high CBD cultivars or no restrictions on the varieties they can plant, depending on the state [7,8]. It is important to reiterate that hemp-derived CBD is regulated in the same fashion as THC under the *Cannabis Act* despite industrial hemp having dedicated regulations. This is a point of disparagement among CBD advocates who contend that the

Table 3. Cultivars of hemp in Canada and Kentucky.

	Canada†	Kentucky†
Total Acres Cultivated (2018)	77,928	6,700
Approved Varieties Only	Yes	Yes
Total Approved Varieties in 2020	52	271
Grain Use	22	13
Fiber or Dual Use	28	19
CBD Use	2	239
Average Price per Pound (2018)	Cost Difference Between Flower and Seed	
Flower	$35.00 USD	
Seed	$0.75 USD	

†Canada and Kentucky both require that only approved hemp cultivars be grown. Approved varieties in Canada are limited almost exclusively to those appropriate for seed and fiber production. Kentucky is the second-leading, hemp-growing US state and focuses on CBD production with many more high-CBD varieties available. Although Canada cultivates significant amounts of hemp, the industry is restricted financially by a dearth of high-CBD strains approved for use.

broad medicinal applications and strong safety profile of the compound justify its regulation as a nutraceutical rather than a prescription drug [9]. It is also a restriction on the Canadian hemp industry as the demand for CBD nutraceutical products in Canada is throttled by the requirement to market finished products as prescription drugs or recreational products with no health claims.

Outlook for the Canadian Hemp Industry

The strict controls over CBD has allowed the US CBD market to blossom in the interim, but the story of economic prosperity on Canadian hemp does not end with CBD. The newly implemented IHRs expand the plant's legal uses beyond seed and fiber, opening the door for Canadian CBD production from hemp. While the new IHRs are meant to open additional revenue sources and market opportunities by allowing producers to harvest flowers, leaves and branches of the hemp plant, high-CBD varieties have yet to be registered for use in Canada. The IHRs have hurt machinations for a CBD industry in Canada, but they have led to an economic prosperity for Canadian hemp in general. More than 70% of the country's 5,400 metric tons of hempseed exports last year went to the US, with the remainder being sent to European Union (EU)-member countries and South Korea. Canada's hemp industry is such a force that the US Department of Agriculture (USDA) commissioned a report highlighting Canadian regulations. In developing the report on Canada's established industrial hemp industry, the US is looking for guidance and ensuring it maintains a share of the global hemp market. The six-page USDA report details Canada's status in various aspects of industrial hemp from regulation trade and industry development to hemp use in animal feed and CBD regulations.

Canada remains the vanguard of the global cannabis industry. In June 2019, Health Canada released a proposal for public consultation, which outlined a regulatory framework for "Cannabis Health Products That Would Not Require Practitioner Oversight," which have been termed over-the-counter CHPs [10]. The consultation acknowledged the general interest in cannabis products for use in treating minor ailments, the need for a legal pathway for marketed such products and appealed to the general public for any efficacy data supporting their use. Although many details have yet to be defined, the basic structure of the proposal indicated that CHPs would be governed in a fashion similar to Natural Health Products (NHPs). A premarket review would be required to assess the safety and efficacy of the product under it proposed intended use. Intended use and health claims would be restricted to minor ailments and must be directly linked to the condition of treatment (i.e. no general health claims). The framework includes no restriction on which cannabinoids can be included in products or at what level and indicates products may contain additional active ingredient typically included in NHPs or over-the-counter pharmaceuticals. Retail would be incorporated into the existing retail structure for recreational cannabis, thereby limiting access to youth. Table 2 details some of the key regulatory features of the proposal and compares CHPs to other existing legal cannabis categories. This proposed framework maintains the key tenets of the *Cannabis Act*; providing access to safe products for consumers, limiting access to youth and eliminating the black market. A substantial segment of the elicit cannabis market that remains in Canada is focused on CBD and other cannabinoid products making health claims. Providing a legal market for licensed companies with easily identifiable hallmarks, such as a CHP number, will suppress the elicit market to some degree.

US Regulatory Approach to Cannabis (Marijuana and Hemp)

The legal and regulatory landscape at both the federal and state level for cannabis-derived products is undergoing profound change in the US, specifically in the area of hemp-derived nutraceuticals. The US Food and Drug Administration (FDA), which is responsible for approving drugs as safe and effective medicine, has declined to approve smoked marijuana for any condition or disease. Therefore, the legality of cannabis-derived products in the US is highly dependent on form (ingestion vs. inhalation) and the amount of THC in the finished product. There is only one cannabis-derived product (Epidiolex®, containing pure cannabidiol isolate), and three cannabis related THC synthetic drugs (dronabinol-containing Marinol, a synthetic THC; dronabinol-containing Syndros, a synthetic THC; and nabilone-containing Cesamet, a synthetic compound similar to THC).

Marijuana is categorized in the US under Schedule I of the Controlled Substances Act (CSA), title 21 U.S.C. Section 801. In 1970, Congress enacted the CSA and its scheduling of marijuana in part on its conclusion that marijuana has no scientifically proven medical value. The evidence available to DEA has been that smoked marijuana has a high potential for abuse, no accepted medicinal value in treatment in the US, and a complete lack of accepted safety for its use, when smoked, even under medical supervision. Therefore, all state medical cannabis programs and state-approvals to sell CBD nutraceuticals are prohibited federally.

The current regulatory framework for cannabis and cannabis-derived products is not designed to champion tremendous market growth like the Dietary Supplement Health and Education Act (DSHEA) did for the dietary supplement industry. The current rules in the US therefore set the stage for a very uncertain marketplace with unknown regulatory risks from federal jurisdictions, state police, the plaintiff's bar, and city district attorneys. There is the conflicting view over medical cannabis between states with approved medical cannabis programs and federal laws as well as enforcement by city ordinances. There are ten states as well as the District of Columbia with broad marijuana acceptance for medicinal and recreational use. Unless a person lives in one of these ten designated states or the District, there is an unknown as to how CBD consumers and retailers will be treated at the state and local level. There are 43 states with hemp growing programs. There are 33 US states as well as the District of Columbia and 4 US territories[1] with

1

Table 4. Medical Use of *Cannabis* in Canada and in Individual States and Territories of the US.

