Fact and Fiction about Cannabidiol (CBD)
Introduction to GW
GW Pharmaceuticals

• Founded in the UK in 1998 by Dr Geoffrey Guy and Dr Brian Whittle;
  ▸ Specialists in development of plant-based pharmaceuticals, controlled substances and drug delivery systems;
  ▸ Goal was to develop a range of prescription medications derived from components or combinations of components of the cannabis plant; developed in accordance with modern medical standards.

• First product Sativex® approved in 28 countries (ex-US) for MS spasticity, CBD:THC 1:1;

• Research programs in broad range of disease areas;

• Collaborations with 36 universities around the world;

• In the U.S., an investigational CBD product finishing Phase 3.
Our Pipeline

- **Unpartnered – GW owns global rights**
  - EPI DIOLEX
  - DRAVET SYNDROME
  - LENNOX-GASTAUT SYN.
  - TUBEROUS SCLEROSIS
  - INFANTILE SPASM
  - **OTHER ORPHAN CANDIDATES**
    - GWP42006 (CBDV)
      - EPILEPSY / AUTISM
    - GWP42003 (I.V.)
      - NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY
    - GWP42002
    - GLIOMA
  - **OTHER PIPELINE CANDIDATES**
    - GWP42003
      - SCHIZOPHRENIA
    - SATIVEX
      - MS SPASTICITY

- **Partnered**
  - SATIVEX
  - MS SPASTICITY

Pre-Clinic | Phase 1 | Phase 2 | Phase 3 | Submit | Approval
The Importance of the FDA Process

• Provisions developed over the past 100 years to protect patient health and safety;

• Standardized by composition; batch-to-batch consistency;

• Administered appropriately and in precise dosages like other pharmaceutical products;

• Clinical and preclinical studies ensure physicians and patients have appropriate information;
The FDA Process cont.

- Reimbursed by health insurance;

- Prescription only; distributed only through monitored health care sources, i.e., pharmacy;

- Registration/inspection ensures that manufacturing process conducted in accordance with validated quality control tools;
  - Manufacturers accountable for defective products;

- Promotional activities of manufacturers limited;

- Products dispensed under the supervision of licensed health care providers, e.g., physicians, pharmacists.
What is CBD (cannabidiol)?
How does CBD work?

• Cannabis plant is unique source of >100 cannabinoid molecules; each as its own pharmacology;
• Only THC is known to cause notable psychoactive effects;
• CBD and THC are the primary cannabinoids;
• Unlike THC, CBD does NOT directly activate the CB1 or CB2 receptors, at concentrations studied in anti-convulsant trials\(^1\);
  ▸ This is why CBD is not psychoactive like THC;
• Until recently, was virtually bred out of modern cannabis

\(^1\) El-Alfy AT et al. Pharmacol Biochem Behav. 2010;95:434-442
Legal Status of CBD

• CBD is not separately listed in the Code of Federal Regulations;
  ‣ it is controlled in Schedule I by definition as a “derivative” of marijuana (21 USC 802);
• This is also true of other individual cannabinoids;
• Only THC is separately listed in Schedule I;
• According to a position statement from the DEA Office of Public Affairs, CBD from any source is a Schedule I substance.
Sanjay Gupta and the Firestorm over CBD
August 2013: Sanjay Gupta’s CNN program “Weed,” featured remarkable improvement in a child with Dravet’s syndrome treated with “high CBD” cannabis oil;
  - Stanley Brothers/Realm of Caring and their product become famous;
• Produced a tsunami of interest among desperate parents; many moved to CO;
• Seventeen states pass laws allowing access to CBD products;
• CW Botanicals now sells over the internet and ships their product to most states;
• CBD vendors are multiplying; they advertise that “CBD hemp oil” is a “legal nutraceutical in fifty states.”

1http://www.biocbdplus.com/the-difference-3
What is “CBD hemp oil” and is it really a legal nutraceutical?
Is CBD a Nutraceutical?

• Term was coined by Stephen DeFelice in 1989, who defined it as “a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease”;

• It does not “fit” into any regulatory category and hence has no meaning from a regulatory perspective;

• Relevant FDA-regulated categories are: prescription medications, OTC products, veterinary products, dietary supplements, foods, food additives, and cosmetics.
The Controlled Substances Act\(^1\) does not define hemp; it merely exempts certain parts of the plant--stalk, fiber, and sterilized seeds (and preparations made from them)--from the definition of “marijuana;”

However, if CBD is **extracted** from **any** part of the plant, including the “exempted parts” like the stalk, it is still considered marijuana and is in Sch. I;

The whole hemp plant with roots in the ground is still defined as marijuana under the CSA.

