Medical Cannabidiol Board

Annual Report to the Iowa General Assembly

January 2026

Medical Cannabidiol Board

2025 Annual Report to the Iowa General Assembly

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Acknowledgments:

Iowa Medical Cannabidiol Board Members:

- Cpt. Mike McKelvey – Chair, Law Enforcement
- Dr. Robert Shreck, MD - Oncology
- Dr. Stephen Richards, DO – Family Medicine
- Dr. Andrea Weber, MD - Psychiatry
- Dr. Mohamad Mokadem, MD - Gastroenterology
- Dr. Cory Garvin, PharmD – Pharmacy
- Morgan Brown, ARNP – Pain Management

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Executive Summary

Iowa Code chapter 124E was enacted on May 12, 2017. This code chapter established the Medical Cannabidiol Board (Board). The Board is tasked with the following responsibilities:

1. Accepting and reviewing petitions to add medical conditions, medical treatments or debilitating diseases to the list of debilitating medical conditions for which the medical use of cannabidiol would be medically beneficial under this chapter.
2. Making recommendations relating to the removal or addition of debilitating medical conditions to the list of allowable debilitating medical conditions for which the medical use of cannabidiol under this chapter would be medically beneficial.
3. Working with the department regarding the requirements for the licensure of medical cannabidiol manufacturers and medical cannabidiol dispensaries, including licensure procedures.
4. Advising the department regarding the location of medical cannabidiol manufacturers and medical cannabidiol dispensaries throughout the state.
5. Making recommendations related to the form and quantity of allowable medical uses of cannabidiol.
6. The Board also has the authority to make a recommendation for a statutory revision to the definition of medical cannabidiol to increase the allowable tetrahydrocannabinol (THC) level in medical cannabidiol products manufactured and sold in the state of Iowa.

This report summarizes the Board's activities, recommendations for improvement, and program data during calendar year 2025. The data within the following figures and tables for this report were obtained through November 2025, from the Patient Registry and Secure Sales-and-Inventory-Tracking-System. The Board recommendations highlighted in this report were developed to improve Iowa's Medical Cannabis Program.

The objective of the medical cannabis program within the Bureau of Cannabis Regulation (BCR) at the Iowa Department of Health and Human Services is to have a high-quality, effective, and compliant program for Iowa residents with qualifying medical conditions. The BCR works to balance a patient's access to treatment of their qualifying condition, while also ensuring the safety and quality of the products. The BCR oversees the registration of patients and caregivers, the licensing of manufacturers and dispensaries, and manufacture, testing, transfer, and dispensing of medical cannabis products.

Report on Activities of the Board

I. Board Meetings

The Board held three meetings during calendar year 2025.

- May 16, 2025
- August 22, 2025
- November 14, 2025

May 16, 2025

Chair Cpt. McKelvey called the meeting to order with a quorum of members present. Public commenters addressed proposed legislation on vaporizable raw cannabis, federal compliance concerns, patient experiences, advocacy for adult-use considerations, and differing views on whether new forms should be added to the program.

Owen Parker provided program updates, including a legislative review of program bills related to additional dispensaries, vaporizable flower, out-of-state patient access, consumable hemp regulations, psilocybin, and kratom. Board members discussed provider certification requirements, the lack of medical evidence supporting smokeable cannabis, and whether emerging substances would fall under the Board's purview.

Owen noted publication of the annual report and outlined priority Bureau projects, such as IT system procurement, independent laboratory pathways for medical cannabis, and redesign of consumable hemp product management. He also reviewed the Bureau's organizational structure and discussed public health considerations raised during legislative analysis. The meeting concluded with an update on board vacancy recruitment efforts for the summer and adjourned at 10:52 a.m.

August 22, 2025

Chair Cpt. McKelvey called the meeting to order with a quorum of members present, including newly appointed pain-management representative Morgan Brown, ARNP. Public commenters addressed federal rescheduling discussions, opposition to raw cannabis flower, market and safety implications of hemp product recalls, and concerns about Iowa falling behind neighboring states that permit flower sales. Program updates showed active patient totals holding steady at approximately 18,000 with a recent increase in applications.

The Board discussed its 2023 denial of vaporizable flower and unanimously established a subcommittee—Drs. Shreck, Weber, and Garvin—to update the prior decision document using current medical literature and relevant public health data. Members

emphasized maintaining scientific standards, noting ongoing concerns about smoking as a medical route of administration and the influence of commercial interests. The Board also discussed refining recommendations for the 2025 annual report and noted that neurology and pediatrics positions remain vacant. The meeting adjourned at 10:51 a.m.

November 14, 2025

Chair Cpt. McKelvey called the meeting to order with a quorum of members present. Public commenters raised topics including patient access to alternative product forms, concerns about smoking risks, implications of federal legislation limiting consumable hemp, and continued advocacy for raw or vaporizable flower as a lower-potency option.

The subcommittee of Drs. Shreck, Weber, and Garvin discussed their review of literature on vaporizable or raw cannabis and their report. The subcommittee concluded that evidence does not support dried, raw cannabis—whether vaporized or otherwise—as an effective or appropriate medical treatment and noted its high potential for diversion for combustion. The subcommittee recommended that the Board reaffirm its opposition to dried, raw cannabis in all forms within the Iowa Medical Cannabis Program. The Board unanimously adopted a motion to incorporate the subcommittee's conclusions and recommendations directly into an annual report recommendation. (attached as Appendix A). The Board also voted to remove the prior recommendation to add PAs and ARNPs to the Board given the recent appointment of an ANP.

Owen then reviewed the final annual report recommendations, including:

1. Reaffirmation for prohibition of a combustible or raw forms of medical cannabis
2. Statutory renaming to "Medical Cannabis"
3. Expansion of dispensary licenses
4. Removal of sales tax on patient purchases at dispensaries
5. Uncoupling IA from federal 280E tax laws
6. Improved provider access to patient purchase data
7. Strengthened telemedicine oversight
8. Continued pursuit of a federal exemption.

The Board also voted to remove the prior recommendation to add PAs and ARNPs to the Board, given the recent appointment of an ARNP, and voted unanimously to incorporate the subcommittee memorandum directly into the annual report.

Ongoing vacancies in neurology and pediatrics were noted and the meeting adjourned at 10:58 a.m.

II. Recommendations for Adding or Removing Medical Conditions

In the calendar year 2025, there were no petitions for new qualifying debilitating medical conditions submitted by the public for the Board's consideration.

III. 2025 Recommendations to the Iowa General Assembly

1. Reaffirmation of the Board's Position on Raw Cannabis Forms
   Throughout the history of the medical cannabis program, the Board has received and reviewed multiple formal petitions, public comments, and stakeholder requests advocating for the availability of raw cannabis—whether intended for smoking or vaporization. After additional consideration and review of the clinical evidence, public health implications, and statutory intent of the program, the Board reaffirms its longstanding position that raw cannabis should be prohibited as an allowable form in Iowa's medical cannabis framework.

   In August 2025, the Board convened a Subcommittee to update its review of the scientific and medical literature related to raw cannabis products. The Subcommittee's findings are summarized in Appendix A (p. 25), which provides a detailed evidence review and outlines the rationale supporting the Board's position. This reaffirmation is intended to provide clarity and ensure consistency in understanding the Board's position for patients, providers, policymakers, and the public.

2. Renaming Chapter 124E as the "Iowa Medical Cannabis Act" The Board
   The Board recommends amending the title of Chapter 124E to "The Iowa Medical Cannabis Act." This change more accurately reflects the scope of the program, which authorizes the manufacture and sale of products containing tetrahydrocannabinol (THC) in addition to cannabidiol (CBD) and other cannabinoids. Updating the terminology will improve scientific accuracy, align Iowa's program with national norms, reduce stakeholder confusion, and support more effective public and professional education.

   The term "medical cannabidiol" was historically relevant when Iowa permitted only products with no more than 3% THC; however, Iowa is now the only state in the country that continues to use this nomenclature. Since the passage of HF 2589 (2020), Iowa's product formulations have become consistent with those available in other state medical cannabis programs, making the existing title outdated and increasingly misleading. Moreover, the rapid growth of intoxicating cannabinoids in

the consumable hemp marketplace has further blurred public understanding and contributed to ongoing confusion among law enforcement, healthcare professionals, and other stakeholders. Modernizing the statutory title will help ensure clarity, reinforce program intent, and enhance stakeholder comprehension across regulatory, clinical, and public settings.

3. Authorization for Additional Medical Cannabis Dispensaries

The Board recommends that the Department be allowed to license dispensaries additional to the currently prescribed by Iowa Code chapter 124E. Many patients travel two or more hours, and more licenses will provide Iowans with greater geographical access to medical cannabis products. This could be accomplished by removing the prescribed number of licenses, and giving the Department authority to issue additional licenses based on evidence-based demand analysis.

4. Exempting Medical Cannabis Products from Sales Tax

Under current law, patients purchasing medical cannabis products at state-licensed dispensaries are required to pay sales tax. To reduce the cost burden of products on patients, the Board recommends that the sale of medical cannabis products be exempt from sales tax, as is the case for traditional prescribed medications. Senate File 2157 was introduced in 2022 and provides a template pathway.

5. Tax Treatment of Medical Cannabis Licensees

The Board recommends that Iowa decouple its individual and corporate income tax code from Internal Revenue Code Section 280E to ensure equitable tax treatment for licensed medical cannabis businesses. Because cannabis remains a Schedule I substance under federal law, Section 280E prohibits plant-touching operators from deducting ordinary and necessary business expenses when calculating federal taxable income. Iowa's tax code generally conforms to federal tax provisions unless explicitly decoupled, resulting in a disproportionate tax burden for state-regulated medical cannabis licensees.

Decoupling from Section 280E would align Iowa's tax policy with the state's regulatory intent to treat licensed medical cannabis businesses as traditional businesses. Senate File 2157 (2022) provides a potential framework for implementing this change in Iowa and illustrates a clear legislative pathway for achieving tax parity with traditional businesses operating under state authorization.

6. Authorizing Provider Access to Patient Purchasing Information

The Board recommends amending Chapter 124E to authorize HHS to provide patient-specific purchasing information to the certifying healthcare provider, consistent with information-sharing practices used in traditional Prescription Drug Monitoring Programs (PDMPs). Under current statute, the Department is not

permitted to share a patient's medical cannabis purchase history with certifying practitioners.

Granting providers access to purchasing data for the patients they certify would strengthen clinical oversight and support more informed decision-making. This change would align Iowa's program with established best practices in controlled substance monitoring.

7. Strengthening Oversight of Patient Certifications via Telemedicine

The Board recommends that Chapter 124E be amended to incorporate the Board of Medicine's telemedicine standards of practice, specifically those outlined in 653 IAC 13.11(7), to ensure appropriate oversight of medical cannabis patient certifications conducted through telehealth. The Board has observed concerns that some telemedicine providers may not be establishing or maintaining a legitimate patient–provider relationship, consistent clinical documentation, or continuity of care when issuing certifications for medical cannabis use.

