developing cannabis-based medicines

by Matt Elrod

In November 1998, a year before the Institute of Medicine [1] rekindled North American interest in cannabinoid research and the development of cannabis-based Pharmaceuticals, the UK House of Lords Select Committee on Science and Technology published its report "Cannabis: The Scientific and Medical Evidence" [2], which recommended that clinical trials of cannabis "should be mounted as a matter of urgency". The committee recognized the deficiencies of existing orally administered cannabis derivatives, such as dronabinol. "Research should be promoted into alternative modes of administration (e.g. inhalation, sub-lingual, rectal), which would retain the benefit of rapid absorption offered by smoking, without the adverse effects". One expert who provided testimony to the Committee, Dr. Geoffrey W. Guy, was uniquely positioned to fulfill the parliamentary mandate. Dubbed "the man most likely to succeed at going to pot" by the *Financial Times*, [3] Dr. Guy is an entrepreneur and physician who specializes in phytopharmaceuticals, plant-based medicines and their delivery systems.

Having founded Phytopharm [4] in 1989 to develop botanical extracts and shepherd them to market, Dr. Guy is adept at navigating the cumbersome regulations governing both natural health products and controlled substances. Perhaps more significantly, unlike most medicinal cannabis enthusiasts, Dr. Guy has a reputation within Europe's conservative medical community for playing and winning by their rules. Dr. Guy's background made him distinctly qualified to overcome the clinical, social and bureaucratic hurdles that have thus far prevented cannabis from regaining its place in the pharmacopoeia.

Dr. Guy founded GW Pharmaceuticals [5], still the only company dedicated to developing cannabis-based medicines, in early 1998. A collaboration with HortaPharm BV of the Netherlands gave GW a commanding "first mover" advantage. HortaPharm's medicinal cannabis varieties, known as "chemovars", had been standardized and stabilized for over 20 years to consistently express specific cannabinoids, however, HortaPharm lacked the ability to develop pharmaceuticals and sought drug company partners to take the next step. GW was the only company with the vision to take the HortaPharm research through the development and approval process.

Botanists initially chose 10 Dutch chemovars bred to express high quantities of either THC (delta-9 tetrahydrocannabinol) or CBD (cannabidiol) for their first crop of 5,000 plants grown organically in secretive and exceedingly secure glasshouses in the south of England. The computer-controlled glasshouses are among of the most sophisticated in Europe. No chemicals are used and all pest control is biological.

A GW contractor uses supercritical fluid extraction (SFE), a fairly new technique for extracting lipophilic and volatile compounds. [6] SFE utilizes carbon dioxide, which is Generally Regarded As Safe (GRAS), making the extraction process free of organic solvents. Liquid CO_2 is forced into supercritical state (SC-CO_2) by regulating its temperature and pressure. Supercritical fluid is heavy like a liquid but has the penetrating properties of a gas. SC-CO_2 is inert and does not interact chemically with the botanical material or the extraction apparatus.

GW is developing 3 delivery technologies; an oral spray, a tablet which dissolves under the tongue, and a compact inhaler containing miniature heating elements that vapourize cannabis extracts. The spray technology is being utilized for the Group's lead product, the CBD/THC mixture. Active compounds in the "oro-mucosal" spray are primarily absorbed by the lining of the mouth and the tongue and begin to take effect within about 15-20 minutes. Some of the extract may also be swallowed, providing symptomatic relief for 4 to 6 hours. The inhaler's effects are felt almost immediately and do not last as long.

Depending on government requirements, both the spray and the inhaler may be equipped with the company's "Advanced Dispensing System (ADS)", a solid-state device resembling a portable phone, which measures and monitors use to help ensure optimal dosages and prevent diversion to the black market. The tamper-resistant device can also be connected to the internet, so doctors and clinicians can remotely monitor their patients' consumption. As Orwellian as digital drug dispensing systems that phone home might appear, currently many controlled subtances must be consumed under close medical supervision. The ADS promises to grant patients who need such drugs more freedom and autonomy. For example, GW, encouraged by the Home Office, is currently collaborating with the National Addiction Centre (NAC) to trial the ADS for the administration of methadone and diamorphine (heroin) in the treatment of drug addiction. If successful, the program will extend to other countries in Europe and North America.

