How Cannabis-Derived Medications Go Through the FDA Approval Process: Development and Regulation

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SAM Summit 2019

Greenwich Biosciences

- Parent company founded in in the UK in 1998 by Drs. Geoffrey Guy and 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 the cannabis plant or its individual components
  - Developed under conventional regulatory standards for pharmaceutical products

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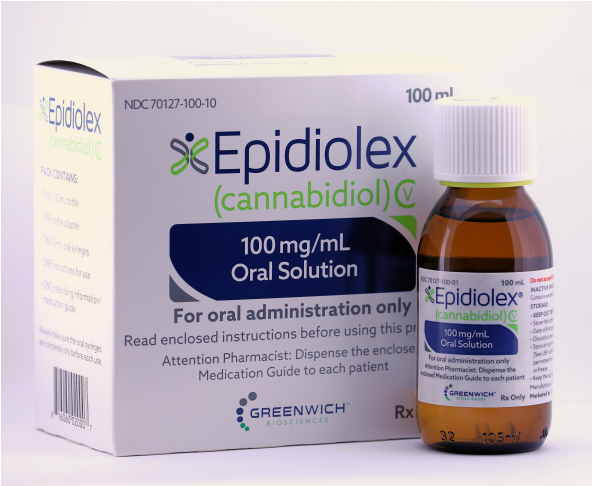
Epidiolex® (cannabidiol) oral solution CV

- Oral solution containing highly purified cannabidiol
  - Crystallization process removes all but trace amounts of THC
- Positive data from four Phase 3 placebo-controlled trials in initial target orphan indications of Dravet syndrome and Lennox-Gastaut syndrome (LGS)
- Epidiolex approved by FDA on June 25, 2018, moved into Schedule V by DEA
- EMA submission accepted for review



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Sativex® (nabiximols)

- Sativex®* is derived from a complex cannabis extract;
- 1:1 cannabidiol (CBD) to tetrahydrocannabinol (THC) ratio (of its main cannabinoids);
  - Retains minor cannabinoids and other active plant components;
  - Oromucosal spray absorbed by the mouth
- Approved in > 25 countries ex-US for spasticity in multiple sclerosis
- US development planned
- *not approved in US

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Quality, Safety, Efficacy

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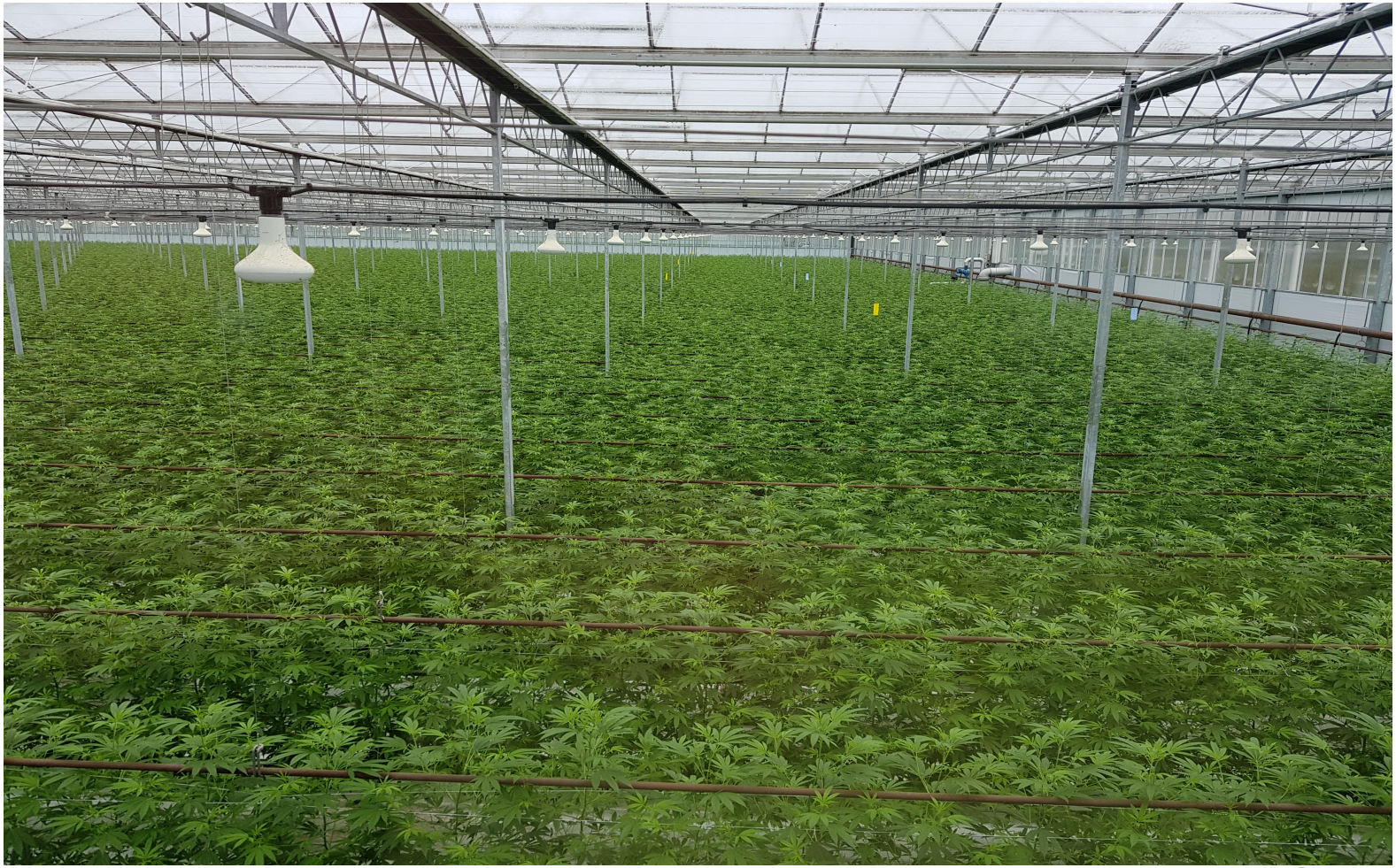
Production of Botanical Raw Material (BRM)