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\(^1\) 21 USC 802(d) (16)
Is Hemp a Good Source of CBD?

• As defined in Canada and Europe, specific hemp strains may be grown that have no more than 0.2-0.3% THC; these strains are generally also low in CBD;

• Traditional hemp is an inefficient source of CBD
  - Also, hemp is a “bioaccumulator” or “phytoremediator” and absorbs heavy metals and other chemical waste from the soil.
Hemp Seeds and Hemp Seed Oil

- Hemp seeds are a good source of protein and the oil is very rich in Omega 3 and 6;
  - the nut is used to make bread, cereals, protein powder;
  - the oil is used for margarine, salad dressing, cosmetics.

- However, hemp seeds contain virtually no cannabinoids; the cannabinoids are in the flowers and (a little) in the upper leaves. Hemp Industries Association position statement, 2014. [http://www.thehia.org/HIAhemppressreleases/3346474](http://www.thehia.org/HIAhemppressreleases/3346474).

- Hemp seed oil is often used to dissolve the thick CBD extract/paste (hence the name “CBD hemp oil”)
  - but olive oil, refined coconut oil, etc., can also be used.
True Hemp Seed Oil

“Just like hemp seed, the oil contains the ideal 3:1 omega-6 to omega-3 ratio. Unlike flax, hemp has valuable Super Omega-3 (SDA) and Super Omega-6 (GLA), which can help the body metabolize fat.” [https://store.nutiva.com/cold-pressed-hemp-oil/](https://store.nutiva.com/cold-pressed-hemp-oil/)
CBD Hemp Oil

Hemp CBD Oil

Hemp CBD Oil is our most basic and frequently used hemp product. One fluid ounce contains 250mg of cannabidiol (CBD). The ingredients include European-sourced CBD extract based in hemp seed oil, with no fillers, preservatives or additives.
FDA Enforcement Actions
FDA: CBD Products Cannot Make Medical Claims

- Any item is considered a drug (subject to the FDA approval process) if it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

- **February 2015 and 2016**: FDA issues Warning Letters to vendors covering numerous CBD products, stating that the products are misbranded due to medical claims; [http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm](http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm); [http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm](http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm)

- **FDA tested the products and most of them contained little or no CBD**: others had higher THC content than on the label. [http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm](http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm); [http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm](http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm)
FDA has concluded that CBD products are excluded from the dietary supplement definition under section 201(ff)(3)(B)(ii) of the FD&C Act because:

- If an article (such as CBD) is being studied in “substantial clinical investigations” and the existence of such investigations has been made public, then products containing that substance are outside the definition of a dietary supplement.

- When the Dietary Supplement Health and Education Act (DSHEA) was enacted, this was part of a compromise between protecting the resources involved in pharmaceutical development and permitting access to dietary supplements;
CBD as a Dietary Supplement cont.

- There is an exception if the article or substance was “marketed as” a dietary supplement or as a conventional food before the new drug investigations were authorized;
- CBD was being studied as of 2006 in US clinical trials (involving a 1:1 CBD:THC investigational product);
- Based on available evidence, FDA has concluded that CBD had not itself been previously marketed in food or as a food or dietary supplement.
- Must be overtly marketed; presence of trace amounts of CBD in hemp seed oil products is not sufficient to constitute “marketed as.”
Recent UK MHRA Action

• On Oct. 7, the UK Medicines and Healthcare Products Regulatory Agency sent letters to CBD manufacturers and vendors advising them that:
  
• CBD has now met the “second limb” of the definition of “medicinal product,” because it is being “used by or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action…”
  
  ▸ Promotion of products for these purposes satisfies the first “limb”;  

• All sales of CBD-containing products must cease within 28 days;  

• CBD products will be required to go through the new drug approval process.
The Scope of the Farm Bill

• Section 7606 of the Agricultural Act 2014 ("Farm Bill", 7 USC 5940) authorizes institutions of higher education or State departments of agriculture to grow "industrial hemp" for "research conducted under an agricultural pilot program or other agricultural or academic research";
  - Industrial hemp is defined as cannabis with ≤ 0.3% THC.

• The U.S. Department of Agriculture, the Department of Health and Human Services (DHHS) and DEA recently issued a Notice concerning the Farm Bill:

• Limited to research; industrial hemp not removed from Sch. I.
Farm Bill cont.

