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From Mockery to Medicine: The Story of the Development of a Serious Modern Medicine

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Introduction

In the United States, the effort to legalize cannabis for use as "medical marijuana" has focused on making it available to people as a home remedy, or perhaps an herbal treatment akin to a dietary supplement, but not as a Food and Drug Administration (FDA) - approved medicine. To obtain such approval, a therapeutic product must be quality-controlled in all aspects of manufacture, standardized by composition and dose, tested in preclinical and clinical studies, and administered by means of an appropriate delivery system or dosage form. It must, in short, meet the rigorous standards for quality, safety and efficacy that have been laid down by regulatory authorities. Crude herbal cannabis could never pass the FDA's rigorous standards.

The FDA recognizes that under appropriately controlled conditions, modern research and technologies enable complex botanical materials to be developed into pharmaceuticals in accordance with both scientific and regulatory rigor. The agency has issued a guidance document for these circumstances, acknowledging that complex composition is not inherently problematic.[1] Rather, as with all pharmaceutical products, the important factors are the application of quality control processes at each stage in the manufacturing process; characterization, specification, and standardization of the components; and the completion of appropriate preclinical and clinical studies—in other words; proof of quality, safety, and efficacy.

Crude herbal cannabis varies significantly in composition and consistency, depending on which strain is being propagated and under what conditions it is cultivated, harvested, stored, and prepared. Persons using crude herbal cannabis use materials that vary in quality and content. These materials may be contaminated with harmful pesticides, fungi, or heavy metals. Such contaminants have the potential to pose a threat to both seriously ill and healthy people. There is at least one report of death from a rare neurological condition, which may have occurred as a complication of an allergic reaction to pesticide-laden cannabis handled at the dispensary .[2]

Evidence-Based Medicine

Crude cannabis and the methods used to deliver it to patients have not met the minimum standards required of legitimate medicines and, therefore, do not belong in our system of modern medical practice. Modern medical practice is evidence-based. In advising patients, physicians rely in large part upon the results of controlled clinical trials conducted in accordance with established scientific principles. Preclinical studies and early (Phase 1) clinical trials demonstrate whether the product is likely to be harmful to humans. Randomized, double blind, placebo-controlled clinical trials (Phases 2 and 3 clinical trials)—the "gold standard" of scientific research—provide information about a medical product's safety and efficacy that usually accurately predicts real world expectations for a new medication.

GW Pharmaceuticals' Development Program

GW Pharmaceuticals (GW) has embarked on a full pharmaceutical development program for cannabinoids that pursues both scientific and regulatory rigor, making it the first company in the world to produce a complex, heterogeneous pharmaceutical product derived from the cannabis plant. As GW's research has shown [3,4,5], the process of developing botanically derived cannabinoid medicines is a challenging one, necessitating standardized raw materials and innovative extraction methods for the non-water soluble active ingredients.

Moreover, GW has rigorously adhered to the high principles of science and evidence-based medicine in its development program, having already conducted eight Phase 3 clinical trials and numerous smaller Phase 1 and Phase 2 studies with more than 2,000 patients participating. These clinical studies have investigated the use of Sativex® in the treatment of symptoms of multiple sclerosis, including spasticity [6], bladder dysfunction [7], tremor, spasm, sleep disturbance, pain [8,9], neuropathic pain of various origins—such as spinal cord injury, diabetic neuropathy, MS, brachial plexus avulsion—[10,11,12], rheumatoid arthritis [13], and cancer pain [14].

Using the latest technology, GW produces highly standardized cannabis "chemovars"—plant strains characterized by their chemical composition—that serve as the starting materials for its pharmaceutical development process. Computer-controlled glasshouses rigorously monitor and control growing conditions. Sensors automatically adjust light exposure to respond to changes in length and quality of daylight. Organic growing medium and specific quality control techniques ensure that no pesticides, heavy metals or microbiological contaminants are present. Botanists employ sophisticated breeding techniques to create unique chemovars that express specific cannabinoid ratios. Clonal reproduction maintains cannabinoid ratios and chemical composition throughout subsequent generations.