Medical conditions	Alzheimer's Disease	AIDS or HIV	ALS	Cancer	IBD (Crohn's, UC)	Glaucoma	Multiple Sclerosis	Parkinson's Disease	PTSD	Cachexia, anorexia, wasting	Severe or chronic pain	Severe or chronic nausea	Seizure disorders (epilepsy)	Skeletal muscle spasticity (MS)
United states														
Alaska		✔		✔	✔	✔				✔	✔	✔	✔	✔
Arizona	✔	✔	✔	✔	✔	✔			✔	✔	✔	✔	✔	✔
Arkansas	✔	✔								✔	✔	✔	✔	✔
California	*	✔	*	✔	*	✔	*	*	*	✔	✔	✔	✔	✔
Colorado		✔		✔		✔				✔	✔	✔	✔	✔
Connecticut		✔	✔	✔	✔	✔	✔	✔	✔	✔			✔	✔‡
Delaware	✔	✔	✔	✔					✔	✔	✔‡	✔‡	✔‡	✔
District of Columbia	*	✔	*	✔	*	✔	*	*	*	*	*	*	*	✔
Florida	*	✔	✔	✔	✔	✔	✔	✔	✔	*	*	*	*	*
Hawaii		✔		✔		✔			✔	✔	✔	✔	✔	✔
Illinois	✔	✔	✔	✔	✔	✔	✔		✔					✔
Maine	✔	✔	✔	✔	✔	✔			✔	✔	✔‡	✔	✔	✔
Maryland	†	†	†	†	†	†	†	†	†	✔†	✔†	✔†	✔†	✔†
Massachusetts	*	✔	✔	✔	✔	✔	✔	✔	*	*	*	*	*	*
Michigan	✔	✔	✔	✔	✔	✔			✔	✔	✔	✔	✔	✔
Minnesota		✔		✔‡	✔	✔							✔	✔
Missouri	*	✔	*	✔	*	✔	*	*	✔	*	✔	*	*	*
Montana		✔	✔	✔	✔	✔	✔			✔	✔‡	✔	✔	✔‡
Nevada		✔		✔		✔			✔	✔	✔	✔	✔	✔
New Hampshire	✔Δ	✔Δ	✔Δ	✔Δ	✔Δ	✔Δ	✔Δ	✔Δ		✔Δ	✔‡,Δ	✔Δ	✔Δ	✔Δ
New Jersey		✔‡	✔	✔‡	✔	✔‡	✔		✔	✔‡	✔		✔‡	✔‡
North Dakota	✔	✔	#	✔	#	✔	#	#	✔	#	#	#	✔	#
New Mexico		✔	✔	✔	✔	✔	✔	✔	✔	✔‡	✔‡	✔‡	✔	✔
New York		✔‡	✔	✔‡	✔		✔	✔‡					✔	✔
Ohio	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔		✔	✔
Oklahoma	§	§	§	§	§	§	§	§	§	§	§	§	§	§
Oregon		✔		✔		✔			✔	✔	✔	✔	✔	✔
Pennsylvania		✔	✔	✔	✔	✔	✔	✔	✔		✔		✔	✔
Rhode Island	✔	✔		✔		✔			✔	✔	✔‡	✔	✔	✔
Utah	✔	✔	✔	✔	✔		✔		✔	✔	✔	✔	✔	✔
Vermont		✔‡		✔‡			✔‡			✔‡	✔‡	✔‡	✔‡	
Washington		✔		✔	✔‡	✔‡	✔		✔	✔‡	✔‡	✔‡	✔‡	✔‡
West Virginia		✔	✔	✔	✔		✔		✔		✔		✔	✔
The Northern Mariana Islands**	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Guam^		✔		✔		✔	✔		✔				✔	✔
US Virgin Islands^^	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Puerto Rico§§	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Canada														
Potential Medical Conditions: ALS, Alzheimer's Disease, Cachexia, anorexia, wasting, Cancer, Diabetic peripheral neuropathy, Glaucoma, HIV/AIDS, IBD (Crohn's, UC), Multiple Sclerosis, Parkinson's Disease, PTSD, Seizure disorders (epilepsy), Severe or chronic nausea, Severe or chronic pain of various etiologies, Skeletal muscle spasticity (MS), Sleep disorders														

* State law also covers any condition whose treatment with medical *Cannabis* would be beneficial, according to the patient's physician.

† State law covers any severe condition refractory to other medical treatment.

‡ Additional restrictions exist on the use for this indication in this state.

Δ State law requires providers to certify the existence of a qualifying disease and symptom.

State law permits use for terminal illness and any condition that produces debilitating pain and wasting.

§ State law permits use at physician's discretion using "standards a reasonable and prudent physician would follow when recommending or approving any medication.

** The Territory's *Cannabis* Commission may approve additional serious medical conditions, in consultation with medical professionals.

^ Other conditions include rheumatoid arthritis, patient admitted into hospice care and those with a condition "for which the qualified patient's practitioner has determined that the use of medical *Cannabis* may provide relief".

^^ Other conditions include Huntington's disease, arthritis, diabetes, autism, opiate use disorder and additional conditions as approved by the territory's Office of *Cannabis* Regulation (OCR).

§§ Other conditions include Fibromyalgia, Hepatitis C, anxiety and rheumatoid arthritis.

approved medical cannabis programs; however, the individual programs differ in what they accept as treatment. Medical cannabis programs vary and include treatments for Alzheimer's Disease, AIDS/HIV, amyotrophic lateral sclerosis (ALS), cachexia/anorexia/wasting, cancer, disorders involving skeletal muscle spasticity and rigidity, glaucoma, inflammatory bowel disease, multiple sclerosis, Parkinson's Disease, post-traumatic stress disorder, seizure disorders, severe or chronic nausea, and severe or chronic pain (Table 4 for a listing of specific medical marijuana programs allowed in each state as a function of the permitted medical use).

There is a patchwork of state laws approving the use of cannabidiol in finished dietary supplement products or when added to a food (e.g. conventional food or dietary supplement). FDA considers that adding CBD oil to food products is the same as adding an unapproved prescription drug. FDA has proclaimed CBD is not a dietary ingredient for use in a supplement, largely to GW's current drug trials and exclusionary clause in the 1994 Dietary Supplement Health and Education Act (DSHEA). FDA considers all these consumer products containing cannabidiol (conventional foods, dietary supplements, and cosmetics) to be unlawful. A recently enacted 2018 law in Colorado contradicts federal rules, saying that all parts of hemp plants can be added to food for sale. In April 2020, the state of Virginia passed a law, specifically addressing and defining hemp extracts as approved foods. The law even allows a more liberal amount of THC in these products during the growth phase than does the federal description of industrial hemp. Virginia is the first state to approve and declare hemp extracts as food. Virginia's law also readjusted the compliant crop limit to < 1% THC by dry weight for farmers.

Manufacturers would still need to comply with the 0.3% THC upper limit in finished products. Virginia's actions will set the stage for a potential onslaught of similar laws from other state jurisdictions. In California, public health regulators published guidelines in 2018 to reiterate that the state would not consider CBD to be an approved food additive or dietary supplement until federal or state officials say otherwise. To add to the confusion, California state lawmakers are considering a bill that would explicitly allow CBD-infused foods. The Texas Department of State Health Services just removed hemp from its list of dangerous drugs; however, retailers and consumers of over-the-counter CBD can still be prosecuted under a separate state statute which considers all cannabis products to be illegal. Complicating matters further, officials in Texas, Ohio, Nebraska, and Idaho have arrested individuals for selling CBD products regardless of whether they contain levels of THC higher than the 0.3 percent permitted under new federal laws.