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Epidiolex Process—Drug Substance

Drug Substance

CBD Botanical Raw Material

↓

Milling (GW)

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Decarboxylation (GW)

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CO_2 Extraction (GW)

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CBD Botanical Drug Extract (Crude Form)

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Multi-step Crystallisation (CMO)

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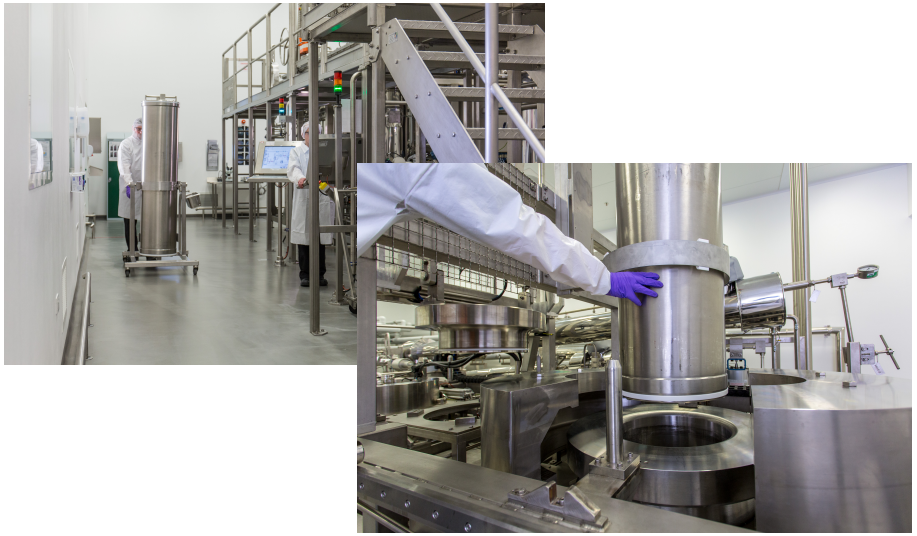
Pure CBD

CO_2 Extraction



Filtration
& Drying

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Epidiolex Process—Drug Product

Drug Product

CBD Pure

↓

Bulk Solution Production (GW)
Sesame Oil/Ethanol

↓

Filling & Capping (GW)

↓

Drug Product Labelling & Packaging

↓

Labelling, Check weigh, Tamper Evidence, Serialization (GW)

