Addressing Regulatory Challenges in Clinical Trials of Cannabis-Related Drug Products

PEER REVIEWED

The past few years have witnessed a burgeoning global interest in the development of therapies related to cannabis (*Cannabis sativa L.*) and its components including cannabidiols (CBD) and other active constituents of cannabis; and many such cannabis-related drug products are currently in various stages of development. There has also been great headway made in exploring ways that cannabis-based chemicals may be used to treat a variety of indications across several therapeutic indications, including but not limited to PTSD, anxiety, chronic pain, epilepsy, and movement and rare disorders. A cursory review of ClinicalTrials.gov suggests that well over 100 clinical trials of cannabis-based therapies have been completed, are currently underway, or are pending recruitment globally; an upsurge that is replicated when reviewing other clinical trial registries such as the EU Clinical Trials register. This increase in clinical trials reflects the general public interest in both medicinal and recreational use of cannabis, and comes at a time of dynamic fluctuations in both state and federal regulations. This review will attempt to summarise the recent trends in clinical trials and point out the most common and salient regulatory and operational pitfalls in an effort to overcome shifting regulatory challenges inherent in the conduct of controlled clinical trials of cannabis-related drug products.

An Evolving Landscape

The past few years have been characterised by diverse opinions and feedback from state and federal regulatory bodies regarding cannabis use and cannabis-based medications. Of note, Congress passed the Agriculture Improvement Act of 2018 (known as the 2018 Farm Bill) which among other things established a new category of cannabis classified as "hemp" – defined as cannabis and cannabis derivatives with extremely low (no more than 0.3 per cent on a dry weight basis) concentrations of the psychoactive compound delta-9-tetrahydrocannabinol (THC)[1]. The 2018 Farm Bill also removed hemp from the Controlled Substances Act, which means that hemp is no longer considered a controlled substance under federal law; however, the FDA Commissioner at the time also issued a clear statement on the status of cannabis-derived compounds. The FDA, much like other global regulatory agencies, stands firm on the foundation that producers are not able to make therapeutic claims regarding cannabis or its derivatives until they have gone through the standard drug development journey, and have been approved via the established regulatory pathways, just as with any other product[2].

Many people use the term cannabinoid products and cannabis-related drug products interchangeably. To clarify the term "cannabinoids" is used often to categorise a wide variety of types of molecules that have an effect on human cannabinoid receptors, including endocannabinoids (produced endogenously in humans), phytocannabinoids (plant-based), and synthetic analogs of both groups. Of note, the cannabis plant produces over 100 different cannabinoids but the most prevalent and well understood are THC and CBD. To date, the FDA has approved three cannabinoids or cannabis-related drug products for medical treatment with a fourth currently under review. The synthetic product dronabinol and nabilone are approved to treat nausea and vomiting associated with cancer chemotherapy. Dronabinol is also approved to treat loss of appetite and weight loss in people with acquired immunodeficiency syndrome (AIDS) and contains synthetic THC, while nabilone contains a synthetic substance with a similar chemical structure. In 2016, the FDA approved Syndros, a liquid form of dronabinol and more recently, in 2018, the agency approved Epidiolex (cannabidiol or CBD) oral solution for the treatment of seizures associated with two severe forms of epilepsy. This approval was the first non-synthetic, cannabis-derived medicine for rare types of epilepsy such as Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older[3]. The drug is known as Epidiolex and is made from cannabis grown in the United Kingdom.