- Private persons must be 1) licensed, etc. by the State Ag. Dept. to conduct the research or 2) employed or contracted to conduct research by the institution of higher education.
- Cultivation must be exclusively for industrial purposes, i.e., fiber and seed (hence, by implication, not the flowering tops).
- Products may be sold for purposes of marketing research under a pilot program, but general commercial activity not allowed.
- Does not affect the FDCA; any human therapeutic research (e.g., involving CBD) would have to be conducted under an IND and approved by an IRB.
In 2013, the Department of Justice issued a memo giving guidance to US Attorneys regarding the exercise of investigative and prosecutorial discretion:

- Not a federal priority to take enforcement action against individuals or businesses who/that are acting in accordance with state cannabis laws (medical or recreational);
- The state must have “strong and effective” regulatory and enforcement systems in place;
- The cannabis-related activities must not adversely affect 8 listed “federal interests,” including prevention of distribution to minors and drugged driving.
• Section 542 prohibits the DOJ from spending funds to prevent states’ implementation of their medical marijuana laws.

• US v. McIntosh (9th Cir.) ruled that §542 prohibits DOJ from spending funds for the prosecution of individuals who engaged in conduct permitted by state mmj laws;

• Conduct must “strictly comply with all relevant conditions” imposed by state law;

• Court stressed the “temporal nature” of the situation; Congress “could appropriate funds for such prosecutions tomorrow” or the next appropriations bill may not contain such a rider.
Developing a CBD medication down the FDA pathway
Manufacturing and Production
Manufacture of Epidiolex®: extraction of pure CBD and removal of THC

1. **CBD Bot Raw Mat**
   - Processing of plant material into CBD extract
   - CO₂ Extraction
   - **CBD Bot Drug Sub**
     - Purification Process to remove THC
     - **Pure CBD**
   - Bulk Solution Production
   - Filling, Capping & Labelling
   - **Final Product**
Is there a need for new treatment options in childhood epilepsies?
Treatment-Resistant Childhood Epilepsy: Significant Unmet Need

466,000
US CHILDREN WITH EPILEPSY

30%
PHARMACORESISTANT EPILEPTICS\textsuperscript{1,4}
SEIZURES THAT PERSIST, DESPITE MULTIPLE AED TREATMENT\textsuperscript{2}

140,000
MEDICATION RESISTANT PATIENTS
REFRACTORY EPILEPSY COMPOSED OF MULTIPLE SYNDROMES

Response to AEDs in patients with newly diagnosed epilepsy\textsuperscript{3}
little change to this statistic over last 15 years

- Seizure-free with 1st drug: 36%
- Seizure-free with 2nd drug: 47%
- Seizure-free with 3rd or multiple drugs: 4%
- Pharmacoresistant epilepsy: 13%

Treatment-Resistant Childhood Epilepsy: Spectrum of Rare Disorders

Many different types of epilepsy syndromes, seizures and causes, including:

- LENNOX-GASTAUT SYNDROME
  - 3 to 4% of childhood epilepsy
- DRAVET SYNDROME
  - Up to 5% of all childhood epilepsies in first year of life
- TUBEROUS SCLEROSIS COMPLEX
- DOOSE SYNDROME
- DUP15q SYNDROME
- RASMUSSEN SYNDROME
- GLUT 1 TRANSPORTER DEFICIENCY
- CDKL5
- ANGELMAN’S SYNDROME
- STXBP1/OHTAHARA SYNDROME
- WEST SYNDROME (INFANTILE SPASM)
- AICARDI SYNDROME

Dravet Syndrome and Lennox Gastaut Syndrome (LGS)

- Considered “orphan” syndromes;
- Suffer multiple seizure types, sometimes multiple seizures a day;
- Most will be cognitively impaired and require lifelong care;
- Both have a much higher incidence of mortality within 11 years of diagnosis;
- A very large percentage of patients do not respond to available treatments.

1 FDA gives Orphan designation to conditions affecting <200,000 people in the U.S. per year
EPIDIOLEX®: a new investigational product
What drew GW to investigate CBD in epilepsy?

- In 2007, GW sponsored preclinical research in many animal models (including epilepsy) involving a number of cannabinoids;
- CBD (and CBDV) were discovered to exert significant anti-convulsant effects in five rodent models of seizure;
- GW intended to study CBDV, the rarer cannabinoid, in adults with a more common types of epilepsy (focal seizures);
  - This study is now underway in Europe;

- **BUT THEN...**
In August 2012, one California family with a son with intractable epilepsy (SV) reached out to GW.