Integrating the Board of Medicine's telemedicine requirements directly into Chapter 124E would reinforce expectations for comprehensive patient evaluation, appropriate recordkeeping, and adherence to clinical standards regardless of whether care is delivered in person or remotely. This alignment would promote patient safety, support responsible certification practices, and ensure that telemedicine is used as a supplement to—not a substitute for—sound medical judgment and ongoing patient care.

8. Seek a Federal Exemption for Iowa's program

The Board recommends that a task force of legal experts be authorized, similar to the current board of medical experts, to assist the department in navigating the legal issues involved with requesting an exemption for Iowa's program from necessary Federal agencies. This is related to a recommendation in the Board's 2019 Annual Report and the passage of HF2589 in June, 2020.

IV. Manufacturer and Dispensary Licensing

Manufacturing

- **Bud & Mary's Cannabis Company** (MedPharm Iowa, LLC)
  - MedPharm Iowa, LLC has been providing medical cannabis products to dispensaries since program launch in December 2018
- **Iowa Cannabis Company** (IA Wholesale OZF, LLC)
  - Iowa Cannabis Company has been providing medical cannabis products to dispensaries since April 2024.

Dispensing

- As of October, 2021, all five available dispensary licenses have been operational and dispensing to patients.
- Bud & Mary's maintains two dispensary licenses:
  - Windsor Heights - 7239 Apple Valley Drive, Windsor Heights, IA 50324
  - Sioux City - 5700 Sunnybrook Drive, Sioux City, IA 51106
- Iowa Cannabis Company maintains three licenses:
  - Iowa City - 322 Highway 1 W, Iowa City, IA 52245
  - Waterloo - 1955 La Porte Road, Waterloo, IA 50702
  - Council Bluffs - 3615 9th Ave, Council Bluffs, IA 51501

V. Industry Employment

All Manufacturer and Dispensary employees must undergo and Class A background check by the Iowa Department of Criminal Investigation (DCI).

At the time of publication, Iowa's medical cannabis program employs 75 personnel across its seven licenses (two manufacturers, five dispensaries).

2025 Program Data

The data for this report, unless otherwise noted, comes from the Department's Secure Sales and Inventory Tracking System and Patient Registry, a secure, web-based application system built on Salesforce.

I. Healthcare Practitioners

Healthcare practitioners are not required to complete specific training on medical cannabis prior to certifying a patient. A healthcare practitioner is defined as a physician (MD/DO), physician assistant (PA), advanced registered nurse practitioner (ARNP), or a podiatrist (DPM).

Figure 1 depicts the number of healthcare practitioners (HCPs) in a month who have certified their first unique patient, as well as the cumulative number of HCPs who have certified at least one patient since the beginning of the program. This data is for 2025.

Figure 1.

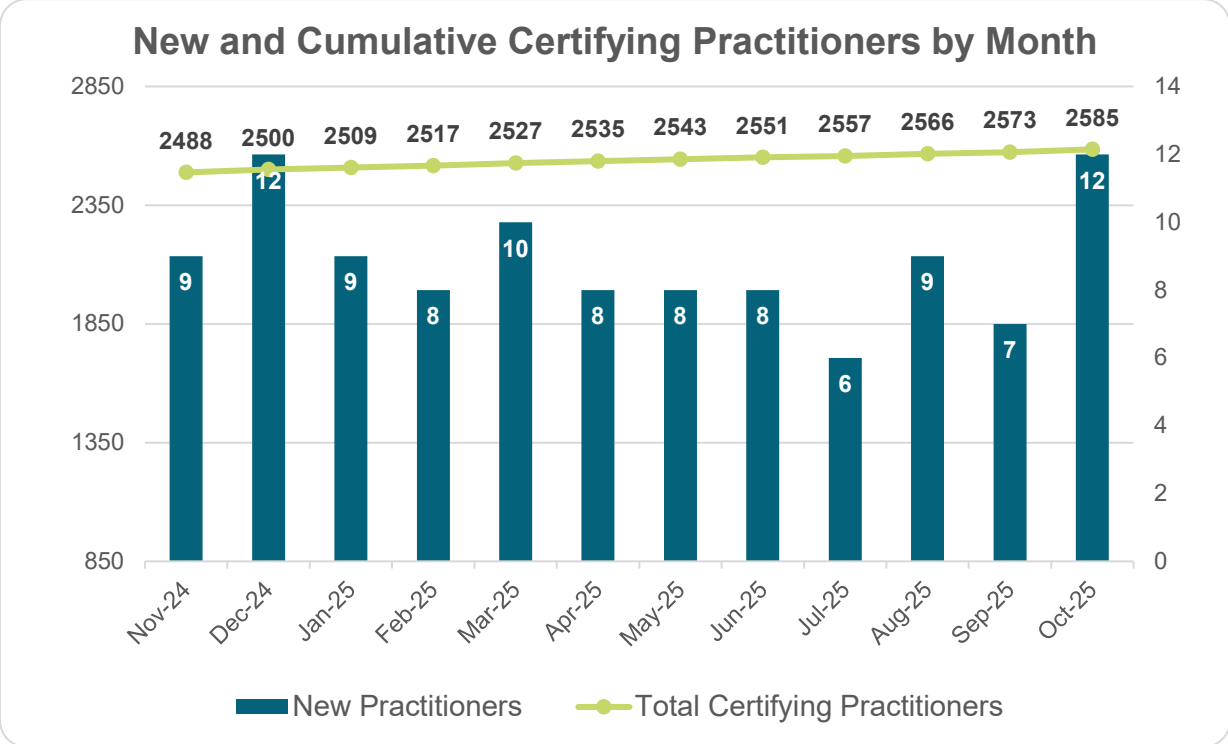


Figure 2 depicts the year-over year number of healthcare practitioners (HCPs) who have certified their first unique patient, as well as the cumulative number of HCPs who certified at least one patient at the end of each program year.

Figure 2

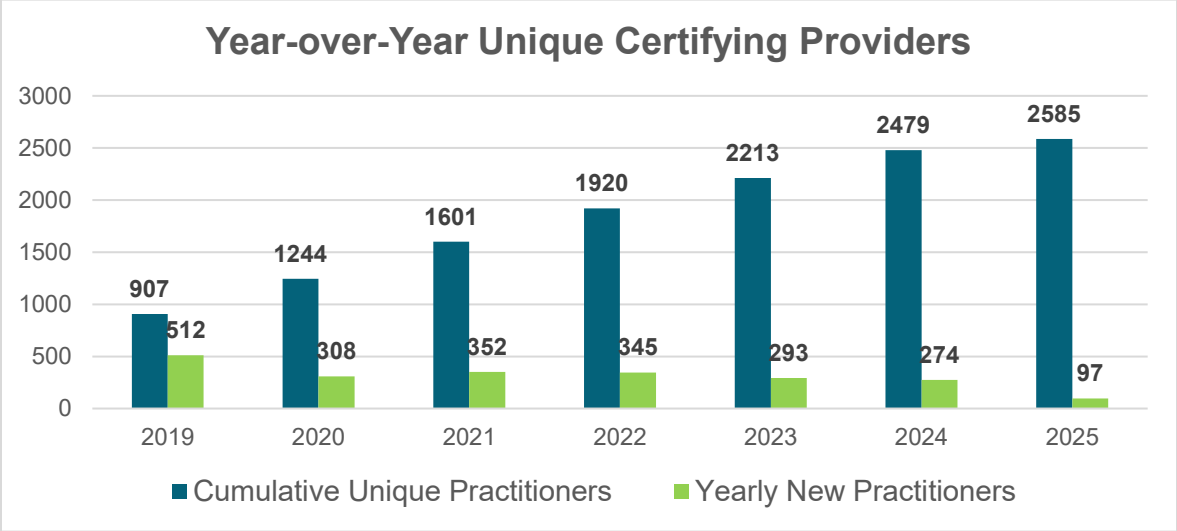
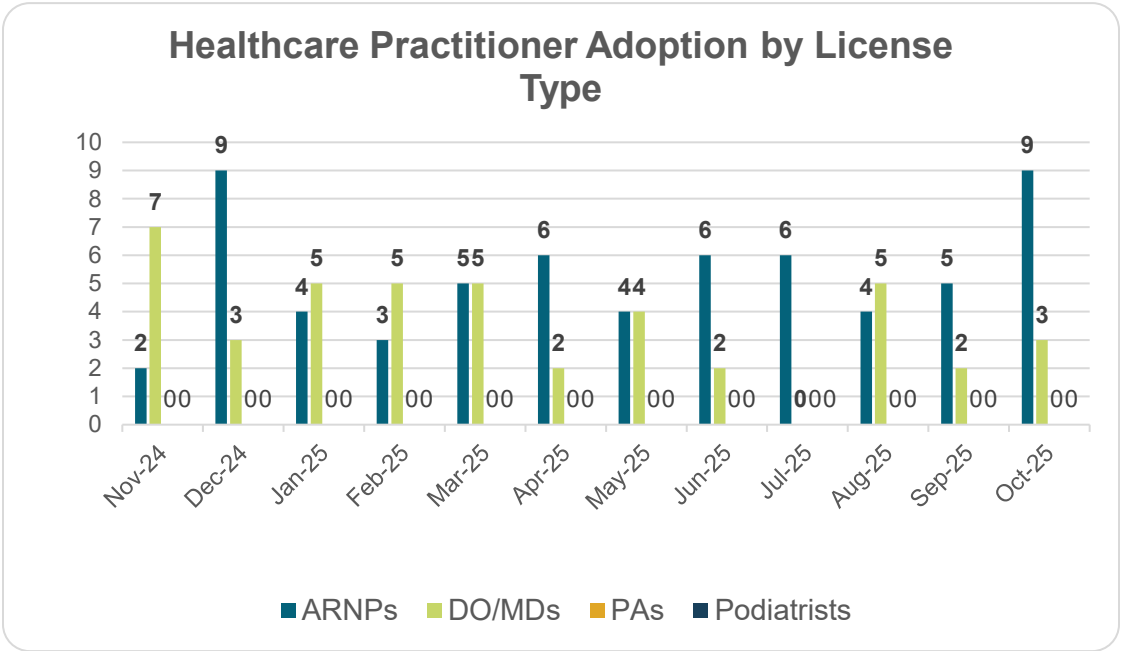


Figure 3 depicts the number of ARNPs, DO/MDs, PAs and podiatrists who have certified their first unique patient in the last year. Prior to July 1, 2020, ARNPs, PAs and podiatrists were not authorized to certify patients.

Figure 3



II. Patients and Caregivers

To purchase medical cannabis products from Iowa's licensed dispensaries, patients must have their qualifying medical condition certified by a Healthcare Practitioner. Once certified, a patient can apply for a registration card that is valid for one year. Figure 4 depicts the number of patients with active registration cards in each month of 2025. Prior to July 1, 2020 registration cards were issued by the Iowa Department of Transportation. IDPH began issuing cards on July 1, 2020.