There are also municipality laws, within states with legalized cannabidiol, which have implemented bans on the ingredient. Local ordinances in large metropolitan cities, moderate municipalities and town boroughs are echoing federal language with threats of embargo language. Officials from Northampton, Massachusetts have made similar municipal laws banning CBD infused foods, and the state of Massachusetts has now moved to ban CBD when added as part of an infused or in dietary supplements. In New York City, the NYC Health Department banned CBD in foods and drinks. In New York state, regulators allow businesses to sell CBD as a dietary supplement, but now it appears the rest of the state is aligning with NYC on infused foods and beverages. In Austin, police have held that CBD products containing less than 0.3 percent THC are legal; however, Tarrant County, home to Fort Worth, will prosecute all CBD cases whether or not any level of THC is present. CBD consumers in San Antonio are in a holding pattern until the Texas legislature clarifies the current laws. City officials from Maine and Ohio have cracked down on CBD edibles. Many states do not allow CBD to be sold to the public at all, whether they are in oil or pill form or mixed into smoothies. Some states with medical cannabis laws include hemp derived CBD into their definition of marijuana, but it means CBD supplements can only be purchased by permission with a doctor's prescription

Marijuana in the US is legally defined as cannabis material from *Cannabis sativa* flower over 0.3% in THC content; hemp is defined as *C. sativa* ≤ 0.3% THC. The use, sale, and possession, despite individual state laws, is still illegal under federal law [11]. As a Schedule I drug under the jurisdiction of the federal Controlled Substances Act of 1970, cannabis containing over 0.3% THC is considered "marijuana" and considered to have "no accepted medical use" and have a high potential for abuse and physical or psychological dependence. While marijuana is a Drug Enforcement Agency (DEA) schedule I drug, defined as "no medicinal use with high abuse potential," hemp and hemp-derived cannabinoid products are no longer considered schedule I with passage of the Agriculture Improvement Act of 2018, known as the 2018 Farm Bill. Hemp is now defined as cannabis that contains < 0.3% THC. While the Farm Bill eliminated regulatory risk for cannabidiol (CBD) companies by removing DEA enforcement, FDA still has jurisdiction over finished hemp-derived cannabinoid nutraceutical products in the US. The Agency has opted for a period of enforcement discretion on nutraceuticals containing hemp-derived dietary ingredients, and the US market has grown to over 1500 products. In May 2019, several months after the passage of the Farm Bill, US FDA held a regulatory townhall with stakeholders to ask questions about the safety of the CBD-containing products being sold in the US. The following month, the US House of Representatives passed report language in their 2020 Agriculture Appropriations Bill directing FDA to look for a regulatory pathway forward and lift the exclusion ban over CBD in dietary supplements. The Senate Appropriations held a similar debate later in 2019. FDA reported back to the House Committee on Appropriations that FDA is actively considering potential pathways for certain CBD products to be marketed as dietary supplements [12]. The number one area of focus in FDA's report was safety of CBD [13,14]. While FDA is actively evaluating what and how much data is required to support a conclusion that CBD can safely be allowed in dietary supplements, we have summarized the toxicology data regarding CBD here.

Relaxation of US regulatory risk for CBD foods and supplements under farm bill and guidance under the bank secrecy act

An amendment to the 2013 Farm Bill, known as Section 7606 "Legitimacy of Industrial Hemp Research" of the Agricultural Act of 2014 (P.L. 113-79), allowed for the creation of pilot programs to study industrial hemp. These programs would be approved by both the US Department of Agriculture (USDA) and state departments of agriculture. This Act defined hemp for the first time as separate from marijuana and with the specification that it contains less than 0.3% delta-9 tetrahydrocannabinol. This 2013 Farm Bill allowed small scale expansion of hemp cultivation under specific state hemp grower licenses. It also did not give growers carte blanche to grow hemp whenever and wherever. Hemp cultivation would be done for limited research purposes because the goal of the 2014 Farm Bill was to generate and protect research into hemp.

The US Farm Bill is typically limited to five years. The 2018 Farm Bill, also known as the Agriculture Improvement Act of 2018 (P.L. 115-334), was more expansive than its predecessor. The major impact of the 2018 Farm Bill was to take hemp-derived products containing 0.3% THC or less out of Schedule I. This reduced the regulatory risk for many US nutraceutical companies that did not want to be the target of the Drug Enforcement Administration and Department of Justice. The 2018 Farm Bill also generated and protected hemp research, similar to its predecessor farm bill, but it went further. It allowed for broad cultivation across the US and not simply reserved as pilot programs for higher education and marketing interest for hemp-derived products. It allowed for the transfer, in particular, of hemp-derived products and raw materials across state lines for commercial and other purposes. It also placed no restrictions on the sale, transport, or possession of hemp-derived products, as long as they were produced in a manner consistent with both federal and state laws. This ultimately means it must come from hemp cultivators under the supervision of state license programs or the USDA, in the case of states opting not to devise their own hemp regulatory program. It protected hemp farmers by equating them as equal to other farmers. Hemp farmers became eligible for protection under the Federal Crop Insurance Act. Banking rules have changed for hemp businesses. Four federal agencies and state bank regulators clarified the legal status of hemp growth and product under the Bank Secrecy Act in December 2019. Banks are no longer required to file suspicious activity reports (SARs) for customers solely because they may be engaged in growing or cultivating hemp. Banks are expected to file a SAR only if suspicious activity warrants. USDA's interim final rule on the production of hemp and the BSA considerations when providing banking services to hemp-related business has helped provide protections to this farming. While marijuana businesses were exempt from benefits of US economic stimulus funding to bolster small business and the agriculture industry because of its illegal status under federal

law, the Small Business Administration clarified that business selling hemp-derived products legally are eligible for SBA loans.

Ramifications of US policy on marijuana and CBD

The legality over smoked marijuana and recreational edibles of the flower has the greatest clarity among all cannabis-derived products in the US. These marijuana products will not be legalized federally any time soon, given the evidence available to DEA, DOJ, and FDA. There are no medical uses approved by US FDA when marijuana or other cannabis herbs are smoked or ingested. The only naturally occurring drug approved in the US is for a CBD isolate. All other THC forms are synthetic or synthetic analogs of THC, and there is no equivalent dataset of safety and efficacy for ingestion of the same levels of THC from edibles. Therefore, the pathway to federally legalize marijuana for either ingestion or smoking in the US will maintain the status quo, in spite of the varied state programs for medical cannabis use.