GW cultivates two primary cloned lines not normally found in nature, one in which cannabidiol (CBD), a non-psychoactive cannabinoid, is predominant. CBD is believed to significantly attenuate delta-9-tetrahydrocannabinol (Delta-9-THC) - associated side effects, such as intoxication and tachycardia [15](6). This CBD clonal line and a predominantly Delta-9-THC plant strain were developed through applied Mendelian genetics and are proprietary to GW.

Manufacture and Formulation Considerations

Cannabinoids are not water-soluble; therefore, studies are required to identify excipients that will permit the formulation of cannabinoids into finished pharmaceutical products. Cannabinoids, particularly Delta-9-THC, are also very unstable; therefore, research is required again to select formulations and to structure the manufacturing and storage processes to ensure that the medicines will maintain an appropriate shelf life. A small change in formulation can have substantial effects on both bioavailability and stability. GW has conducted numerous trials to ascertain the optimal formulation for its lead product, Sativex®, which contains a specific proportion of cannabinoids with ethanol and propylene glycol excipients.

Once crude cannabis plant material is standardized, as is achieved in the manufacture of Sativex®, it is only the first step in producing a modern medicine. A cannabis-based medicine must be fully researched and strictly regulated at every step in its manufacturing cycle; therefore, the subsequent steps of the manufacturing process—from harvesting to drying to the various steps of extraction and formulation—are also standardized and subject to stringent quality control testing procedures. GW blends the extracts from the two clonal lines to produce Sativex®, a ratio of 1.08:1 of Delta-9-THC and CBD. The final product is highly characterized, and tight specifications are set for all the significant cannabinoids and other components, such as terpenes, plant waxes, and flavonoids. These are common plant components present in many food and flavoring items.

Delivery System Considerations

Once standardized in composition, a cannabinoid medication must be administered in a manner that enables a patient to obtain a reliable dose with predictable effect. It is especially important to allow the patient to adjust his or her dose in order to obtain relief of symptoms while minimizing side effects, particularly disabling psychoactivity. It is also essential that the delivery system does not expose the user to harmful impurities, such as pyrolytic products.

There is no proven safe and reliable delivery system for crude herbal cannabis. If crude cannabis is smoked, it exposes seriously ill patients to dangerous pyrolytic products. If it is eaten in baked goods, ground and packaged in gel caps, or consumed as tea, the intestinal absorption is very erratic from day to day or even throughout one day, and hence its effect, including its psychoactive effect, is quite variable and unpredictable. It is also subject to first-pass metabolism to metabolites with more psychoactivity than the parent compound. In such delivery methods the dose and composition are uncertain.

Pulmonary Delivery Carries Associated Risks and Harms

Tests of the crude cannabis plant in all studies to date show that burn-and-inhale administration is simply a toxic alternative delivery system for high doses of Delta-9-THC. Given that oral Delta-9-THC is available as a Schedule 3 prescription drug, one might argue that there should be no need for smoked crude marijuana. The individuals who prefer the smoked, home remedy approach say they do so because smoking marijuana gives them the ability to titrate their dose or control rate of onset of action. The formulation issue is a valid one in clinical medicine that needs to be addressed and has been done so by GW such that patients can achieve a therapeutic effect with significantly reduced risk of psychoactive effects.

Vaporization, a popular trend among cannabis smokers, does not resolve these issues. A recent study showed that when herbal cannabis is vaporized, several harmful carcinogens (polyaromatic hydrocarbons)—while reduced—were still delivered to the lungs[16] . Furthermore, currently available vaporizers do not provide the precise standardization of dose necessary for a prescription medicine. In addition, when patients inhale cannabis (whether smoked or vaporized), their Delta-9-THC blood levels rise rapidly to high levels, making it probable that many of them will not be able to control psychoactive side effects. Rapid increases in Delta-9-THC blood levels are also associated with greater tendency to intoxication and dependence.