The ADS was originally developed to make cannabis-based products more palatable to U.S. regulatory authorities, who still classify cannabis at the highest (most restrictive) level as a Schedule I substance. [7] Attempts by various petitioners to have cannabis rescheduled have been unsuccessful. [8] Despite overwhelming evidence to the contrary, U.S. authorities maintain that cannabis has no

recognized medicinal value and a high potential for abuse, a position they have not seriously reconsidered since before the discovery of cannabinoid receptors over a decade ago.

GW's clinical trials have demonstrated that, once patients are no longer "cannabis naive" and have become accustomed to the psychoactive effects, they are both able and inclined to titrate and personally individualize their dose to achieve improvement in their symptoms without experiencing unwanted effects that might interfere with their day-to-day activities. GW consultant Dr. Ethan Russo expects precautionary labeling will be similar to that found on synthetic cannabinoid packaging, advising patients to avoid driving or operating heavy machinery until they have become accustomed to the drug. Based on their experiences and the remarkable safety profile of cannabis and cannabis-based products, GW does not anticipate a need for the ADS outside of the USA.

GW currently has 3 extracts under investigation; one derived from CBD-rich chemovars, one from THC-rich varieties and one with an even mixture of these two most promising cannabinoids. Proportions of terpenoids, flavonoids and other therapeutically active cannabinoids, such as CBC, CBG and THC-V, are consistent and monitored but left unaltered. Dr. Russo explains "Flavonoids are antioxidants and anti-inflammatory components with anti-aging and cell protective responses. Terpenoids are the essential oils that give cannabis its aroma. There are many with important medical benefits that include anti-inflammatory, analgesic, bronchodilating and memory-enhancing effects. The patient receives the full complement of synergistic phytochemicals. Only the cough is removed. Together this herbal mixture produces effects and medical benefits unobtainable with synthetic THC such as Marinol". Plant varieties bred to express these less understood compounds are already being cultivated and clinical trials designed to explore their pharmacological properties are on the drawing board or underway.

One of the significant medical benefits of using whole-cannabis extracts appears to be some attenuation of the sometimes unpleasant psychoactive effects of pure THC. CBD in particular seems to "soften" the effect of THC and is known to have anti-psychotic properties. Another benefit is the unusual breadth of effect. "These medicines have unique effectiveness for a wide range of conditions, and within the same condition, can often target multiple symptoms. For example, GW research has found that "patients with multiple sclerosis have experienced substantial relief from spasticity, poor sleep, bladder dysfunction and pain," says David Hadorn, M.D., a GW consultant. Currently, MS sufferers must orchestrate the carefully timed and measured administration of several distinct, interacting, chemical entities to achieve this broad "shot gun" effect.

Another advantage of GW's pharmaceutical-grade extracts is that they are likely to reach many people who would otherwise miss out on the benefits of cannabis-based medicines. This is perhaps especially true for elderly patients, many of whom have chronic pain and other symptoms, for which cannabis-based medicines would likely provide substantial relief. Most elderly patients are cannabis-naive, however, and would have great difficulty accepting the idea of "toking up". A prescription oral spray would be perfectly acceptable to many such patients - literally "just what the doctor ordered".

In previous Phase II trials, there was a 50% average reduction in the participant's use of opiates. The reduction in opiate use suggests future analgesics may combine opiates and cannabinoids for their very different but complementary effects. In fact, animal studies have found that opiate/cannabinoid mixtures do not cause the severe withdrawal symptoms associated with long-term opiate use. [9] Perhaps cannabinoids will eventually be integrated into GW's methadone and diamorphine products.

Try as they might to divorce their company and its research from the politically-charged debate over cannabis law reform, research on whole plant extracts, more than research on synthetic analogs, is applicable to the forbidden herb. When reporting GW progress, the media tend to equate their cannabis-based medicine extracts with cannabis, often exploiting the "snicker factor" with pot puns and allusions to stoner stereotypes. Interpretations also seem linked to geopolitical preconceptions. Most British papers herald GW's encouraging findings as further evidence of the medicinal benefits of cannabis - more reason to reform medicinal cannabis laws - while U.S. papers tend to characterize cannabis-based medicines as a socially acceptable, non-psychoactive alternative to smoked cannabis. A magic prohibitionist bullet that will render herbal cannabis, and therefore efforts to reform cannabis laws, obsolete.

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