Ingestion of hemp-derived constituents in the US is a different story with an unclear future. Finished packaged foods containing marijuana or THC > 0.3% is not a possibility because THC is a drug and drugs are not permitted to be added to foods. US hemp-derived CBD products do not contain THC in any amount that could cause intoxication or induce a "high". Furthermore, if the CBD product contained marketing materials touting a legal "high", they would also be considered adulterated and removed from the marketplace because of US federal prohibitions on the marketing of street drug language. In the US, CBD has been kept in a state of virtual purgatory and suspended animation since its arrival to the US market as the principle ingredient in some cosmetic and dietary supplement products. FDA's reluctance to either enforce even-handed across the board as an unlawful ingredient or create a regulatory pathway through stakeholder notice and comment rulemaking has left CBD scarred by uncertainty and doubt. It has left the regulatory pathway in the hands of states, while the federal government has deemed it unlawful. This regulatory approach has led to great confusion and does not instill confidence in manufacturers, retailers, or consumers. State and municipal laws have created a patchwork of varied, non-uniform CBD laws that can be pre-empted by one over-arching federal law of the land. Instead, a reluctance to federally regulate the CBD industry has left contract manufacturers, own label distributors, retailers, shippers, packagers and even consumers open to lawsuits and prosecution. While some companies have immersed their products into the murky, ill-defined waters of the US CBD marketplace, much of the responsible dietary supplement contract manufacturers have stayed on the sideline waiting for cues from federal regulations. This has the unintended consequence of attracting the illicit black market. The lack of federal rulemaking is further complicated with federal efforts on enforcement. Federal enforcement discretion is applied only on CBD products making egregious claims, those failing to meet label claim, a section 403(a) misbranding statutory charge levied on products for being false and misleading, or findings of technical adulteration after cGMP inspections.

While Farm Bill has clarified the rules for CBD and hemp for cannabis farmers, it did not create clarity on finished product manufacturing. This equates to having a large regulatory hole in safeguarding the CBD supply chain. One basic question is over the daily serving level of CBD that is considered safe and tolerable for human consumption. US Federal regulators with FDA are concerned over CBD safety but hesitant to set safe levels based upon publicly available information. State laws permitting CBD have avoided the question altogether. Other countries have begun to discuss safe upper limit thresholds for daily human consumption, which sets regulatory parameters for CBD products, including UK and Australia. The net effect to address even this most basic of questions was the flooding of over 1500 CBD-containing products to the US marketplace. It has forced FDA into a reactionary regulatory posture by necessitating post-market surveillance for egregious product claims, analytical testing to identify products failing to meet label claim, identify ones with hidden, undeclared ingredients or monitor products for heavy metal contaminants and pesticides. While there is no lawful federal category for CBD products, there are no cGMP regulations that would apply. If they were deemed as dietary supplements, the Agency could apply part 111, the dietary supplement cGMP final rule, of the Federal Food, Drug, and Cosmetic Act if products failed to meet federal quality standards and limits on contaminants. A better strategy would have been a proactive approach of setting a safe level for use in products, given the recent pressures placed on the Agency from Congress.

Under pressure from Congress, the states, and economic pressure from its northern neighbor, FDA is headed in the direction of finally developing a federal pathway for CBD. US Congress will probably be instrumental in nudging FDA to open a path to market for CBD in dietary supplements. Both the US House of Representatives and US Senate subcommittees have discussed provisions for safety notification as a prerequisite for finished CBD dietary supplement products. The same requirement of safety notification will probably be levied for cosmetics as cosmetic reforms over the past 7 years in Congress have discussed safety assessment and notification by companies of new cosmetic ingredients in cosmetic products, which would include topical delivery of hemp-derived CBD, for FDA oversight. The food pathway making the most sense for FDA would be removing the current exclusion for CBD as a New Dietary Ingredient (NDI) for use in dietary supplements for human oral consumption. NDIs require a pre-market notification with detailed specifications on identity and a basis for reasonable expectation of safety. This pathway would provide FDA with an easier task of asserting regulatory oversight over all CBD-containing food products entering the marketplace. An enforcement strategy is essential to compel firms into regulatory compliance. A commitment by the Agency to enforce the NDI notification process for all CBD products entering the marketplace will be critical to whether this will be a successful strategy going forward. As FDA wrestles with the topic of CBD safety, it is unclear which CBD form (full spectrum, broad spectrum, or CBD isolates) would be permitted in products. After FDA adopts its regulatory framework and enforcement strategy, the industry and press will be curious as to how well the two mesh to eliminate the black market.

The Future of US Cannabis Derivatives — CBD Nutraceuticals

It is a fallacy to believe that the federal government has relaxed its stance on marijuana. The Attorney General remains committed to enforcing the CSA, even with prosecutors in states that have enacted laws authorizing the use of marijuana for medical or recreational purposes. Interstate commerce is federal, not state jurisdiction. The DEA targets criminals engaged in the cultivation and trafficking of marijuana, not in its medical use for those moribund and afflicted with illness. FDA has remained steadfast in its determination that hemp-containing CBD products ($\leq$ 0.3% THC) are illegal federally when contained as ingredient in conventional foods (e.g. Nutrition Facts labels) or as dietary ingredients in dietary supplement (e.g. Supplement Facts labels).

While the risk for jumping into the US CBD-nutraceutical market was lessened over the past 18 months, it is not without risks altogether. Farm Bill had no effect on state-legal cannabis programs. Thirty-three states have legalized cannabis for medical purposes (Table 4) and over the last 7 years, 10 states have legalized cannabis for adult recreational use. Each one of those state cannabis programs is illegal and runs counter to federal laws. Similarly, while states have allowed for finished CBD-containing nutraceutical products, finished packaged goods containing hemp-derived CBD are still unlawful federally. FDA considers all of these products, whether they contain CBD in conventional foods or as dietary ingredients in dietary supplements, to be unlawfully marketed at present.

In late February 2020, FDA Commissioner Hahn submitted his 15-page report covering CBD in drugs for animals, its use in dietary supplements, foods and cosmetics and vape products. It offered an update on enforcement activities and a glimpse at what the future may hold for hemp-derived CBD in the US. The report was delivered to the US House and Senate Committees on Appropriations after being mandated by Congress within 60 days of appropriating additional funding to FDA for hemp-CBD market surveillance activities and testing to determine the scope of products failing to meet label claim. FDA's report came shortly after the Agency's increase in warning letters on hemp-CBD products, a public speech by Lowell Schiller, FDA's principal associate commissioner for policy in late Fall, and a warning by FDA about the use of hemp-CBD products by pregnant or lactating women. Commissioner Hahn's report to Congress vowed to maintain the status quo on FDA's legal

and regulatory position on CBD and exercise of enforcement discretion, but it was also a pledge to look at creating a regulatory pathway forward for CBD in non-pharmaceutical products. On March 8, 2020, US FDA reopened its docket asking for additional safety and manufacturing information. The initial docket, opened in conjunction with FDA's public town hall meeting with stakeholders regarding CBD safety on May 31, 2019, was met with unfortunate disappointment from federal regulators. FDA will need to come up with a solution sooner than later in order to deal with a burgeoning industry that is poised to grow from its record highs in the number of products (1500+ products as at 2019) and sales projected to be more than $600+ million by 2022 [15,16]. It will also be interesting to see if, how and when FDA's Center for Tobacco Products will allow CBD vape products. FDA has remained fairly silent on the topic of inhaled cannabinoids in the face of increased sales for e-liquid and greater consumer access to vaping devices. Canada has been the leader in the *Cannabis* vape market.