Auspiciously prompted by the recent approval of Epidiolex, the Drug Enforcement Agency (DEA) announced that "finished dosage formulations" of CBD with THC below 0.1% would be considered a Schedule 5 (which is the least regulated) drug as long as the medications have been approved by the FDA. This downgrading of a type of cannabis product from its original Schedule 1 classification was a first for the DEA and allowed Epidiolex to be distributed through traditional pharmaceutical channels. Without this change, physicians would not have been able to freely and easily prescribe this medication. Significantly, this rescheduling affects more than Epidiolex and has paved the way for other sponsor companies to follow a similar pathway to market. In May 2019, the FDA held a public hearing, the purpose of which was to clarify the FDA's stance regarding the use and testing of cannabis-related drug products, to understand the public's questions and concerns regarding these policies, and to put manufacturers of CBD-based products making unsubstantiated claims on notice that they will continue to receive warning letters from the agency and that action may be taken, noting that "selling unapproved drug products with unsubstantiated therapeutic claims is a violation of the law, and puts patients at risk". Although a minority of speakers supported a prohibition of cannabis-based products, most speakers endorsed a sanctioned regulatory pathway that would lead to uniform labelling and quality standards for cannabis-based drugs[4].

Current Regulatory Pathways

To avoid any confusion regarding apposite regulatory pathways for cannabis-related drug products, it is imperative to specify that in order to progress a cannabis derived product through the drug development journey, the pathways established by regulatory authorities for non-cannabis derived must first be adhered to, whether this be the NDA(b)(1) route or the NDA 505(b)(2) route. In all of these pathways, it is essential to note that robust trial data which demonstrates safety and efficacy must be presented. As with all medicinal compounds, it is highly recommended to seek early and frequent engagement with the FDA when developing these products, and to seek advice on the clinical development of such a programme. Appropriate regulatory designations are also applicable, which include, but are not limited to, the Orphan Drug Designation (ODD) pathway, rare disease paediatric disease

vouchers, and priority review/fast track and breakthrough designations.

It is also advisable to take advantage of the early engagement mechanisms that are available to sponsor companies through the type-B FDA meetings; such as a pre-IND meeting where the opportunity exists to ask the FDA questions regarding the development of the product before an IND is submitted. Through such interactions, sponsor companies can receive clear and explicit guidance from the agency regarding requirements for their specific compound. The FDA have also provided detailed information and guidance on the specific data requirements that are necessary to develop a drug that is derived from a plant such as cannabis through its updated Guidance for Industry on Botanical Drug Development[5].

After pre-IND meetings, and as with other drug development journeys, an IND application is submitted to the appropriate division in the Office of New Drugs in CDER, depending on the therapeutic indication under review. A complete and thorough evaluation of the safety of the product, as well as the quality (CMC) data, will be undertaken; and the timelines for approval ("no objection") are 30 days unless the product is placed on clinical hold until such time any outstanding questions are resolved to the satisfaction of the FDA. Once the IND approval is in place, sponsor companies can then begin navigating the complex pathway to getting the study drug to investigational sites in the various states. A complicated array of state-by-state legal differences and challenges, each impacting study conduct in different ways, has been the norm for US studies. These state edicts also interrelate with not one but several federal agencies. For example, all scheduled substances are subject to DEA regulations; the lower the scheduled number, the more restrictive the regulations. For Schedule 1 substances (the most restrictive of all and which currently includes cannabis and its derivatives), the request for approval to use such substances in clinical studies (which has to be made separately to the DEA) can only be initiated once an IND has been approved[6].

For any medical research to be performed with cannabis, the cannabis product must be provided by a DEA-registered source (such as a sponsor company) or by the National Institute on Drug Abuse (NIDA), which is part of the National Institutes of Health. When provided by NIDA, the cannabis supplied is research-grade. The DEA is responsible for overseeing the cultivation of such cannabis supplied for medical research and has contracted with universities to grow cannabis for research at a secure facility in order to ensure uniformity in potency and compositions. However, some research sites have opined that the NIDA-supplied cannabis can be of varying quality and have been critical of federal control of cannabis for research[7]. This has resulted in an effort by the DEA to increase the number of bulk growers.