Unique Delivery System Developed

Because Delta-9-THC is psychoactive, it is essential that a Delta-9-THC-containing product be delivered in a manner that enables a patient to remain within the "therapeutic window," i.e., predictably to obtain symptom relief without experiencing untoward central nervous system side effects. Seriously ill patients with debilitating chronic disorders do not wish to "trade one disability for another" to be intoxicated; they want to work, care for their families, and be productive. Accordingly, the delivery system must not only provide standardized doses but must also enable the physician and patient to manage the dosing increments. The regulated system of medicine offers the only hope in the area of formulation to safely address the delivery system needs of patients.

To address this issue, GW Pharmaceuticals pioneered the development of an oromucosal spray for the delivery of Sativex®. Its onset of action is 15-40 minutes, which is rapid enough to enable chronically ill patients to titrate their dose, but not so rapid as to be rewarding for its euphoriant effects. The oromucosal spray contains exactly 100 micro liters of Sativex® (2.7 mg. of Delta-9-THC and 2.5 mg. of CBD)[17] . GW has monitored "intoxication scores" of its patients, and the level of intoxication among patients (who are receiving relief of symptoms) is essentially no higher than placebo [9]. It is, therefore, clearly not the case that patients achieve symptom relief only at the cost of intoxication. Furthermore, many patients have been taking Sativex® for one to four years and have not escalated their dose during that time [6 18] . Although evidence suggests that illicit users may become tolerant to the psychoactive effects of cannabis and must increase their use, patients using Sativex® do not develop tolerance to its therapeutic benefits.

Additionally, a group of MS patients on Sativex® for one year or more voluntarily stopped Sativex® administration abruptly. While symptom re-emergence occurred within seven to 10 days for most, none had significant withdrawal symptoms [18], and all who resumed the medicine regained symptomatic control at previously established doses. It is common to see symptom re-emergence after adequate control when medications are abruptly discontinued, sometimes paired with withdrawal.

This intermediate-onset delivery system, which also permits patients to take small increments of medicine, is believed to be an improvement over other forms of administration, particularly oral administration. Gastrointestinal absorption of oral Delta-9-THC exposes the compound to a first pass effect and hepatic metabolism of Delta-9-THC to 11-hydroxy-THC, thought to be more psychoactive than Delta-9-THC with an onset of effect that is long and unpredictable. Patients, therefore, cannot reliably titrate their dose after oral administration to avoid side effects, including psychoactivity. As the Institute of Medicine has stated [19]:

> The poor solubility of Marinol® in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10-20% of an oral dose reaches the systemic circulation. The onset of action is slow; peak plasma concentrations are not attained until two to four hours after dosing…
> Variation in individual response is highest for oral Delta-9-THC and bioavailability is lowest.

Abuse Liability Varies with Rate of Change of Blood Level Over Time

Inhaled Delta-9-THC is neither an optimal nor desirable delivery system for most patients. When Delta-9-THC is inhaled (as in smoking or vaporizing cannabis), Delta-9-THC blood levels rise to high levels quickly, with the resulting rise in blood level over a short period of time associated with greater tendency to intoxication and dependence. In a Phase 1 study, using a predominantly-Delta-9-THC extract delivered by means of a high technology vaporizer, GW found that concomitantly high intoxication levels accompanied such a rapid Delta-9-THC blood level rise [17]. A similarly high rise in Delta-9-THC blood levels was demonstrated in a recent Phase 1 trial that tested an inhaled version of dronabinol; therefore, it is likely that many patients who inhale Delta-9-THC will have a difficult time controlling intoxication and remaining within the therapeutic window [20] . Most patients with chronic conditions do not need an immediate onset product, particularly when there is such an undesirable tradeoff of symptom relief vs. intoxication. Sativex's® onset of action of 15-40 minutes provides sufficiently rapid symptom relief for such conditions, especially as patients learn over time to adjust their small doses to stabilize and maintain therapeutic blood levels.