GW researched US laws and regulations to determine if CBD could be provided to children as an investigational medicine.

Regulations allow physician-sponsored “expanded access” INDs for patients with serious/life threatening conditions, no other treatments options and no access to controlled clinical trials.

This is Sam. He’s my son. His epilepsy caused him to have up to 100 seizures a day. After seven years we were out of options. Our last hope: an untested, unproven treatment. The only problem? It was illegal.

• SV’s family takes him to London in December 2012 to be treated with GW’s CBD by Dr. Helen Cross.

• Upon his return, SV’s physician at UCSF seeks approval to treat him under an individual IND relying on FDA’s “expanded access” regulations.
  - another individual IND later sought for a second patient.

• GW had already conducted safety and toxicology studies with CBD as part of Sativex program;

• FDA was also familiar with Sativex and with GW’s manufacturing and quality control capabilities.
• NYU epileptologist seeks and secures FDA and DEA approval for a 25 patient EAP;
• 4 more epileptologists at major medical institutions apply for similar programs;
• Throughout 2013-2015, the Expanded Access Program grew in size and scope (now 22 individual sites and over 500 patients under physician-sponsored INDs).
State government collaborations with GW

- Faced with pending bills or laws requiring them to do research or dispense CBD, and mindful of their federal (FDA, DEA, funding) obligations, state governments and universities sought assistance from GW.
  - **Georgia**: Governor publicly announced plans to collaborate with GW to conduct research; program underway;
  - **New York**: public announcement of collaboration with GW; 5 sites;
  - **Alabama**: UAB Department of Neurology; underway.
  - **Florida and Idaho**: programs are underway;
  - **Nebraska and Pennsylvania**: are setting up;
  - **These state programs will include another 400+ approved patients.**
• Significant body of data being generated.
  ‣ Because each IND is independent, protocol differences do exist; however
  ‣ Patients treated according to standardized treatment plan so physicians can consolidate data for scientific presentations and publications, including:
    ‣ Multiple syndromes and seizure types;
    ‣ Interactions with other medications;
    ‣ Side effects.

• **NOTE:** these EAPs are not placebo-controlled and cannot be used to demonstrate efficacy for purposes of FDA approval.
Expanded Access Program Data

- Results from poster by Devinsky et al at 2015 AES
- Mean age 11.8 yrs, range 4 mos-46 yrs
- N=313 exposures, 261 ≥ 3 months
- N=234 evaluable for efficacy after 12 weeks
  - 47% had > 50% reduction in total seizures
  - Seizure-free at 3 months- 9% in total patients, 13% in DS
  - LGS (N=14): 71.1% median reduction in atonic seizures
- Most common AEs: somnolence-23%, diarrhea-21%
- Discontinuations: AEs-4%, LOE-12%
- Related SAEs-5%
GW Clinical Program for Epidiolex

- In spring 2014, GW approached FDA to open a company-sponsored IND;
- Epidiolex has both Orphan Drug Designation and Fast Track Designation from the FDA for Dravet and Orphan Designation for LGS;
- Four large Phase 3 trials in Dravet and LGS commenced 2015 enrolling more than 500 patients;
- GW is conducting 11 additional Epidiolex Phase I and II trials including a complete assessment of abuse potential.
- Program in Tuberous Sclerosis has begun; IS to begin Q4; Orphan Designations secured.
Dravet Syndrome Phase 3 Trial Results

- Primary endpoint achieved with statistical significance (p=0.01)
  - Primary: Epidiolex reduction in convulsive seizures compared to placebo
  - Epidiolex (n=61): -39%, placebo (n=59): -13%
- Secondary efficacy endpoints reinforced the overall effectiveness
- 120 patients (average age: 10, 30% <6 years)
- On average, Epidiolex administered as 8th AED in treatment regime
  - Average of 3 concomitant AEDs, previously tried and failed average of >4
- Median baseline convulsive seizure frequency was 13 per month
- Epidiolex was generally well tolerated in this study
  - 84% of patients on Epidiolex reported AEs as mild or moderate
  - SAEs: 10 on Epidiolex, 3 on placebo
  - Only 8 Epidiolex patients discontinued treatment due to AEs vs 1 on placebo
LGS Phase 3 Trial Results