Figure 4

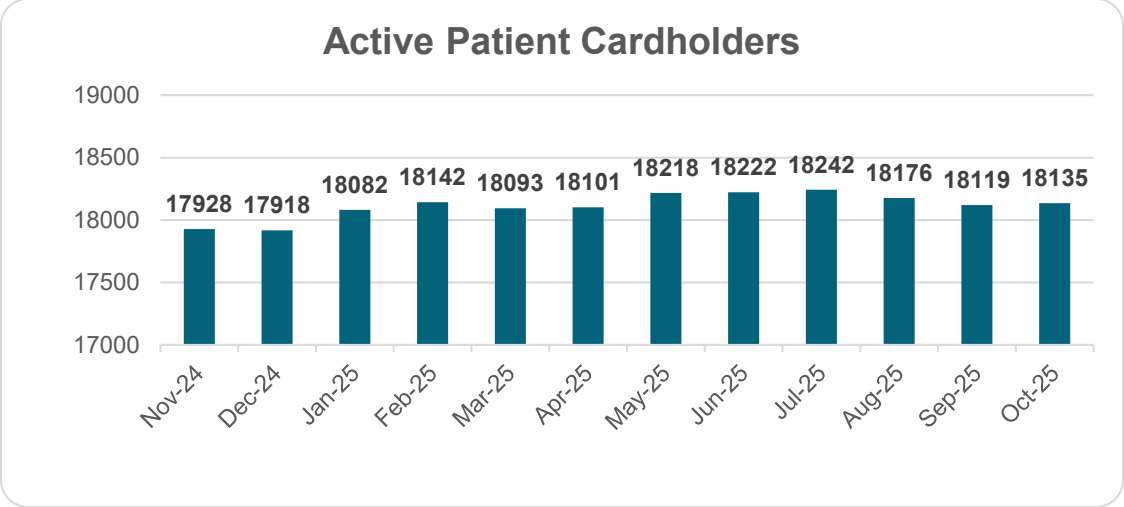
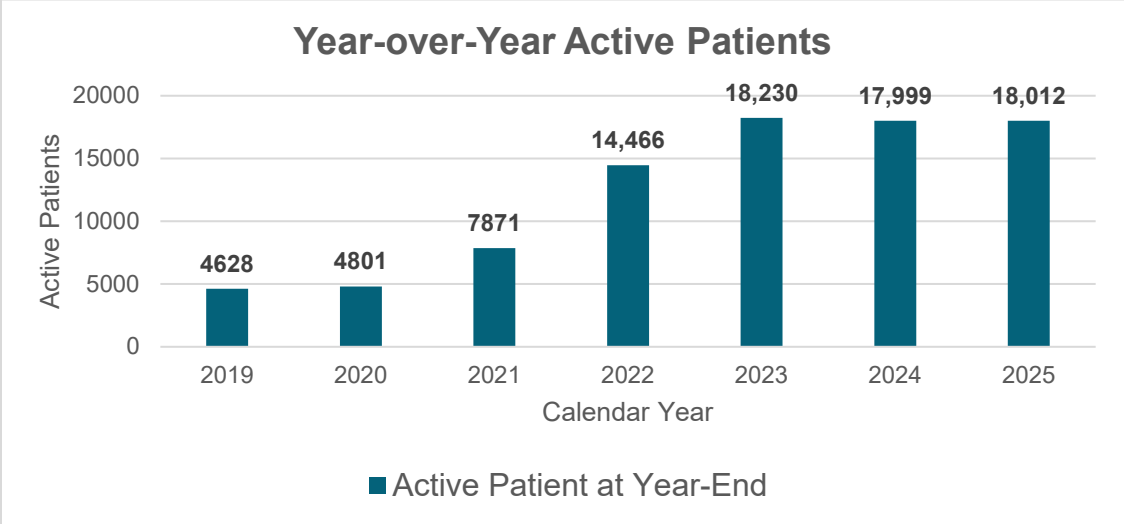


Figure 5 depicts the number of patients with active registration cards at the end of each year of the program since implementation.

Figure 5



Designated caregivers are individuals who are certified by a patient's healthcare practitioner to purchase and possess medical cannabis products on behalf of a patient. A caregiver is designated if a patient is too ill, immobilized or otherwise unable to visit a dispensary. Figure 6 depicts the number of caregiver registration cards issued in each month of 2025. The cumulative number of caregiver cards issued since the beginning of the program is also depicted as a trend line.

Figure 6

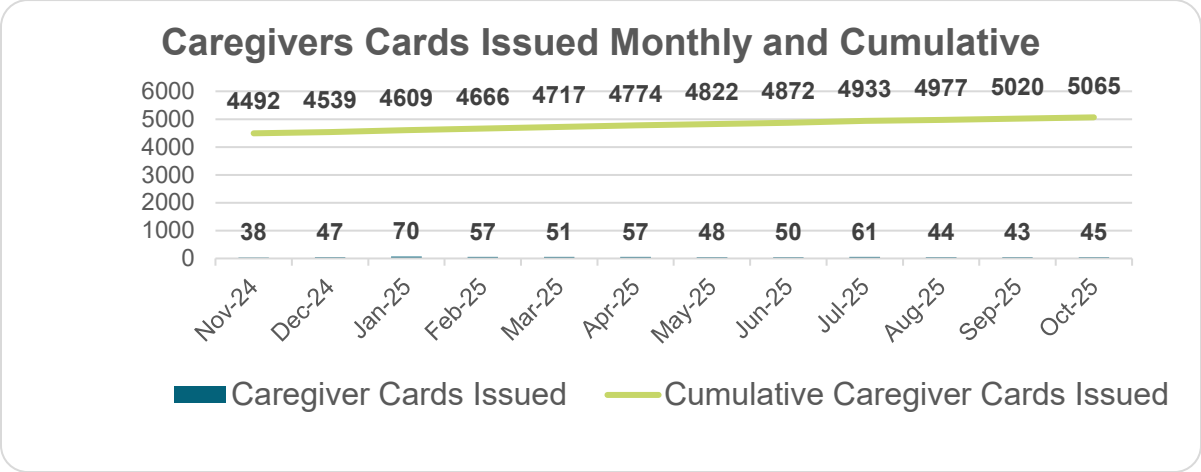


Figure 7 depicts the number of registration cards issued to patients in each of the last 12 months. The monthly patient cards issued includes new patients, as well as patients who may have renewed their registration card. The cumulative numbers of patient cards issued since the beginning of the program are displayed using a trend line.

Figure 7

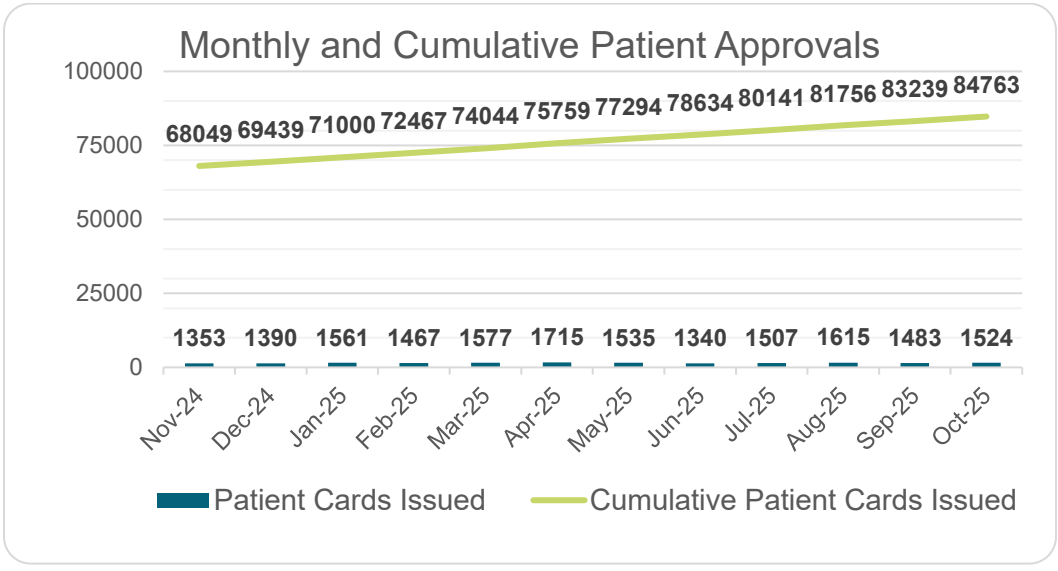


Figure 8 depicts the average number of patient registration cards issued per month for each program year, as well as the cumulative number of patient cards issued for each program year.

Figure 8

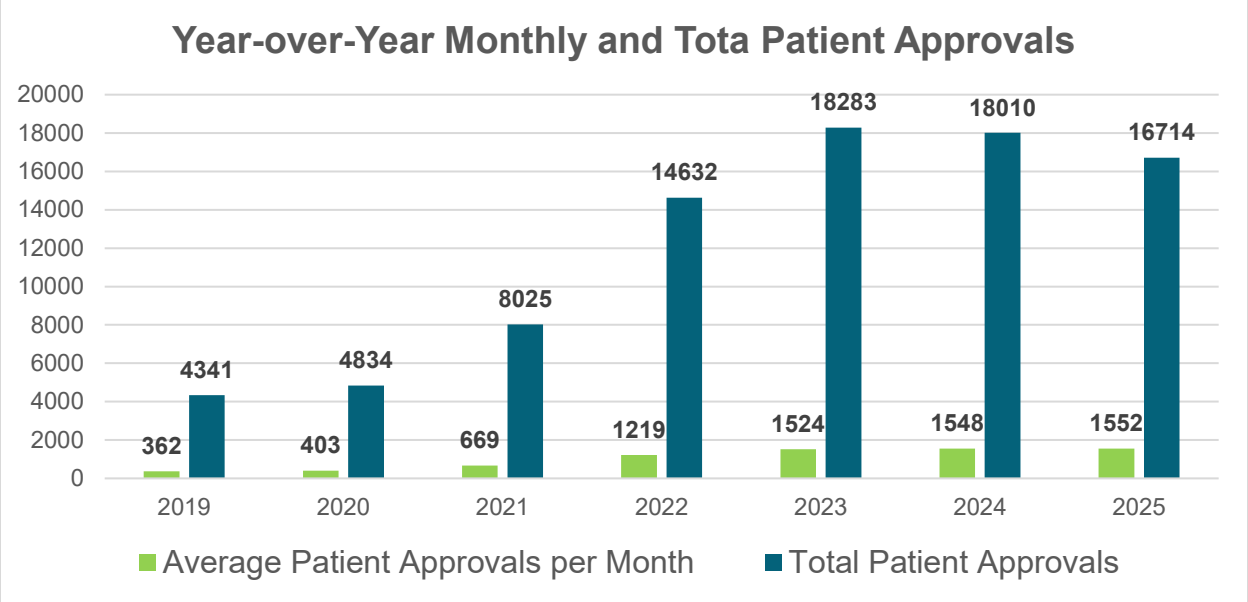


Figure 9 depicts the certifications by age bracket for each qualifying debilitating medical condition for all active patient cardholders.