Competition for the Global Hemp Industry

Comparing the US population (329 million) to Canada (37 million) and the clear consumer demand driving the marketplace, growth in the US hemp industry has captured its northern neighbor's attention. The friendly competition over cannabis has sparked a chess match of regulatory moves between the two North American trading partners, but there are new hemp markets that have yet to be carved out. Canada and US will soon be trading bragging rights over hemp farming. Hemp farming in Canada has grown at a much slower rate than its North American rival. In 2017, Canada grew approximately 123,000 acres but that number sharply declined to 78,000 acres the following year. US hemp farming, which began after the 2013 farm bill, has grown rapidly. There are up to 250,000 acres of production in 41 states in 2019, despite not having federal crop insurance in place. While Canada has nationwide marijuana, it is still working to develop cannabinoids as ingredients for either human or animal consumption. Production and distribution of cannabinoids and products that contain cannabinoids are still regulated as cannabis under the 2018 regulations; however, any Canadian products containing CBD must be accessed through licensed cannabis retailers or by prescription for medical purposes.

The sale of NHPs containing cannabinoids, including CBD, remains illegal. Transporting cannabinoids and all cannabis from Canada internationally also remains illegal without a permit. US face similar transportation issues with their patchwork laws on CBD. CBD dietary supplements are still illegal federally, making their interstate transport a prohibited act under the Federal Food, Drug, and Cosmetic Act. Despite the limitations surrounding CBD federally in the US and in Canada, consumers are buying CBD products outside legal channels. Cannabinoid products with unauthorized health claims are commonly sold in unregulated channels. The US is experiencing similar trends but almost to a greater degree as FDA applies enforcement discretion on products making egregious disease claims.

Cannabis for animal feed and pet products are emerging markets gaining interest from companies on both sides of the border. One similarity between Canada and US are approvals over livestock feed ingredients. Neither country has approved hemp or hemp-derived cannabinoids as feed ingredients. Canada has a process in place for companies to apply for approval of each ingredient. The pathway to market of such products is more unclear in the US given CBD's illegal branded status by FDA. Pet food products hold similar prohibitions. There is no clear legal pathway for veterinarians in Canada to prescribe CBD or other cannabis-based medicines or for companies to produce pet products containing cannabis. In the US, veterinarians in all states are prohibited from prescribing medical marijuana, but pet owners are allowed to administer cannabis to their animals. While competition between the two North American juggernauts heats up for new markets, international trading partners have opened their markets to cannabis-derived products.

International Regulation of Cannabis and Trade

There are three main United Nations international drug treaties that member countries must adhere to: 1) the 1961 Single Convention on Narcotic Drugs, 2) the 1971 Convention on Psychotropic Substances, and 3) the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances [17]. The legalization of cannabis on the federal level in Canada and Uruguay has led the UN to question the adherence of legalized countries with these treaties [18]. The consequences of these contraventions for Canada, if any has yet to be determined [19]. However, with the spread of cannabis legalization reaching countries in every continent, international organizations are beginning to change their stance from that of the old guard. In January 2019, the World Health Organization released a letter of recommendation that described a final position based on the scientific review of cannabis and cannabinoid products which resulted from the 39th, 40th and 41st meetings of the WHO's Expert Committee on Drug Dependence (ECDD). These reviews recognized the medical benefits of cannabinoids and balances the potential risks, while repealing the WHO's 1954 statement that "there should be an extension of the efforts towards the abolition of cannabis from all legitimate medical practice." [20]. The recommendation from EDCC called for a rescheduling of cannabinoids, most notably a recommendation to not include CBD from scheduling in International Drug Control Conventions [21]. In April 2020, the President of the International Narcotics Control Board (INCB), Cornelis P. de Joncheere indicated that the old drug conventions may no longer be relevant, suggesting new instruments for control may be appropriate [22]. In December 2020, the 63rd Commission on Narcotic Drugs of the United Nations voted to reclassify cannabis for medicinal purposes from Schedule IV, the list of most dangerous drugs [23]. The winds of change appear to be blowing towards rescheduling cannabinoids on the international level which may have significant impact on way in which nations view international trade of cannabis commodities such as CBD.

Canada has thus far escaped international repercussions for establishing a nationwide industry producing recreational substances that are outlawed for open trade by International Drug Conventions. This has been carefully managed with imports and exports thus far being restricted to medical or scientific research purposes. The Canadian cannabis industry is already supplying medicinal markets around the world, primarily in Europe and most of the large Licensed Producers have been obtaining the necessary GMP certifications to allow them to trade with any nation that permits it [24-26]. The limiting reagent thus far has been the ability of Canadian Licensed Producers to obtain supply contracts for medical cannabis due to a restricted demand and limits on the annual amounts by medical cannabis programs of importing nations. Revisions of the UN Drug Conventions to deschedule CBD would permit international trade and open the flood gates, allowing producers of high-quality product to extend their target markets. THC-containing products are not suggested to be removed from UN Drug Convention Scheduling and therefore is likely to still be restricted to medical markets. Canadian producers are well positioned to be the first to trade THC products internationally, but due to restricted access to high-CBD producing hemp strains, they may lag behind in CBD production. However, with many nations moving towards federal legalization of cannabis, treaties limiting trade of THC may be regarded as irrelevant and trade agreements between legalized nations are likely to be established over the next decade. Switzerland, Luxembourg and Mexico are among the nations that are likely to pass legalization laws soon; with Mexico likely to be the first, having recently approved a bill that could be passes by their Congress in April 2021 [27]. Federal legalization of cannabis in Mexico is of relevance to cannabinoid trade in North America as this will mark two of the three partners in the recently ratified United States-Mexico-Canada Agreement (USMCA) (or Canada-United States-Mexico Agreement (CUSMA) as it is known in Canada) as permitting legal medical and recreational use nationally. Of particular interest will be the effects on trade that the culmination of events surrounding cannabis legalization and regulation of hemp, drug rescheduling and the USMCA will have on the trade of cannabidiol.