Although the exact requirements vary from state to state, there are some generalities that can be noted regarding the conduct of research involving Schedule 1 compounds. First, sponsor companies conducting such research must have DEA approval to import materials into the US (if needed) and/or then across US state lines. All US investigational sites participating in a clinical trial of a Schedule 1 substance are subject to a DEA inspection prior to trial activation, regardless of previous clinical trial experience with Schedule 1 compounds. Any company or

facility (including any third-party vendor companies) that handle study drug or test Schedule 1 substances also require DEA licensure, and any site researchers conducting trials of Schedule 1 substances have to prepare and submit a research protocol to the DEA that includes details regarding the security provisions for storing and dispensing the substance. Local DEA officials have the jurisdiction to perform a preregistration inspection of the facility where the proposed research will take place. DEA security requirements include storing cannabis in a safe, a steel cabinet, or a vault which cannot be easily removed from the site and which has controlled access (key card or otherwise) to the storage facility. It is very likely and/or expected that the inspections and diligence could also be initiated at the state level in addition to the federal level.

Furthermore, a robust supply chain for the investigational product is also subject to international controls. In 2018, the Who Health Organization (WHO) Expert Committee on Drug Dependence (ECDD) recommended that preparations predominantly containing cannabidiol and not more than 0.2% THC not be under international control[8]. An endorsement by the United Nations is being considered next year and would effectively remove certain restrictions on the control of CBD, perhaps easing the complexity of undertaking clinical research from an international perspective.

Operational Considerations

In order to conduct an investigational clinical trial of cannabis-related drug products, careful consideration must be given to the management of the controlled investigational product (IP) as well as to the myriad regulations that as previously noted vary by country and even from state to state within the US. It is important to not only consider that approvals have to be obtained, but that the logistics in running these studies are both cumbersome and convoluted[9]. For sponsor companies seeking to develop cannabis-related drug products, it is imperative to plan the trial well in advance of study conduct and to allow for extended start-up timelines – as much as one full year as operational success requires comprehensive preparation and strategy to manage the strictly controlled processes for shipment, delivery, diversion control, dispensation, and accountability. Pre-planning is particularly essential in order to avoid inevitable delays in start-up activities associated with the import of a controlled substance as most (if not all) companies conducting cannabinoid research may choose to incorporate outside of the United States (US) due to the ambiguity surrounding cannabinoids at the federal level. Of note, the US has specific approval, shipment, import and licensing requirements for cannabis-related drug products, including the assignment of the correct drug code prior to importation and distribution, which is dependent upon the source of the cannabis and the exact ratio of THC/CBD.

To increase the chances for seamless study conduct of clinical trials in the US involving cannabis and its derivatives, there are a number of recommendations that can be made. First, it is recommended to begin the DEA Schedule 1 application (which is protocol-specific at the site level) as early as possible as it could take at least three months and perhaps as much as twice this long to obtain the necessary approvals. If possible, the use of sites that have experience in this process at their state and local levels may help to expedite this process. As noted above, sites should also fully expect to be inspected at the state level as well following the DEA application but prior to, and as a condition of, DEA approval. Prior inspections for previous Schedule 1 studies may obviate the need for this inspection; however, sites should assume an inspection will take place for each and every protocol. During this inspection, state authorities may examine the site carefully to assess storage conditions, floor plan, presence of crawl space, and that a diversion plan is in place. The IP manufacturer and the distributor (if different) must also have a licence in place at the state level in order to be able to import the IP into the state to which the IP is being shipped. If not already in place, it is recommended that this process begin as early as possible to remove it from the critical path for study start-up procedures.

Principal investigators must have DEA authorisation in the state in which they practice, in order to prescribe, dispense, administer, and conduct research with controlled substances with a separate licence requirement for Schedule 1 studies. Importantly, the address to which the drug will be shipped must exactly match that on the investigator's licence. Some states may also have a separate state-issued controlled-substance licensing requirement for prescribing, dispensing, or administering controlled substances, while other states may have a separate state-controlled substances authority that requires practitioners to obtain a separate registration, in addition to the licence granted by their respective board. Federal registration is also required and the authority for granting federal registrations is vested in the DEA. The DEA registration for practitioners is predicated on licensure or authorisation by the competent state authority. Once approved, a certificate of DEA registration is issued by the DEA in the category of "Practitioner". Schedule 1 controlled substances require a separate DEA "Researcher" registration. The DEA also performs an investigation/audit of a site prior to granting the DEA "Researcher" registration which is only valid for one year.