Figure 9

Age	AIDS/HIV	ALS	Autism	Cancer	Chronic Pain	Crohn's	MS	Parkinson's	PTSD	Seizures	Terminal Illness	Ulcerative Colitis	Total
10 or Under	0	0	39	0	2	0	0	0	1	9	0	1	52
11-17	0	0	45	2	15	2	0	0	6	4	0	1	75
18 - 30	7	1	33	21	1370	21	7	3	857	61	0	24	2405
31 - 40	16	0	10	47	2657	46	27	8	1244	70	2	39	4166
41 - 50	12	2	4	102	3154	36	58	11	880	69	1	35	4364
51 - 60	17	2	4	136	2214	20	35	21	354	30	0	15	2848
61 - 70	7	0	1	197	2212	11	28	33	161	17	2	8	2677
71 - 80	2	0	0	116	873	6	8	34	38	5	3	3	1088
81 - 90	0	0	0	17	182	1	2	12	2	1	2	1	220
Over 90	0	0	0	3	25	0	0	2	0	0	0	1	31
Total	61	5	136	641	12704	143	165	124	3543	266	10	128	**17926**

Figure 10 represents the patient population percentage by gender.

Figure 10

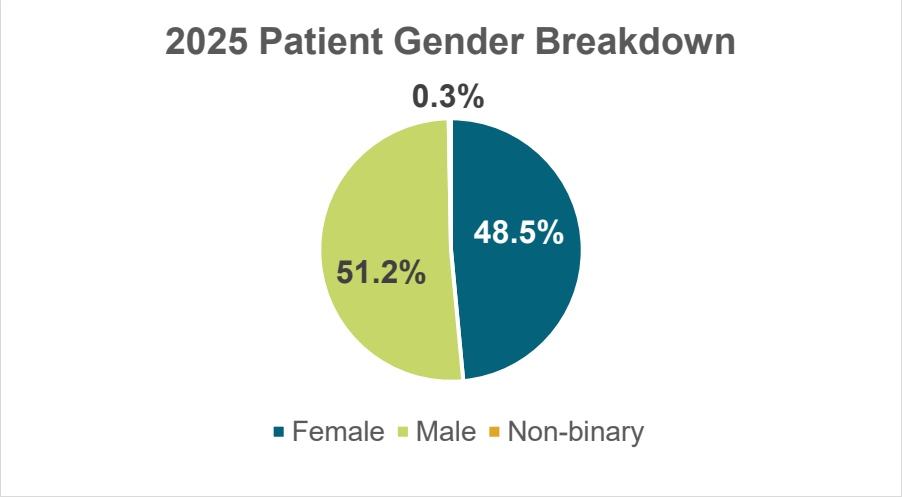
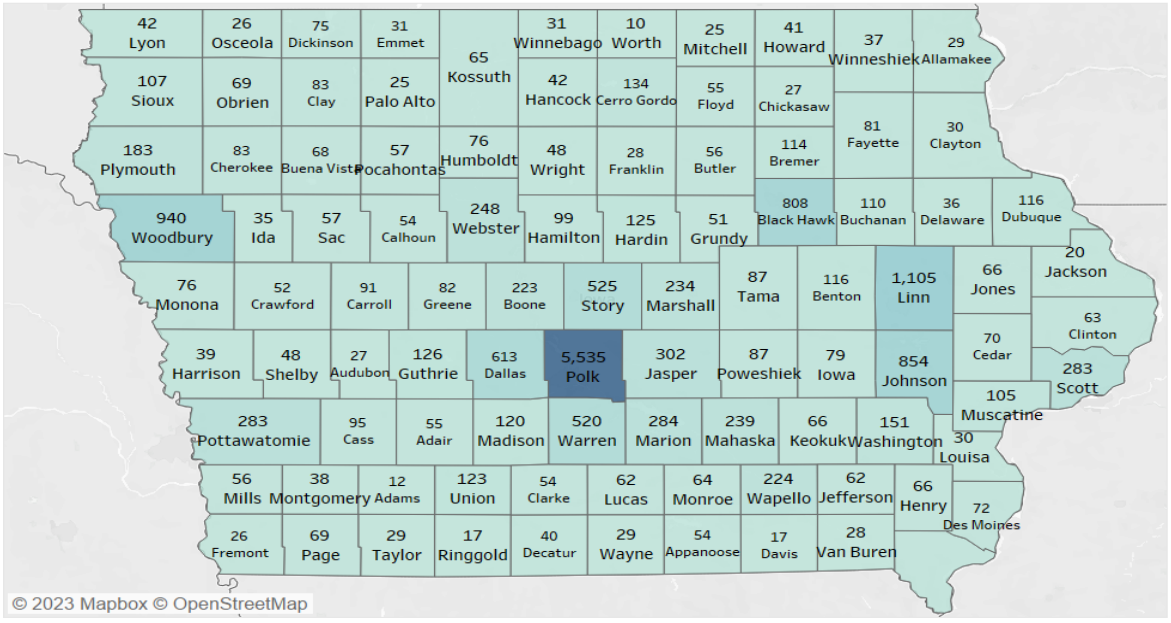


Figure 11 represents the density of active patient cardholders by county in Iowa.

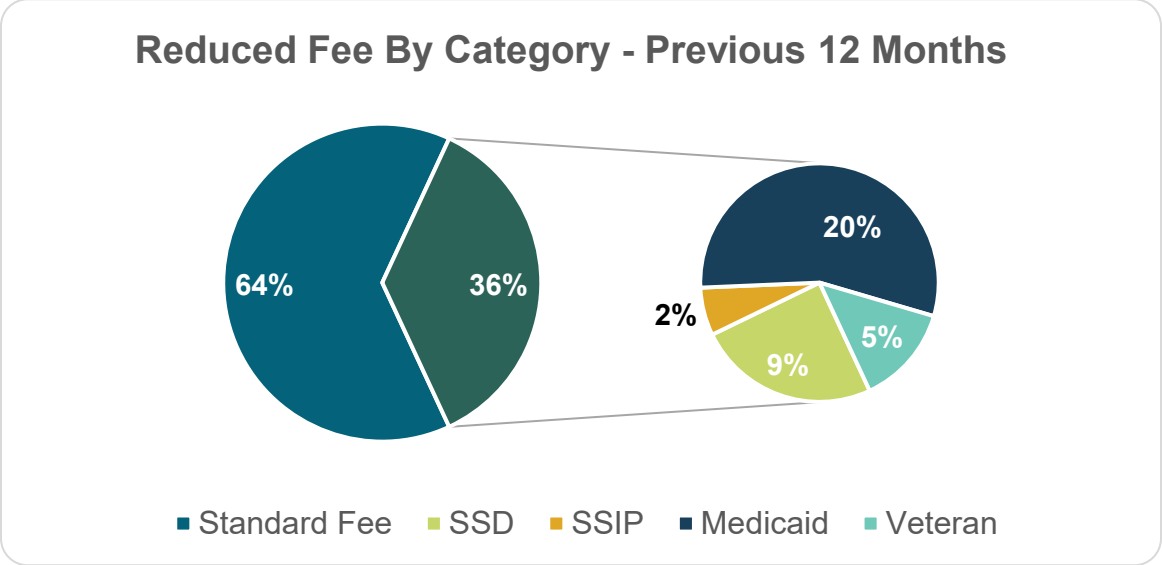
Figure 11



Map based on Longitude (generated) and Latitude (generated). Color shows Number of Records - Supressed. Size shows details about County (group). The marks are labeled by Number of Records - Supressed and County (group). The data is filtered on Record Type Name and Application Status. The Record Type Name filter keeps Minor_Patient and State_Patient_Record. The Application Status filter keeps Approved, Issued and Minor. The view is filtered on Longitude (generated), which keeps non-Null values only.

Patients in Iowa are eligible for a reduced fee when applying for their registration card. If a patient can provide proof of Social Security Disability Insurance (SSDI), Supplemental Security Income (SSI), or Medicaid, they are eligible for a reduced fee. In 2022, via updates to administrative rule, proof of Veterans status became eligible for the reduced application fee. Figure 12 depicts the percentage of standard ($100) or reduced ($25) fee applications, as well as the percentage of each reduced fee type.

Figure 12



III. Dispensary Sales

Iowa's licensed dispensaries are required to transmit their medical cannabis dispensing data to the state's Secure Sales and Inventory Tracking System on a real-time basis.

Figure 13 depicts the number of unique patient transactions in each month of the last 12 months, as well as the total dispensary transactions in each month.

Figure 13

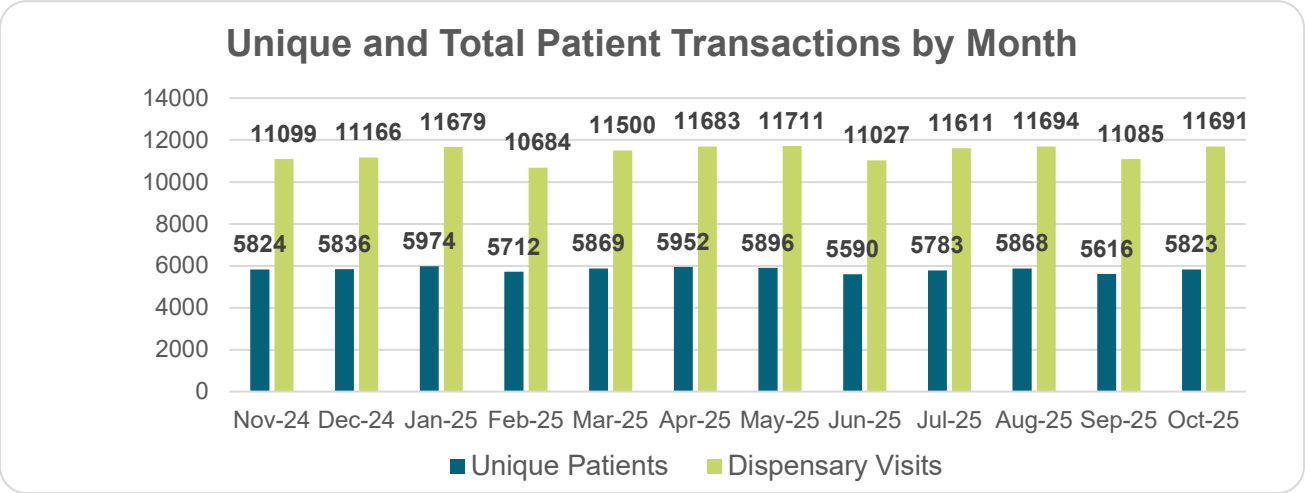


Figure 14 depicts the average number of monthly transactions for each program year, as well as the total number of transactions for each program year.