A major focus of the USMCA was the intellectual property protections put in place for the agricultural and pharmaceutical sectors. Although cannabis and hemp trade were not explicitly addressed during the formation of the agreement, the protections put in place regarding trademarks and patent term adjustment may become important factors in CBD trade. Language in the agreement also allows the countries to maintain their ability to consider

some inventions unpatentable. This would be particularly relevant to cannabis; however, all three countries exclude patents on plants as they are party to the World Trade Organization's TRIPS agreement. With cannabis-related patents becoming prevalent in both Canada and the US, it is also important to consider the implications that patent term adjustments and removal of the obligation to provide patents for new uses, methods or processes in USMCA will have down the line as the industry matures. US patents do not require for the invention to have legal status in the US, so cannabis patents are permitted and are the first front on which the cannabis industry is fighting to gain traction on the national and international level. The first cannabis patent infringement case has already gone before the Colorado District court in the US [28]. US legalization of cannabis remains the critical component to unlocking free trade of all cannabinoids under the USMCA across North America. Until cannabis is rescheduled in the US, it is unlikely that an open North American market will establish. However, Mexican legalization will be a critical step for the Canadian market as growing conditions in Mexico permit far cheaper production of cannabinoids that could be imported into the Canadian market. As the USMCA does not account for the trade of cannabis, CBD or other cannabinoids specifically, amendment to the agreement may be required. Canadian producers have a significant head start on US and Mexican producers in establishing the infrastructure required for international trade of cannabis. This may lead to a protectionist stance over domestic production, especially for Mexico, which could also affect an open North American market. Nonetheless, Canadian producers still face a more immediate opportunity in the trade of CBD, should it be removed from the schedules of UN Drug Conventions. Despite Canadian cannabis producers and hemp farmers having a significant first-mover advantage US counterparts, the same regulations that have permitted this advantage may hamstring the industry in capitalizing on the potential international CBD market by limiting the agility of the industry to introduce new cultivars and scale up production nationally.

International organizations are adapting to remain relevant as nations progress towards decriminalization and legalization. The 40th meeting of the World Health Organization's Expert Committee on Drug Dependence, held June 2018, recommended that pure CBD preparations not be subject to international drug control conventions. This committee will also be pursuing a critical review of other cannabinoids, including a variety of cannabis formulations and compounds such as plant, resin, extracts, tinctures, △-9-THC, and THC isomers. A favorable review from this international body will likely affect the global status of cannabis and cannabinoids, providing the necessary spark for federal agencies in the US and elsewhere to reconsider marijuana and CBD. The United Nation's Commission on Narcotic Drugs will vote on whether implement the committee's recommendation to de-schedule CBD in December 2020 [23]. These revisions to the worldview of cannabis are likely to have far-reaching implications for trade both legal and illegal. Time is of the essence for Canadian producers as the industry south of the border continues its growth trajectory in the absence of meaningful federal regulation. The next hurdle for both countries will be in how they enforce regulations to curtail an increasing, illicit black market.

Cannabis Enforcement and Elimination of the Black Market

Regulation without enforcement weakens a market over time. It leads to an increase in the number of fly-by-night companies with no invested interest in long-term viability. Consumers lose confidence over stories of products not made to cGMP quality. The overall industry lacks maturity. Demonstration of a mature cannabis and CBD industry hinges on even-handed enforcement to curtail the black market. Canada requires cannabis and health products to be manufactured according to good production practices and current good manufacturing practices (cGMPs), respectively. If FDA designates CBD as a dietary ingredient for use in supplements, hemp-derived CBD would move entirely into the legitimate realm of finished packaged manufacturing and away from recreational products. The former requires intended use with specific instructions to inform consumers as to how much product can safely be consumed on a daily basis. Recreational products tend not to have this important disclosure to consumers. The advantage here is the elimination of the illicit black market.

The movement of CBD from recreational to finished packaged food represents a certain level of maturation required for long-term industry growth. US Companies who engage in finished product dietary supplement manufacturing typically have cGMPs in place in order to remain in compliance with federal statutes. US and Canada both have cGMP rules in place for finished product manufacturers of foods and nutraceuticals. These rules ensure product quality and provide assurances to consumers about safety. The illicit black market is not compliant with federal regulations for quality and safety. Products developed from the illicit industry are not produced in established factories but rather out of the home and in residential kitchens. Whether food or dietary supplements, US companies and foreign countries importing product into the US, must register their facility, which identifies the firm to the various FDA district offices. Canada requires similar registration of NHP facilities as well as the product themselves. While FDA does not have product registration at the moment, it has approached the subject on numerous occasions; however, only Congress can authorize FDA with the power to compel product registration. Facility and product registration would help eliminate the black market.

Active enforcement is an essential component to eliminate members of the illicit industry. The regulatory framework in concert with federal statute, final rules, and guidance are useless without active enforcement of those rules. US FDA has experienced benefits from implementing vigorous enforcement of their inspectional authorities in the form of cGMP inspections to the dietary supplement cGMP final rule. Some large manufacturers were being cited in the early days of dietary supplement manufacturer inspections in 2008. Today, compliance to cGMPs is really an issue for small and some moderate-sized companies. During that 12-year period, inspections grew from 30+ inspections per year to nearly 700 annual domestic inspections. US FDA also inspects nearly 100 foreign manufacturers and distributors annually for compliance to the US dietary supplement cGMP final rule. A rigorous enforcement strategy of hemp companies involving identification of fly-by-night companies for cGMP inspection would serve as an effective way to eliminate the illicit black market.

Health Canada has historically been weak on enforcement in the NHP arena, relying heavily on self-reporting and whistle-blowers to identify compliance issues and take enforcement actions [29]. With cannabis, Health Canada has implemented a much more rigorous system of inspections for Licensed Producers and Processors. Since legalization in 2018, a major cannabis producer has already had their licenses suspended for operating unlicensed growing areas and several smaller operators were subject to enforcement actions [30,31]. Industry growth has led to understaffing concerns with Health Canada's inspection program. Compliance issues are also being overlooked [32]. However, the industry has heeded the examples set by enforcement actions taken thus far with some major cannabis producers having disclosed transgressions to the regulator, while avoiding significant backlash and repercussions [33]. Health Canada inspections only addresses non-compliance of the licensed industry. Suppression of the black market relies heavily on the action of Canadian Border Services Agency (CBSA), Canadian Revenue Agency, Provincial Governments and Law Enforcement.

It remains to be seen how Canada handles recreational cannabis products in the future to eliminate the black market. One of the pillars on which the *Cannabis Act* was built is the elimination of the black market. The approach being that accessible safe cannabis, produced under regulated conditions and sold in licensed stores would supplant the illicit market through the virtue of public trust in the products. This is a long-term approach to eliminating criminal enterprise but allows for the CBSA and law enforcement to target their resources to criminal production and sales, rather than all production, sales and possession. Health Canada has thus far taken a staged approach to expanding the legal recreational market, starting with only dried flower and cannabis oils in 2018, then introducing edibles, extracts and concentrates, and topicals in 2019.