Finally, although it may not be a specific state or federal requirement, it is strongly recommended that each site implement a study-wide drug diversion plan. The purpose of such a plan is multi-faceted and should outline the minimum requirements at the site level for the storage, security and accountability of study drug; as well as provide guidance as to potential signs of study-drug diversion in both subjects and site staff. This policy should guide the sites as to the appropriate steps to be taken in case of suspected or confirmed study drug diversion, including reporting of the event to the authorities. Similar plans are commonly used in opioid use disorder studies to help prevent diversions of the study drug, and this heightened level of diligence will be helpful and appreciated by auditors and state/federal officials who may inspect the site. The plan should

outline the measures designed to help manage the potential for diversion by subjects and site staff. Minimally, this is through employment of a meticulous drug accountability regimen at each site. It is only when the study drug is carefully tracked that it can be identified as missing in the first place. All members of the site staff that come in contact with study drug should be required to read and acknowledge the policy by wet-ink signature, with the original signed diversion plan filed in the study trial master file[10].

Summary

It is an interesting yet vexing time to undertake clinical trials designed to determine the efficacy and safety of cannabis-related drug products. There appears to be a confluence of fluctuating state laws regarding the medicinal and recreational use of cannabinoids with evolving federal attitudes towards research seemingly buttressed by heightened public interest and calls for rigorous well controlled clinical studies. Until recently, evidence was mostly based on anecdotal reports, as this research was very difficult if not impossible to conduct, due to the restrictions placed on the use and availability of these compounds for clinical research. Recent developments in state, federal and international guidance, paired with increased numbers of trials with rigorous results, suggests that the current regulatory challenges can now be successfully addressed with careful preparation and planning that will ease the regulatory pathway to approval of this much needed class of compounds.

REFERENCES

1. Agriculture Improvement Act of 2018: Highlights and Implications. https://www.ers.usda.gov/agriculture-improvement-act-of-2018-highlights-and-implications/
2. Agency is expediting work to evaluate regulatory policies related to cannabis and cannabis-derived ingredients like CBD (FDA; 07/23/19) FDA warns company marketing unapproved cannabidiol products with unsubstantiated claims to treat cancer, Alzheimer's disease, opioid withdrawal, pain and pet anxiety
3. FDA-approved drug Epidiolex placed in Schedule V of Controlled Substances Act [news release]. Washington, DC; September 27, 2018: DOJ Office of Public Affairs. https://www.dea.gov/press-releases/2018/09/27/fda-approved-drug-epidiolex-placed-schedule-v-controlled-substance-act
4. Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing MAY 31, 2019 https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/scientific-data-and-information-about-products-containing-cannabis-or-cannabis-derived-compounds
5. Botanical Drug Development: Guidance for Industry December 2016 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/botanical-drug-development-guidance-industry
6. DEA Drug Scheduling https://www.dea.gov/drug-scheduling
7. https://www.pbs.org/newshour/nation/scientists-say-governments-pot-farm-moldy-samples-no-guidelines
8. WHO Expert Committee on Drug Dependence https://www.who.int/medicines/access/controlled-substances/ecdd/ecdd/en/
9. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. Washington (DC): National Academies Press (US); 2017 Jan 12. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. 15. Challenges and Barriers in Conducting Cannabis Research. https://www.ncbi.nlm.nih.gov/books/NBK425757/
10. Dussault, B. and Riordan, H. (2015). Methodological Issues in Design and Conduct of Opioid Use Disorders Studies. Journal for Clinical Studies Vol 7 (4) July pp 36-38. https://www.jforcs.com/7/wp-content/uploads/2015/06/13.-Methodological-Issues-in-Design....pdf

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