Figure 14

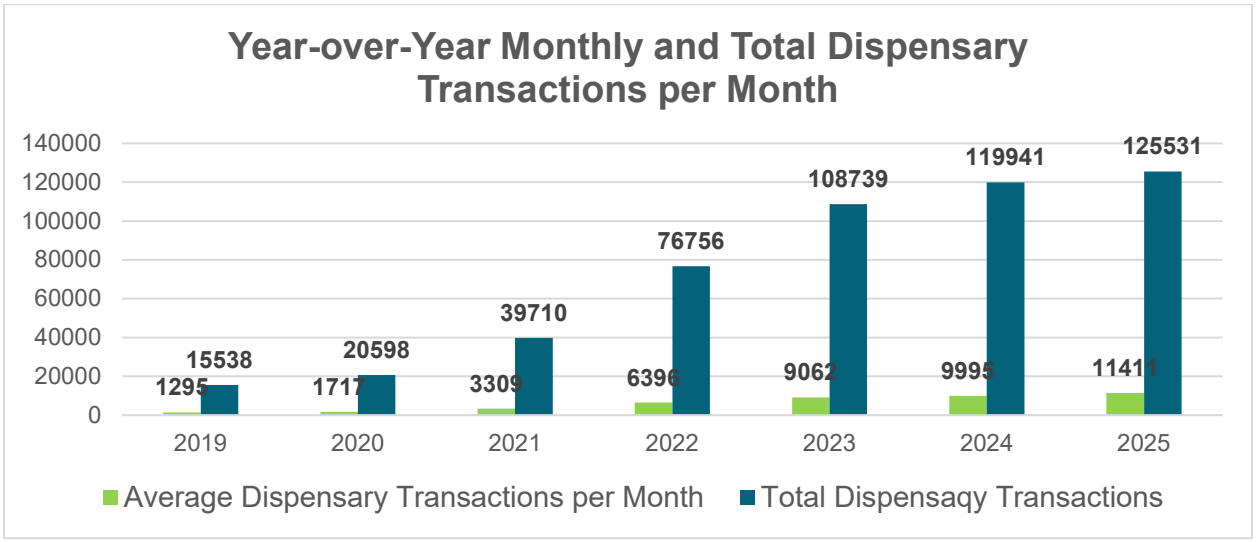


Figure 15 represents the average transaction price (excluding tax) amongst Iowa's licensed dispensaries over the last 12 months.

Figure 15

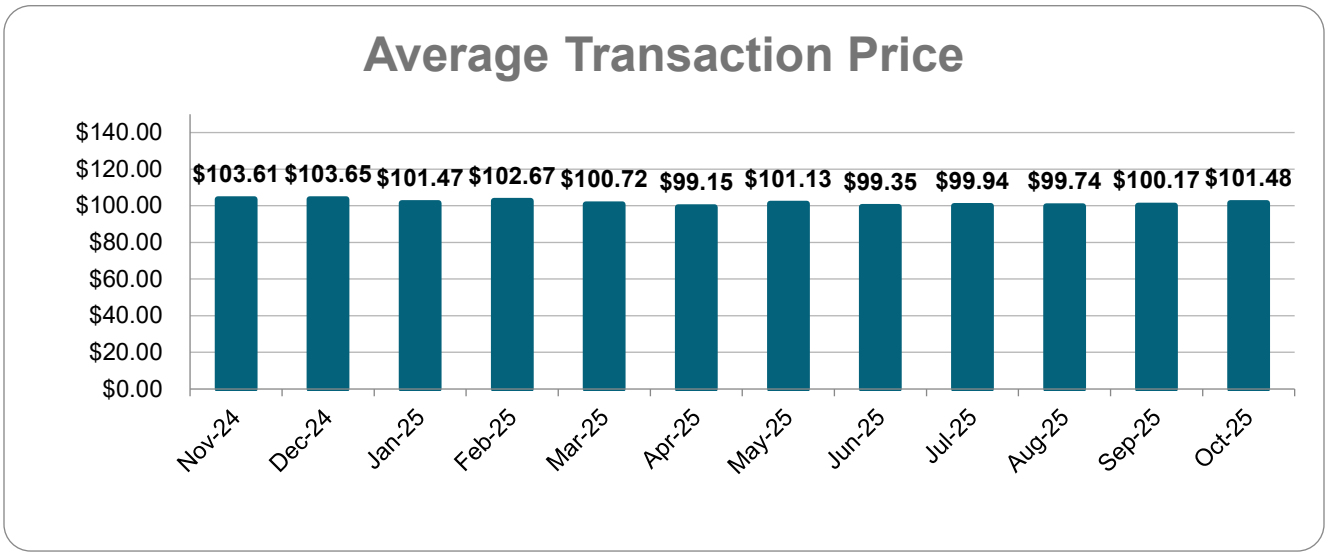


Figure 16 represents the total sales (excluding tax) in each of the last 12 months among Iowa's licensed dispensaries.

Figure 16

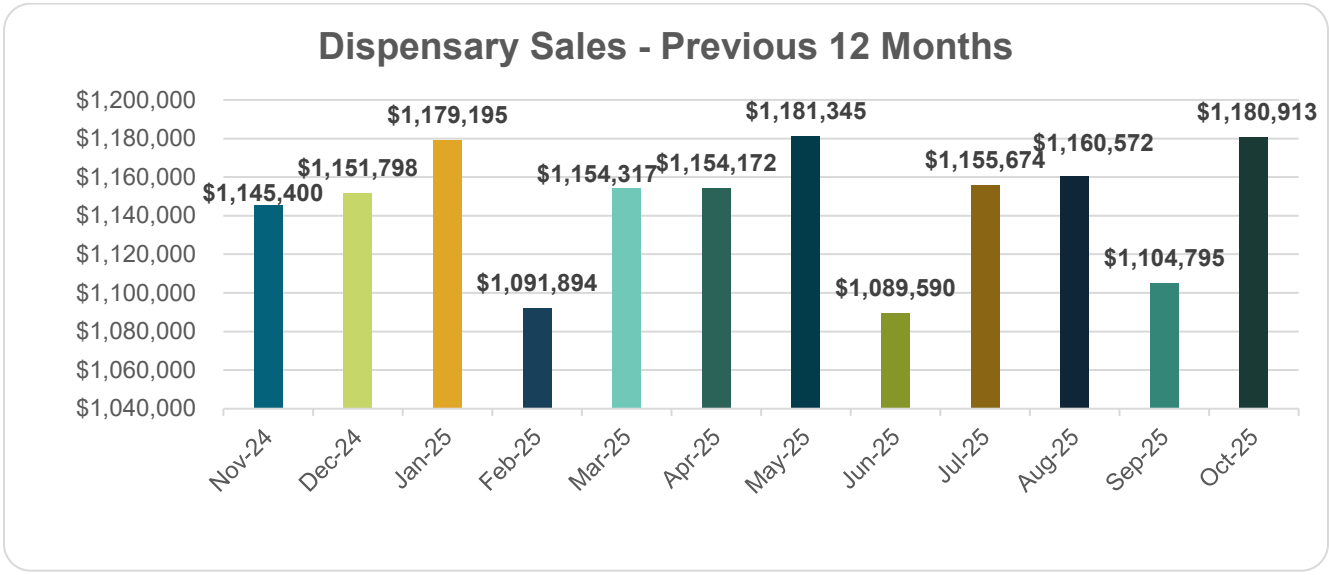
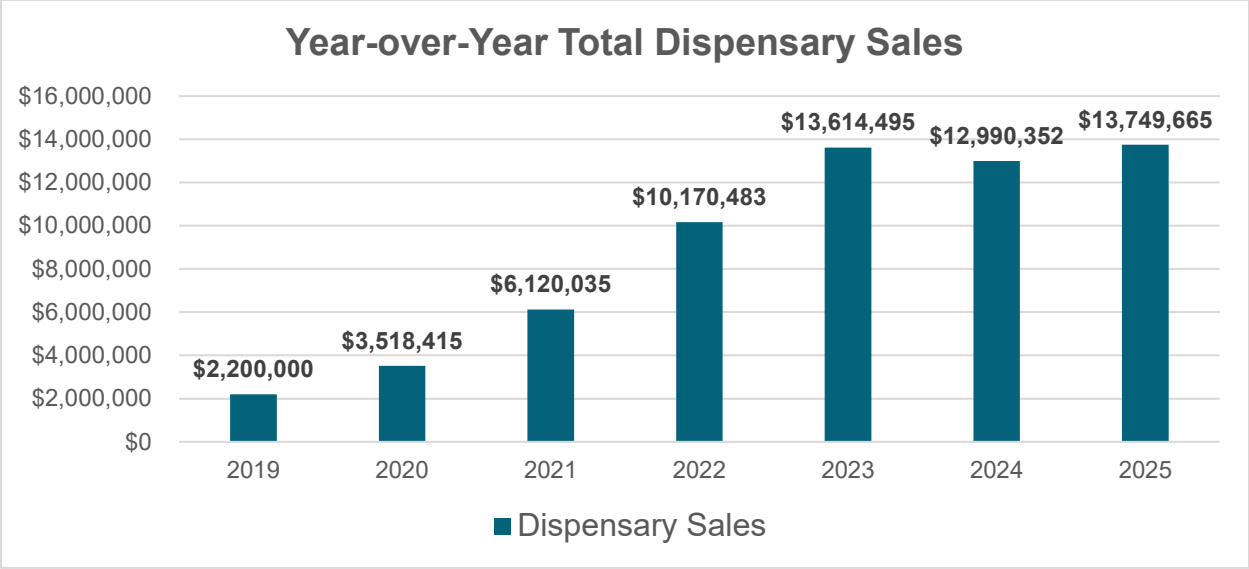


Figure 17 depicts the cumulative dispensary sales for each program year since implementation.

Figure 17



Chapter 124E allows Iowa's two licensed manufacturers to manufacture products in the following forms: oral forms (tinctures, capsules, tablets and sublingual forms), topical forms (gels, ointments, creams, lotions and transdermal patches), nebulizeable forms, suppository forms and vaporized forms (vaporized forms became available for sale on August 7, 2019). Figures 18 & 19 show the percentage of product sales by formulation and product type over the past 12 month.