- **Patient demographics**
  - 171 patients (average age 15; 34% ≥18 years old)
  - Currently taking an average of 3 AEDs, having previously failed an average of 6 other AEDs
  - Median baseline drop seizure frequency was 74 per month

- **Efficacy**
  - Primary endpoint of change in the monthly frequency of drop seizures achieved with statistical significance (p=0.0135)
    - Drop seizures: Epidiolex (n=86): -44%, placebo (n=85): -22%
  - Secondary efficacy endpoints reinforced overall effectiveness

- **Safety**
  - Epidiolex was generally well tolerated in this trial
    - 86% of Epidiolex patents experienced an AE; of those, 78% reported the AE’s as mild or moderate. 69% of patients on placebo experienced an AE.
    - SAEs: 20 on Epidiolex (9 treatment related), 4 on placebo (1 treatment related)
    - 1 death in the Epidiolex arm, which was deemed unrelated to treatment
    - 12 Epidiolex patients discontinued treatment due to AEs vs 1 on placebo
LGS Phase 3 Trial Results (Second Trial)

• Patient demographics
  ‣ 225 patients (average age 16; 30% ≥18 years old)
  ‣ On average of 3 other AEDS, having previously tried an average of 7 other AEDs
  ‣ Median baseline drop seizure frequency was 85 per month

• Efficacy
  ‣ Primary endpoint of drop seizure reduction achieved with statistical significance in both dose cohorts
    ‣ 20mg/kg: Epidiolex (n=76): -42% (p=0.0047)
    ‣ 10 mg/kg: Epidiolex (n=73): -37% (p=0.0016)
    ‣ Placebo (n=76): -17%
  ‣ Secondary efficacy endpoints reinforced overall effectiveness

• Safety
  ‣ Epidiolex was generally well tolerated in this trial
    ‣ 89% of patients on Epidiolex 20mg/kg reported AE’s as mild or moderate
    ‣ 88% of patients on Epidiolex 10mg/kg reported AE’s as mild or moderate
    ‣ SAEs: 13 on Epidiolex 20mg/kg (5 treatment related), 13 on Epidiolex 10mg/kg placebo (2 treatment related), 8 on placebo (none of which were treatment-related)
    ‣ 6 patients on Epidiolex 20mg/kg discontinued treatment due to AEs vs 1 patient on Epidiolex 10mg/kg and one patient on placebo.
GW’s Epidiolex Program Timeline

• New Drug Application expected to be submitted to FDA in first half of 2017;
• Priority Review, if granted, could be as short as 8-10 months;
• DEA rescheduling will follow (now 3 months).
Rescheduling of CBD products following FDA approval
DEA actions

• On August 11, 2016, DEA denied the two most recent marijuana rescheduling petitions.
• It also noted that DEA, NIDA, and FDA have been separately working together to consider the potential rescheduling of pure CBD.
Abuse Potential of CBD

- As CBD is a component of cannabis, it will need to undergo assessment for abuse potential in compliance with regulatory guidance;
- The sponsor will perform an 8-Factor Analysis (8FA) and propose a schedule as part of the New Drug Application (NDA) preparations for a CBD product;
- This will include specific preclinical studies and clinical study/data:
  - **Preclinical**
    - Drug discrimination
    - Self-administration
    - Withdrawal / dependence study
  - **Clinical**
    - Human Abuse Liability study
    - Adverse Events from clinical trials
“Differential” scheduling

• Under the Controlled Substances Act, generally a substance and all products containing it are in the same schedule, eg, opium poppy and morphine.

• **BUT** “differential” scheduling is possible.
  - Marinol (Schedule III) vs. THC (Schedule I);

• Therefore, if a specific cannabinoid or cannabinoid preparation is FDA approved, **cannabis itself and other individual cannabinoids are likely to remain in Sch. I.**
Most states also have their own version of the CSA, and CBD is in Schedule I under those state laws.

An FDA-approved CBD product cannot be distributed in pharmacies in States which control it in CI until it is rescheduled in those States;

States Employ One of Three Processes:
- Automatic - 30 days after DEA action;
  - Very few states are automatic
- Administrative - Boards of Pharmacy, etc.
- Legislative.

Could take a year to complete in some cases.
Closing remarks
Conclusions

• Current technology and research tools now make it possible to develop a wide range of cannabis-derived and cannabinoid medications for specific medical conditions.

• These products can be researched and developed in the U.S. despite their Schedule I status.

• GW believes that it is essential properly to research and develop new CBD and other cannabinoid products in accordance with modern medical standards.
THANK YOU!!

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