The introduction of the legal recreational cannabis market has seen marginal success thus far in reducing the black market and the main reason is often attributed to cost and accessibility. Legal cannabis sources have

been 35-45% more expensive than illicit cannabis [34]. On top of this, limited accessibility to legal sources of cannabis products due to slow rollout of retail stores in some provinces and the staged launch of edibles and extracts, deterred cannabis users from switching sources. Cannabis companies are now adjusting prices and launching an ever-widening array of products to compete more directly with the illicit market. Economic forces will drive the ability of the legal industry to combat the illicit market and it is likely to be a long-term solution that is bolstered by introducing new product types and opening retail channels that are safe and appropriate, as well as international trade to decrease to cost of goods. These practical economic considerations are highlighted by a remaining sector of illicit products that are plaguing the legal market in Canada; CBD-based health products.

Although the recreational market currently offers high-CBD- low-THC products ranging from vapes to oil capsules to topical creams, health claims are not permitted. As in the US and other countries around the globe, CBD products have become ubiquitous in Canada, being sold illegally in health food stores, big box stores and gas stations. These sales contravene the *Cannabis* regulations but are driven by consumer demand for CBD products that are clearly labelled for their intended purpose as a health product — not a recreational drug. CBD products sold on the recreational market are not labelled with health claims, as these are not permitted, nor are they labelled with dosing instructions. Much in the same way a bottle of whisky or pack of cigarettes is not labelled with daily serving instructions, recreational cannabis is not either. Recreational products sold in the black market at "head shops" across US college campuses are also typically not labeled with restrictions on daily serving levels and conditions of use.

Cannabinoid Safety — Setting Safe Levels for Use in Humans

Most countries are facing the same quandary and that is assigning a safe daily serving level for CBD consumption in humans and enforcing clear labelling policies in order to make it a legal over-the-counter health product. Although this has yet to be publicly addressed by Health Canada, the first step towards implementing the next phase of CHPs has been taken. In February 2020, Health Canada announced the formation of a Scientific Advisory Committee for Health Products Containing cannabis to support the development of a pathway for the establishment of a legal pathway for CHPs [35]. Presumably, part of the tasks of this committee will be to define the safe daily dose levels for over-the-counter CBD products, a requirement for labelling the intended use of a health product or food. A crucial determinant in successful introduction of legal CHPs, while suppressing the black market, will be the retail environment in which they are sold. Part of the popularity of illicit CBD products can be attributed to their accessibility. The current proposed framework for CHPs indicates that non-intoxicating (e.g. CBD) and intoxicating (e.g. THC) cannabinoids will be treated the same (as is currently the case), and sales will be limited to licensed cannabis retailers. This will severely limit access of the general public to CBD products currently available today and in the process may undermine the ultimate goal of eliminating the black market for these products. Both the safety and efficacy of CHPs will need to be supported by the available evidence in order to introduce a legal market that expands beyond the bounds of the current cannabis retail environment. Health Canada has emphasized this point in their consultations on the matter thus far and is actively soliciting relevant data in order to assess the available information in conjunction with industry, academic and medical stakeholders [10,35].

Regulators around the world are facing the same issues in North America — simultaneous regulation of an illicit black market and cannabinoid-based health products that are currently illegal but have become so widespread that prohibition is not in the best interest of law-enforcement and industry. Canada may actually have an advantage in facing this as the *Cannabis Regulations* and Industrial Hemp Regulations provide an existing regulatory framework for production, processing and sale of cannabinoids that can be amended as required. CBD is the cannabinoid of immediate concern. All regulators appear to be facing the same issue of defining a safe limit of consumption of CBD before a legal market for CBD health products or foods can be implemented. In January 2019, the EU declared CBD a novel food ingredient, thereby opening the door for member countries to further define limits and for industry to submit Novel Food applications which support the safe use of CBD in foods. In May 2019, US FDA held an open town hall, requesting input from industry stakeholders and the general public pertaining to data supporting the safety of cannabinoids for use in foods and dietary supplements. This was followed in June of the same year by Health Canada's public consultation on CHPs. In February 2020, on the heels of the results of a survey it commissioned, the UK's Food Standards Agency published recommendations indicating that healthy adults should not consume more than 70mg of CBD per day [36]. This was accompanied by a deadline for all companies producing CBD products to submit Novel Food applications by March 31, 2021 or withdraw their products from the market. In April 2020, Australia's Therapeutic Goods Administration published an analysis of the existing scientific literature supporting the safety of CBD which concluded that healthy adults should not consume more that 1 mg/kg CBD per day [37]. The report further recommended rescheduling CBD at or below this level for over-the-counter use. While the regulatory frameworks and enforcement actions will differ between nations, a consensus appears to be coalescing around 70 mg/person/day or 1 mg/kg per day as the safe dose for CBD, assuming a typical weight of 70 kg. As countries around the world define what is considered a safe dose or serving size and begin to debate regulations and enforcement strategy specific to CBD health products and foods, international trade of this novel commodity and the influence of international drug treaties bears consideration.

Research into Cannabis and Cannabinoids

Adequate demonstration of safety for cannabis, cannabis-derivatives, and cannabinoids through pre-clinical toxicological studies and post-marketing clinical studies is one important research gap to fill. The other gaps include research into the purported medical uses and various structure function indications claimed on dietary supplement products. In December 2016, the Task Force on cannabis Legalization and Regulation released their final report entitled "A Framework for the Legalization and Regulation of cannabis in Canada". The report established the framework on which the *Cannabis Act* would be built and highlighted the need for research to inform public policy, medical practice and prevention efforts surrounding cannabis use. The final report of the Task Force helped to establish the integrated cannabis Research Strategy of the Canadian Institute for Health Research (CIHR). This was not the initiation of cannabis research by the Government of Canada. In fact, the Canadian government conducted several national cannabis surveys prior to legalization, including the Canadian cannabis Survey in 2017 [38-40]. In the first quarter of 2018, the National cannabis Survey was launched to begin collecting quarterly data on cannabis use in Canada [41]. Health Canada and CIHR explicitly promote cannabis health research in Canada and support open data sharing to inform physicians and policy makers. The Integrated Strategy includes three streams of cannabis research: understanding harms, data standards and medical benefit. CIHR offers significant funding opportunities for health researchers in Canada [42,43].