Figure 18

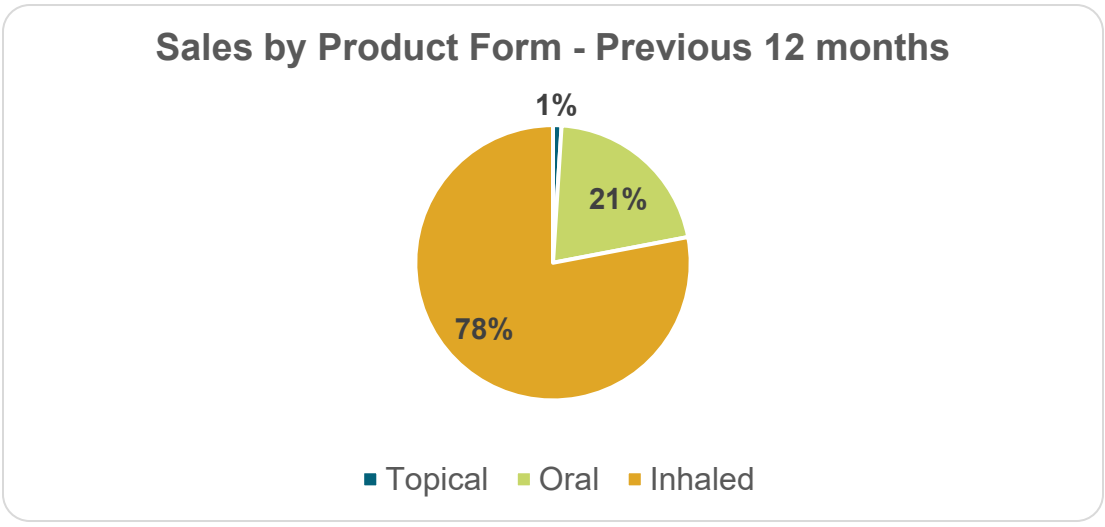


Figure 19

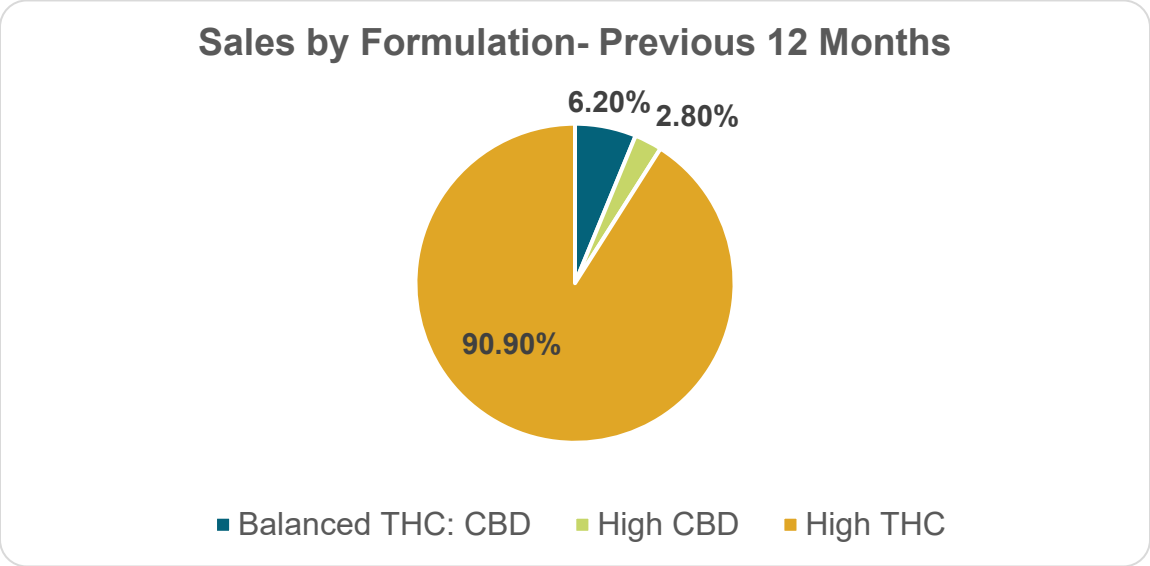
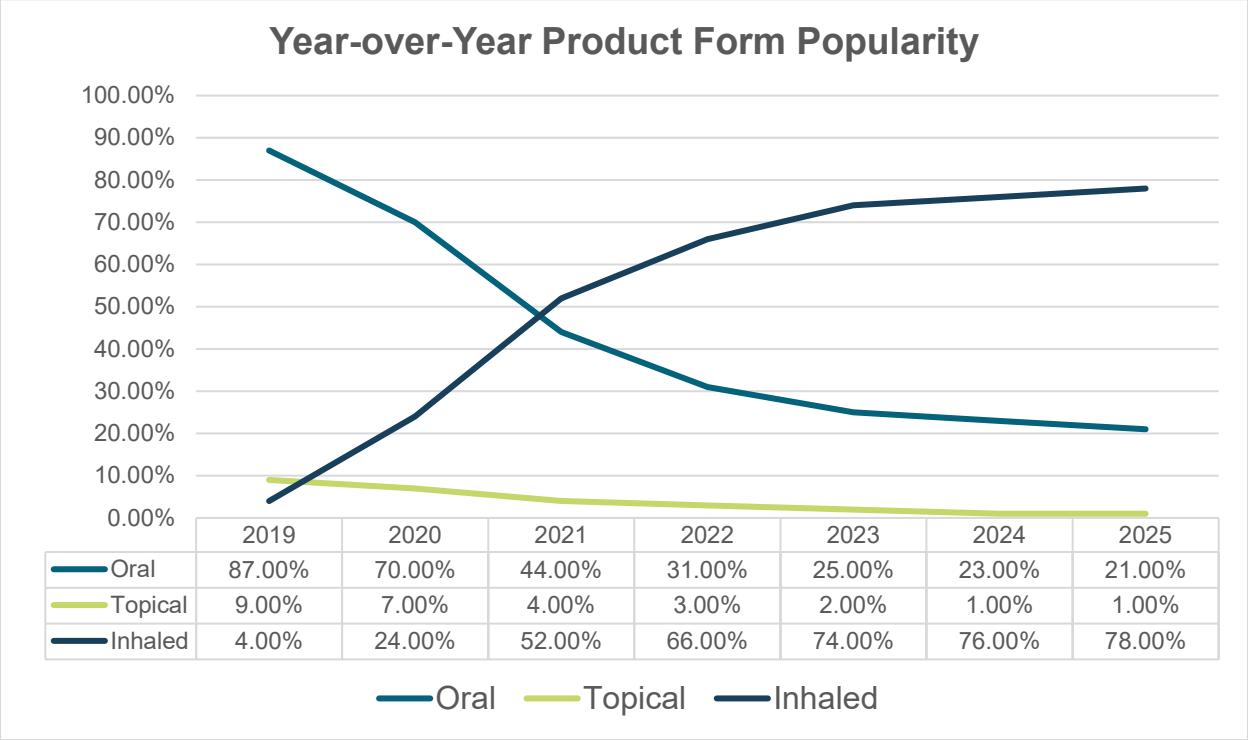


Figure 20 depicts the year-over-year change in product form popularity as a percentage of total dispensary purchases.

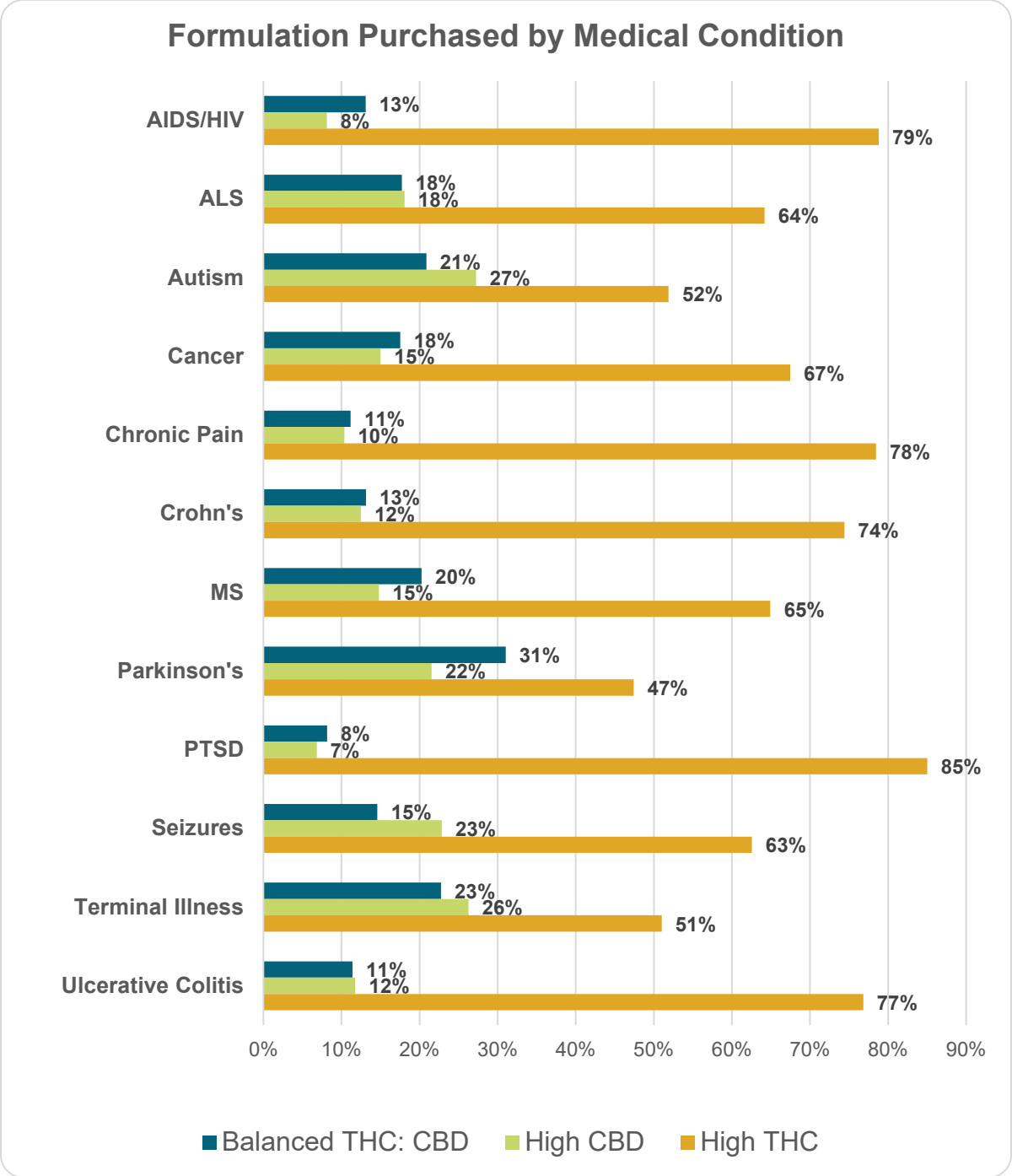
Figure 20



	2019	2020	2021	2022	2023	2024	2025
Oral	87.00%	70.00%	44.00%	31.00%	25.00%	23.00%	21.00%
Topical	9.00%	7.00%	4.00%	3.00%	2.00%	1.00%	1.00%
Inhaled	4.00%	24.00%	52.00%	66.00%	74.00%	76.00%	78.00%

Figure 21 provides percentage-based purchasing behaviors for a given product formulation and qualifying condition.

Figure 21



IV. THC Waivers

Patients are eligible for a waiver to purchase additional THC than the standard 4.5 g per 90-day limit, if: 1. They are certified for a terminal illness, or 2. If having participated in the program, their original certifying provider completes a waiver for a larger amount.

Figure 22 depicts the number of waivers issued each year since implementation in 2020, as well as the percentage of the patient population with a waiver in each program year.