The Scheduling of Cannabinoid-Containing Products under the Controlled Substances Act

Under the federal Controlled Substances Act (CSA), both cannabis and Delta-9-THC are Schedule I substances. If a cannabis-derived product like Sativex® were successful in obtaining FDA marketing approval, that specific product would need to be transferred out of Schedule I to another schedule, since FDA approval demonstrates that the product has "an accepted medical use in the US." This would not, however, necessitate a rescheduling of either herbal cannabis or Delta-9-THC. For example, Marinol® is located in Schedule III, while Delta-9-THC remains in Schedule I. Moreover, even if cannabis and Delta-9-THC (as active ingredients) were moved to Schedule II, that would not mean that crude herbal cannabis, or any cannabis or Delta-9-THC preparation, would become immediately available to patients by prescription. Rather, each and every medical product in interstate commerce must have gone through the FDA process on its own merits and must have satisfied FDA's intense scrutiny before physicians may prescribe and pharmacists may dispense it. Opium and coca leaves are in Schedule II, but crude opium or coca products are not distributed to patients. The entire "rescheduling of cannabis" argument made by cannabis advocates demonstrates a profound misunderstanding of the process by which serious prescription medicines become available to patients in the US.

Conclusion

Sativex® is a pharmaceutical product standardized in composition, formulation, and dose, which is administered by means of an appropriate delivery system, and which has been—and continues to be—tested in properly controlled preclinical and clinical studies. It is not crude cannabis, which is none of those things. Acceptance of Sativex ® [and its proof of efficacy] for specific indications does not suggest the acceptance of crude cannabis or prove its medical usefulness for the reasons set forth and many others. All medicinal products must be subjected to, and satisfy, the FDA's rigorous scrutiny before becoming available to patients in need. GW has consistently maintained that crude herbal cannabis can never meet the regulatory standards of the FDA and those of regulatory bodies in most other countries around the world [21] . These standards are mandatory if the modern medical model—informed patients working with and being advised by knowledgeable physicians to identify appropriate treatment options—is ever to be attained with a cannabis-based medicine.

It is not surprising that the concept of "medical marijuana" has been foisted on a largely unwilling and disapproving medical profession by legislative and ballot initiatives. Physicians who want medicines to meet the tests of quality, safety, and efficacy are not its proponents. Rather, the primary supporters are those whose ultimate agenda is to legalize marijuana for non-medical purposes. For the safety of patients and the security of physicians, physicians must draw a bright line between approved, legitimate medications and drugs of abuse that are used for the purpose of obtaining a euphoric "high." Physicians must insist that the medicinal products they recommend to patients be subjected to, and satisfy, the FDA's rigorous scrutiny.

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18. Canada has approved Sativex® for the treatment of neuropathic pain in multiple sclerosis. GW is currently preparing additional European regulatory submissions for other medical indications. The UK has authorized Sativex® to be prescribed on a named patient basis to patients whose physicians believe they may benefit from the product. Additionally, the Catalonian government in Spain has permitted it to be prescribed on a compassionate basis. On January 3, 2006, GW announced that the FDA had agreed to permit Sativex® to proceed to Phase III clinical trials, the final stage of research that a product must undergo before it is submitted for marketing approval. GW will test Sativex® in patients with advanced cancer, whose pain is not being adequately controlled with opiates. The trials will commence in the latter part of 2006 and a marketing application should be submitted 24-36 months after the trials begin. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Multiple Sclerosis. 2006;(in press).

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I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled except for the following:

Consultant, GW Pharmaceuticals

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Date: July 17, 2006

RESPONSES TO THIS ARTICLE

Sativex: Good for Kids?

DeForest Rathbone

Great article by Andrea Barthwell explaining GW's commitment to going through the FDA approval process for Sativex. But considering the new studies connecting cannabis to mental problems especially in adolescents, it seems that GW may have its work cut out for it. And how about the interaction with other drugs, including alcohol which studies now show to be problematic. Glad to see the affirmation that smoked pot is not now nor should ever be used as medicine.

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