The *Cannabis Act* and *regulations* establish a theoretically efficient pathway for conducting research with cannabis through the issuance of cannabis research licences. This licensing system requires that researchers in any field, including product development, agriculture, preclinical and clinical research, obtain approval to conduct the specific activities with cannabis required by their research. This includes possessing, producing, shipping, distributing and destroying cannabis plants, seeds or products. Health Canada assesses the security measures, procedures and control frameworks in place to ensure that the research is conducted securely and appropriately. In the case of animal studies and human clinical trials, Experimental Studies certificates or No Objection Letters from the Office of Clinical Trials are required to be obtained prior to applying for a cannabis research license for a particular research project. In order to obtain a No Objection Letter from the Office of Clinical Trials, the investigational cannabis product must be produced under drug GMP conditions. A significant burden for cannabis producers who normally operate

under the cannabis GPP standard. Initially, all research licences were required to be related to a specific project, meaning that one researcher or institution would have to submit several license applications, if several research studies were to be undertaken. In September 2019, Health Canada issued guidance for obtaining an Institutional Research License. This development is aimed at reducing the regulatory burden on researchers and institutions conducting multiple cannabis research projects, as well as decreasing the use of Health Canada resources. In December 2020, Health Canada issued a public consultation on proposed changes to the Cannabis Regulations concerning the way in which research of recreational cannabis is regulated. The consultation proposed the regulation of non-therapeutic cannabis research be transferredto the Cannabis Act and Regulations, rather than the Food and Drug Act and Regulations (cite Health Canada, 2020. Canada Gazette, Part 1, Volume 154, Number 50.). This change would align manufacturing requirements with those of the Cannabis Regulations and eliminate a significant regulatory burden that has prevented much clinical research sponsored by cannabis producers thus far.

Even in an era of federal prohibition on marijuana in the US, DEA and the Department of Health and Human Services (HHS) have gone to great lengths to support research into the effects of marijuana and its medical utility of its chemical constituents. In December 2015, DEA announced it was easing the requirements for obtaining a modification of their existing registration for those who wished to conduct research with CBD. This led to the development and FDA-approval of Epidiolex®. In 2018, DEA announced an online portal for researchers to submit qualifications, protocols, and institutional approvals for schedule I research. Over the last 3 years, DEA has increased the aggregate hemp production quota for marijuana by 575% from 472 kg in 2017 to 3200 kg presently [44]. This supported the National Institute on Drug Abuse's (NIDA's) provision of various strains of marijuana to researchers in the US. Over the last 5 years, there has been a 155% increase in the number of active researchers registered with DEA to conduct studies on marijuana, cannabis extracts, and its derivatives. At present, more research is conducted on marijuana, extracts and constituents than any other Schedule I substance in the US. More than 70% of DEA's total schedule I research registrant population, constituting 605 researchers), conduct research on these substances in the US. As a result of the last two Farm Bills, participation of US hemp cultivation has increased. Initially hemp cultivation from the 2013 Farm Bill was designed to support the growth of plant material for research purposes and only a minority of states signed on. Today, there are 41 states with active hemp programs. Furthermore, DEA has never denied an application to conduct bona fide research with marijuana from a researcher who has received a favorable recommendation from HHS. The US is very focused on filling research gaps in cannabis to address safety and efficacy of whole plant, extracts, and cannabinoid isolates. Filling research gaps will be a primary driver to loosen regulatory strangleholds over cannabinoid isolates, hemp-derived extracts, and possibly marijuana.

Discussion

In summary, countries around the globe are developing regulatory frameworks for cannabis products and moving to decriminalize marijuana at the national level. The states have made moves to decriminalize marijuana over the past 50 years with softer sentencing. Other countries are working to decriminalize it completely. Canada followed Uruguay at the forefront of this movement in 2018. According to a United Nations report on drug use, over 230 million people worldwide have tried cannabis on at least one occasion when surveyed about their drug use over a 12-month period [45]. This constitutes 2.7 to 4.9% of the world population [46]. The global regulatory prohibitions placed on cannabis is not unique to the US but reflective of long-standing global positions echoed at the 1912 International Opium Convention [47,48]. There is both a lack of international scientific consensus as well as international standardization with regard to quality (e.g. identity, purity, potency, strength, and limits on contaminants) for production, and much of the world has focused their attention on Canada as the pioneer to setting up rules in the cannabis industry. The sum of all regulatory prohibition has contributed to an absence of an appropriate international drug control framework, legal avenues for importation and use of medical cannabis and global regulation of the cannabis supply chain.

Canada and US have differing viewpoints on the legality and merits of marijuana. Canada has legalized cannabis smoking and edibles for recreational use, while marijuana and its multitude of state-approved medical marijuana programs are federally illegal in the US. These programs have garnered national interest and attention from clinicians, patients, law enforcement bodies, employers, and entrepreneurs. The current social acceptance from Canadian provinces and certain US states and political climate require that clinicians be familiar with the multifaceted aspects of cannabis when used for recreational purposes, licensed medical programs, farming, or as an additive in foods, dietary supplements, and other nutraceutical products. The states are a microcosm of the global patchwork of regulations, which hinders the global cannabis marketplace. Each state and country permitting legal access to medical cannabis operates under its own policies, regulatory standards and medical indications for use. This patchwork of international and US state laws has created confusion for manufacturers, retailers, distributors, shippers, consumers, clinicians, law enforcement, state regulators and federal agencies. The global cannabis industry, federal decision makers, and regulators are currently looking for guidance to Canada as a model for setting up cannabis and cannabinoid regulatory programs.

Conclusion

Canada's *Cannabis Act* was implemented with the overarching goals of providing access to safe, high-quality cannabis, limiting access to youth and suppressing the illicit market and criminal elements. The black market has been minimally affected by the installation of a legal industry and regulatory construct, but the *Cannabis Act* should not be viewed as a short-term solution. Additional product sectors must be introduced to curb the illicit CBD health product market. Since 1998, Canada has been leading the world in cannabis policy and building an industry that has secured a critical first-mover advantage in the trade. Although the spirit of the *Cannabis Act* is one of accessibility and public health, it has also provided Canadians with the required infrastructure and experience to bolster a robust international trade. This is something academics, farmers and licensed producers alike are aware of and actively working to preserve through introduction of new cultivars, novel processes and research programs. In contrast to Canada's cannabis sector, the hemp-derived cannabinoid industry is lagging behind those of its trading partners. The US cannabinoid industry is flourishing, even when it is still considered illegal federally, and the number of hemp farms and acres has grown considerably over the past 7 years. Many states have softened regulatory stances to allow for its sale and distribution, but the patchwork of state and municipal laws highlights the desperate need for pre-emption from a single overarching federal law of the land in the US. The US can look to Canada as they unfold their *Cannabis* regulations in a step-wise fashion. These North American allies and rivals can also look to other countries like UK and Australia, which have opined on the safe serving levels of CBD in food products.

Despite the isolation and recognition of the molecular structure of THC over 50 years ago by Raphael Mechoulam and the decades of research on cannabinoid formulations, there is a lack of clinical safety and efficacy data for a majority of medical indications for cannabis and its cannabinoids. With well over half of the states in the US permitting access for medical indications, coupled with 16 countries that have legalized medical marijuana, the global expansion of cannabis is an absolute certainty for the foreseeable future. Expansion of access, increased global supply chains, softened regulatory positions, enforcement initiatives to curtail the black market, investment in cannabis research programs to substantiate medical indications, and safety assessments for toxicity will drive cannabis growth into the future. Where Canada and the US end up in the final ranking of economic domination of this market will largely depend on how well they address each of these factors.

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