Figure 22

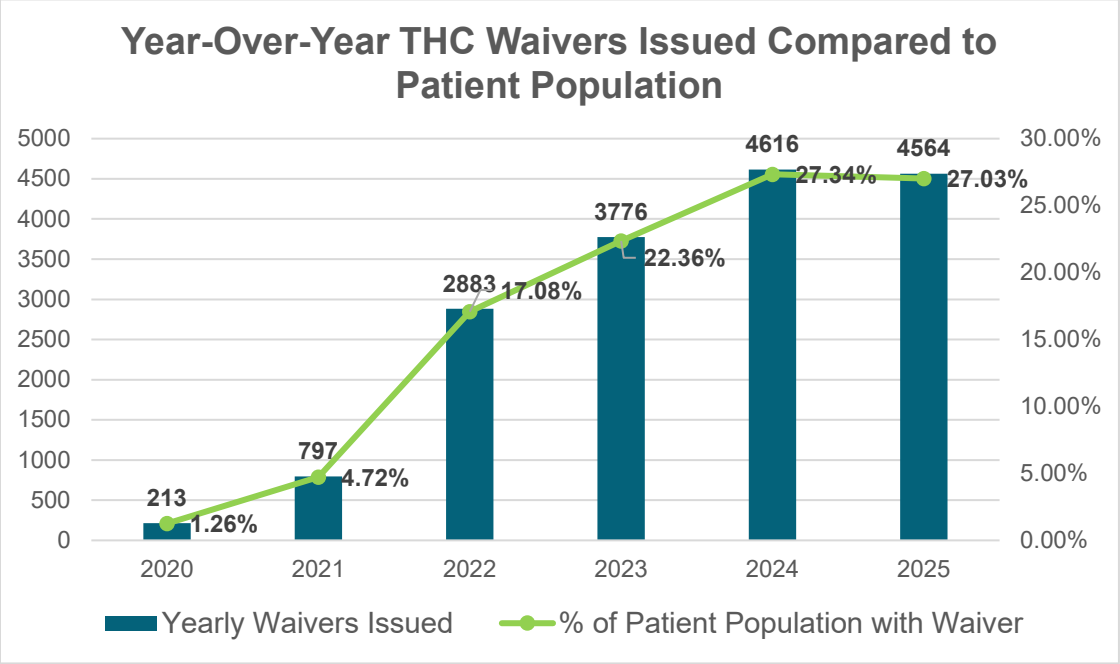


Figure 23 represents percentage-based aggregates of time that a patient participated in the program before being approved for a THC-waiver. The buckets of time defined on the x-axis represent the time spent participating in the program prior to a patient being issued their *first* THC-waiver. The data represents all waivers since implementation in July 2020.

Figure 23

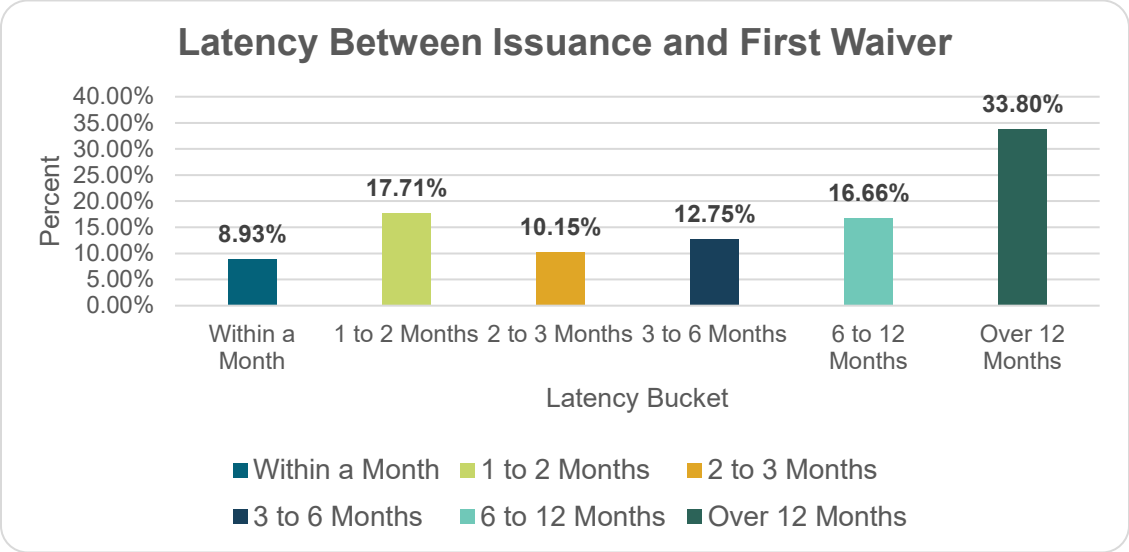
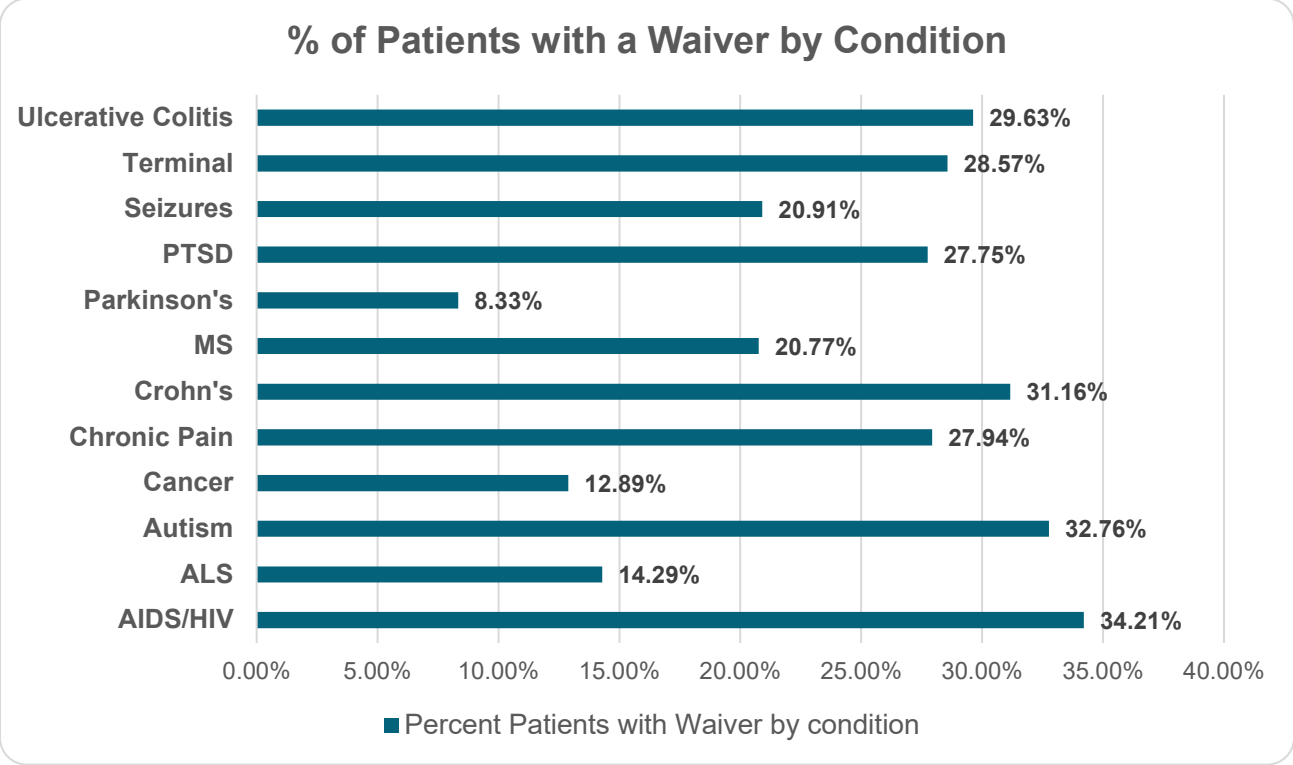


Figure 24 depicts the percentage of the patient population within a qualifying condition that have received a THC waiver.

Figure 24



Appendix A
Medical Cannabidiol Board
Subcommittee Report on Vaporized or Raw Cannabis

Subcommittee Members

- Robert Shreck, MD (Oncology)
- Andrea Weber, MD (Psychiatry)
- Cory Garvin, PharmD (Pharmacy)

Purpose

At the August 2025 Board Meeting, this Subcommittee was assigned to review current medical literature evaluating the safety and efficacy of vaporized dried or raw cannabis for the treatment of qualifying medical conditions.

Previous Board or Subcommittee reviews conducted in 2022–2023 concluded that available evidence was limited or insufficient to support safety, efficacy, or reproducibility of effect, leading to the denial of prior petitions to permit vaporized forms. The Subcommittee's current purpose is to update that review and assess whether new or emerging scientific evidence warrants reconsideration of the Board's prior determinations, and for this document to serve as the recommendation to the full Board.

Methods

The medical literature was reviewed through two different approaches: the National Library of Medicine's *PubMed* site and an artificial intelligence large language model (LLM), specifically *ChatGPT5o*.

1. The AI site was asked to "List placebo-controlled, randomized, controlled trials of vaporized, dried, raw cannabis (flower) as treatment for adverse medical conditions published in the medical literature."
2. *PubMed* was searched using terms "vaporized cannabis" and "vaporized marijuana" and then filtered by "Randomized Controlled Trials"; separate searches were filtered by "Reviews".
3. As a previous petitioner of the product form, MedPharm Iowa (Bud & Mary's) was invited to provide literature to support the assertion that dried or raw cannabis is proven beneficial, but declined to participate.

Results

1. *ChatGPT5o* yielded the most succinct list[1] of a half dozen trials that met the search criteria. Although they are all prospective, placebo-controlled and randomized all trials have substantial defects:
    A. small number of study subjects (<50);
    B. short-term, often just one day, a few weeks at most;
    C. dosimetry was poorly-controlled in most, allowing subjects to self-determine the dose;
    D. as a result euphoria was a common feature, although transient.
2. *Pubmed* yielded essentially the same studies with the same features. Of interest, the "Reviews" filter yielded several compositions[2] virtually all addressing, as experience has been gained, the toxic effects of both combusted and vaporized cannabis, whether whole leaf or in extracted forms [example provided].
3. A search of *Chat GPT5o* for a study directly comparing vaporized dried, raw cannabis with vaporized cannabis extracts yielded nothing. It appears such a study has not been done.
4. A search[3] of the *FDA website* for approved "whole plant medications" yielded a short list of topical forms, none administered systemically, along with statements:
    a. "Whole-plant formulations often contain dozens or hundreds of chemical constituents. . . .not clear which constituents are responsible for therapeutic effect or toxicities."
    b. "Ensuring consistent quality, purity, and potency in each batch is more challenging compared to a purified chemical [extract]."

Recommendations

The Board should make a motion to:

- Affirm its prior opposition to dried raw cannabis in any form as a medical treatment of qualifying conditions, and specifically oppose vaporization as a form in the Iowa's Medical Cannabis Program.

Conclusion

Evidence-based literature supporting dried, raw cannabis in a vaporized form of medical treatment cannot be found. Furthermore, dried, raw cannabis provided for vaporization can readily be diverted for combustion (smoked), a form and use specifically prohibited by Iowa law. On November 14, 2025, the Board voted unanimously to reaffirm its opposition to a raw form of cannabis, to include a recommendation full subcommittee report in its annual report to the legislature.

Annotations

Annotation 1

1. **Neuropathic pain (mixed etiologies)** — Wilsey et al., *J Pain* 2013
   Double-blind, placebo-controlled, 3-period **crossover** RCT (n=39). Volcano-vaporized NIDA cannabis flower (THC 1.29% “low” and 3.53% “medium”) vs placebo flower; significant analgesia vs placebo with minimal short-lived cognitive effects. PubMed

2. **Painful diabetic peripheral neuropathy** — Wallace et al., *J Pain* 2015
   Double-blind, placebo-controlled, 4-period **crossover** RCT (n=16). Volcano-vaporized cannabis flower at THC 1%, 4%, 7% vs placebo; dose-dependent reduction in spontaneous and evoked pain, with higher dose producing some cognitive impairment. PubMed

3. **Neuropathic pain from spinal cord injury/disease** — Wilsey et al., *J Pain* 2016
   Double-blind, placebo-controlled **crossover** RCT (n=42). Volcano-vaporized cannabis flower (THC 2.9% and 6.7%) vs placebo; significant analgesic response; lower dose favored for risk-benefit. PubMed

4. **Fibromyalgia** — van de Donk et al., *PAIN* 2019
   Double-blind, placebo-controlled, 4-way **crossover** RCT (n=20). Single inhalation of pharmacy-grade **flower chemovars** via Volcano (Bedrocan: high-THC; Bediol: THC+CBD; Bedrolite: high-CBD) vs placebo flower. Modest, mixed findings: THC-containing varieties increased pressure pain thresholds; spontaneous pain relief not greater than placebo overall (responder signal for THC+CBD). Lippincott Journals

5. **Acute migraine** — Schuster et al., *Neurology* 2024
   Double-blind, placebo-controlled, **crossover** RCT (92 randomized; 247 attacks treated). Patients self-treated up to four attacks with vaporized **cannabis flower**: THC-dominant (6% THC), CBD-dominant (11% CBD), **THC+CBD (6%/11%)**, and **placebo flower**. The **THC+CBD flower** was superior to placebo at 2 h for pain relief, pain freedom, and most-bothersome-symptom freedom, with sustained benefits; no serious AEs. PMC

Annotation 2

Respir Med 2024 Jan:221:107494.
doi: 10.1016/j.rmed.2023.107494.Epub 2023 Dec 5.

Effects of cannabis smoking on the respiratory system: A state-of-the-art review

Lugain Khoj [1], Vincenzo Zagà [2], Daniel L Amram [3], Karishma Hosein [4], Giovanni Pistone [5], Mario Bisconti [6], Antonella Serafini [7], Liborio M Cammarata [5], Maria Sofia Cattaruzza [8], Marco Mura [4]

Abstract

The diminished perception of the health risks associated with the consumption of cannabis (marijuana) lead to a progressive increase in its inhalational use in many countries. Cannabis can be smoked through the use of joints, spliffs and blunts, and it can be vaporised with the use of hookah or e-cigarettes. Delta-9 tetrahydrocannabinol (THC) is the main psychoactive component of cannabis smoke but contains numerous other substances. While the recreational use of cannabis smoking has been legalised in several countries, its health consequences have been underestimated and undervalued. The purpose of this review is to critically review the impact of cannabis smoke on the respiratory system. Cannabis smoke irritates the bronchial tree and is strongly associated with symptoms of chronic bronchitis, with histological signs of airway inflammation and remodelling. Altered fungicidal and antibacterial activity of alveolar macrophages, with greater susceptibility to respiratory infections, is also reported. The association with invasive pulmonary aspergillosis in immunocompromised subjects is particularly concerning. Although cannabis has been shown to produce a rapid bronchodilator effect, its chronic use is associated with poor control of asthma by numerous studies. Cannabis smoking also represents a risk factor for the development of bullous lung disease, spontaneous pneumothorax and hypersensitivity pneumonitis. On the other hand, no association with the development of chronic obstructive pulmonary disease was found. Finally, a growing number of studies report an independent association of cannabis smoking with the development of lung cancer. In conclusion, unequivocal evidence established that cannabis smoking is harmful to the respiratory system. Cannabis smoking has a wide range of negative effects on respiratory symptoms in both healthy subjects and patients with chronic lung disease. Given that the most common and cheapest way of assumption of cannabis is by smoking, healthcare providers should be prepared to provide counselling on cannabis smoking cessation and inform the public and decision-makers.

Keywords: Asthma; Bullous lung disease; Cannabis; Chronic bronchitis; Lung cancer; Marijuana; Pulmonary aspergillosis; Smoking.

Annotation 3

Here's a summary of how and why the FDA (via its Center for Drug Evaluation and Research, CDER) is typically reluctant or declines to approve "whole-plant" or complex botanical medicinal products. The key reasons relate to challenges in ensuring identity, quality control, reproducibility, safety, and evidence of efficacy.

Regulatory Framework & Context

- The FDA has a **Botanical Drug Development Guidance for Industry** that sets forth the agency's "current thinking" on how to handle botanical products being developed as drugs. U.S. Food and Drug Administration+2U.S. Food and Drug Administration+2
- Under this framework, a "botanical drug" is a product comprising plant materials (e.g. roots, leaves, extracts, etc.), and not one that is highly purified or chemically modified to a single molecular entity. U.S. Food and Drug Administration+2U.S. Food and Drug Administration+2
- The guidance emphasizes that botanical drugs must meet essentially the same standards of safety, efficacy, and manufacturing controls as conventional small-molecule drugs (though with certain accommodations or flexibilities). U.S. Food and Drug Administration+3U.S. Food and Drug Administration+3U.S. Food and Drug Administration+3
- A key concept is that sponsors must show the "identity, strength (potency), purity, and quality" (i.e. reproducible manufacturing) of the botanical drug. U.S. Food and Drug Administration+3U.S. Food and Drug Administration+3U.S. Food and Drug Administration+3

Because many "whole-plant" formulations present special difficulties in meeting those standards, the FDA often declines or refuses approval unless those challenges can be satisfactorily addressed.

Below are the major rationales (barriers) FDA cites or implicitly uses in rejecting or not approving whole-plant medicines.

Common Rationales or Barriers

1. **Complex mixture and lack of a single active ingredient / indistinct "active" constituents**
    - Whole-plant formulations often contain dozens or hundreds of chemical constituents. It may not be clear which constituent(s) are responsible for the therapeutic effect (or toxicities). U.S. Food and Drug Administration+4European Pharmaceutical Review+4U.S. Food and Drug Administration+4
    - Because of that, it becomes difficult to define and standardize "potency" or "strength" in a way acceptable to FDA. U.S. Food and Drug Administration+2PubMed+2
    - The guidance notes the need for "multiple, sometimes overlapping" chemical or biological assays to characterize the botanical material. U.S. Food and Drug Administration
2. **Batch-to-batch (lot-to-lot) consistency / reproducibility issues**
    - The natural variability of plant sources (geography, harvest time, growing conditions, weather, soil, genetic variation) can lead to variable chemical composition. U.S. Food and Drug Administration+3PubMed+3U.S. Food and Drug Administration+3
    - Ensuring consistent quality, purity, and potency in each batch is more challenging compared to a purified chemical. U.S. Food and Drug Administration+3U.S. Food and Drug Administration+3PubMed+3
    - Without that consistency, FDA reviewers may question whether the clinical studies reflect what would be produced commercially.
3. **Insufficient chemistry, manufacturing, and controls (CMC) data**
    - The sponsor must fully describe raw botanical materials, the processing steps, standardization criteria, assays, controls for degradation, contaminants, etc. U.S. Food and Drug Administration+2U.S. Food and Drug Administration+2
    - In past botanical drug reviews, the FDA has declined approval or recommended against it because the identity, strength, purity, or quality assurance data were inadequate. European Pharmaceutical Review+2Fieldfisher+2
    - Because botanical drugs may contain many compounds, establishing a robust CMC package is more complex.
4. **Poor or insufficient evidence of clinical efficacy (and/or safety) via "adequate and well-controlled trials"**
    - Even if a botanical has long history of human use, FDA generally expects *well-controlled, statistically rigorous clinical trials* to support claims. U.S. Food and Drug Administration+5U.S. Food and Drug Administration+5U.S. Food and Drug Administration+5
    - FDA will scrutinize the design of those trials (e.g. endpoints, controls, blinding, patient population) as it does for conventional drugs. European Pharmaceutical Review+1

- Insufficient efficacy evidence is one of the most commonly cited reasons why many botanical drug candidates fail. European Pharmaceutical Review+2Fieldfisher+2
- Safety data must be robust, especially for chronic use. Unknown interactions among the multiple constituents may complicate safety assessment.

5. **Regulatory classification and labeling / intended use issues**
   - Some botanicals may already be marketed as dietary supplements or foods, complicating their transition to drug status. The intended use (e.g. claim of treating disease) is a key discriminator. U.S. Food and Drug Administration+2U.S. Food and Drug Administration+2
   - If prior marketing as a supplement exists, claims made must not mislead or conflict with FDA's expectations for drugs.
   - The sponsor must demonstrate that the botanical drug is appropriate for prescription or OTC use, and that the indications justify the level of regulatory scrutiny.
6. **Safety, toxicology, and drug–constituent interactions**
   - With multiple constituents, there is greater risk of unknown or unpredicted toxicities or interactions among constituents.
   - The FDA expects nonclinical (animal) toxicology studies, pharmacokinetics, ADME, and possibly interaction studies. Botanical complexity can complicate interpretation of these studies. ScienceDirect+3U.S. Food and Drug Administration+3U.S. Food and Drug Administration+3
   - Impurities, contaminants (heavy metals, pesticides, microbial, mycotoxins), adulterants must be controlled.
7. **"Totality of evidence" burden & higher uncertainty risk**
   - The guidance talks about a "totality of evidence" approach, meaning that FDA will weigh all available pharmacologic, toxicologic, clinical, and prior human use data. But the more gaps or uncertainties there are, the more risk that FDA will deem the evidence insufficient. Exploration Publishing+2PubMed+2
   - For botanicals, gaps or variability in data are more common; sponsors have to "connect the dots" more rigorously.
8. **Resource, cost, and strategic factors (less direct but practical)**
   - Because of the complexities above, the cost, time, and scientific risk of developing a botanical drug can be high, which leads some sponsors to abandon or not push through to full approval. European Pharmaceutical Review+1
   - With fewer patent protections or exclusivity, the financial return may not justify the regulatory burden. European Pharmaceutical Review+1

Examples & Lessons

- The FDA has approved very few botanical drugs (e.g. **Veregen®**, a green tea extract for genital warts; **Mytesi™** / crofelemer for HIV-associated diarrhea). European Pharmaceutical Review+3U.S. Food and Drug Administration+3U.S. Food and Drug Administration+3
- In some cases, initial review by FDA has flagged that the CMC package was inadequate, or that the sponsor did not sufficiently show consistency or identity of the botanical material. European Pharmaceutical Review+2Fieldfisher+2
- In reviews of cannabis / cannabis-derived botanicals, FDA has repeatedly noted difficulty in controlling heterogeneity, ensuring quality, demonstrating standard dosing, and dealing with controlled substance issues. Exploration Publishing