Epidiolex

Filling Line

Labelling & Packaging Line

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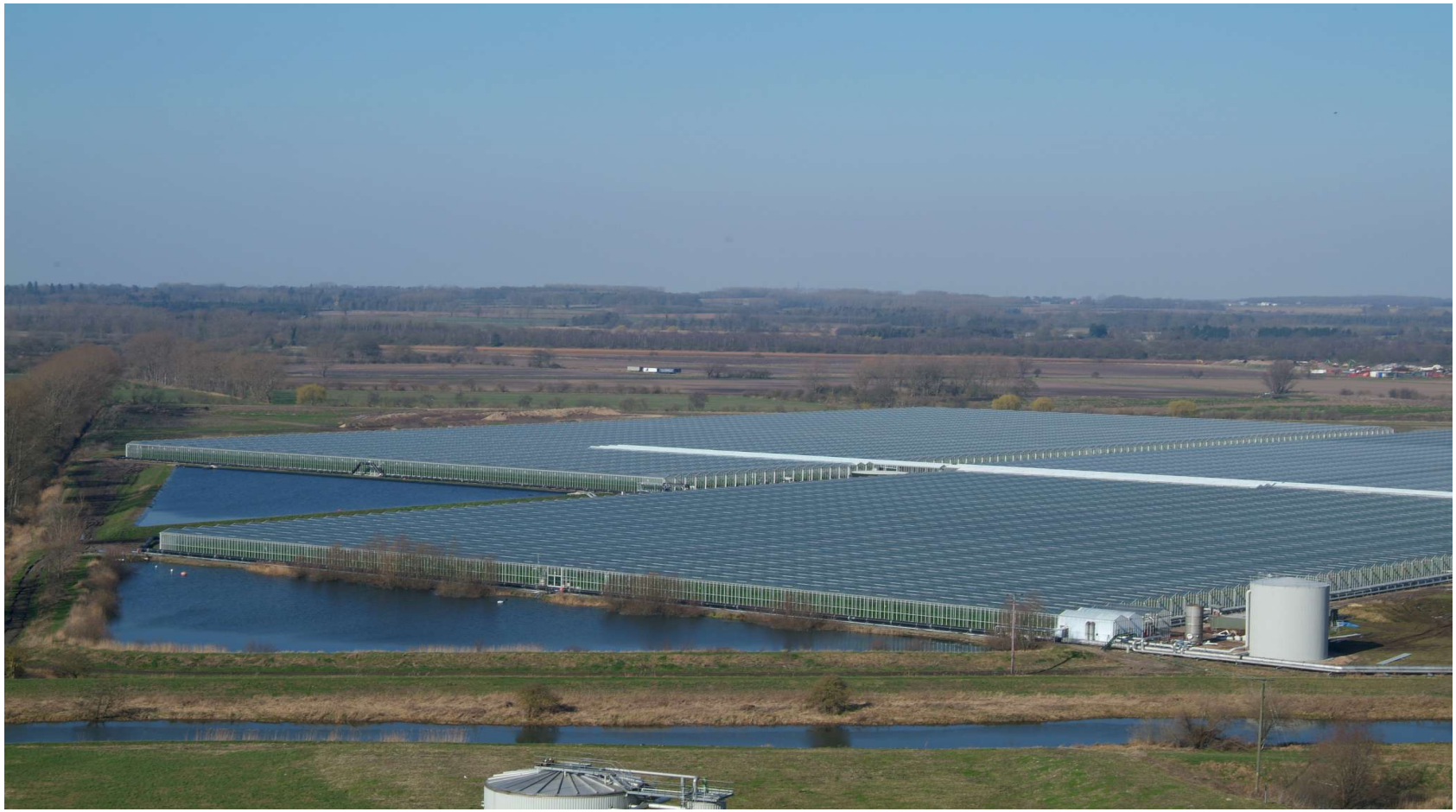
Epidiolex Commercial Growing (45 acres): CBD-rich Chemovars for Efficient Production



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Drug Delivery Systems

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Drug Delivery Challenges

- Inter-subject pharmacokinetic variability
- Rapid rate of rise of THC in plasma levels, e.g., inhalation, can cause intoxication, affect blinding
- Challenges of the oral route and first pass
- Bioavailability
- Poor solubility in water
- Degradation with heat and light, especially acid form
- Decarboxylation usually required
- Placebo effect
- Developing precise, stable, and reproducible dosage forms to FDA standards can be challenging.

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Safety and Efficacy

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FDA-mandated Toxicology Testing in Animals

- Full pre-clinical safety program, including
  - Reproductive toxicology
  - Safety Pharmacology studies
    - Cardiovascular
    - Central Nervous System
    - Respiratory
  - Genotoxicology
  - Acute and chronic toxicology
    - Including 6 month rat and 12 month dog studies
  - Local Irritation Studies
  - Immunotoxicology
  - Rodent abuse liability studies
  - Rodent carcinogenicity study
  - Pharmacology and in vitro and in vivo studies on metabolites to determine if active or inactive
    - May need tox studies on metabolites

NOTE: Product used in Phase 3 must be the same as that used in tox studies or bridging studies required

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FDA-mandated Clinical (Human) Safety Data

- Collection of all adverse events (side effects)
  - Mild/moderate/severe
  - Related and unrelated
- Drug/drug interaction studies, particularly important for CBD
- Food/drug interaction studies, 4-5X more exposure with a high fat meal
- Studies in subjects with kidney or liver impairment
- Thorough QT (cardiac) study

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Efficacy: Controlled Clinical Trials

Phase 1

- **Study Participants**: 20 to 100 healthy volunteers or people with the disease/condition
- **Length of Study:** Several months
- **Purpose**: Assess safety and dosage

Approximately 70% of drugs move to the next phase

Phase 2

- **Study Participants**: Up to several hundred people with the disease/condition
- **Length of Study:** Several months to 2 years
- **Purpose**: Assess efficacy and side effects

Approximately 33% of drugs move to the next phase

Phase 3

- **Study Participants**: 300 to 3,000 volunteers who have the disease or condition
- **Length of Study:** 1 to 4 years
- **Purpose**: Assess efficacy and monitor adverse reactions

Approximately 25-30% of drugs move to the next phase

Phase 4 (post approval)

- **Study Participants**: Several thousand volunteers who have the disease/condition
- **Purpose**: Assess safety and efficacy
- **May be mandated by FDA**

The drug development process: Step3: clinical trials. FDA website. https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm. Accessed August 30, 2017.

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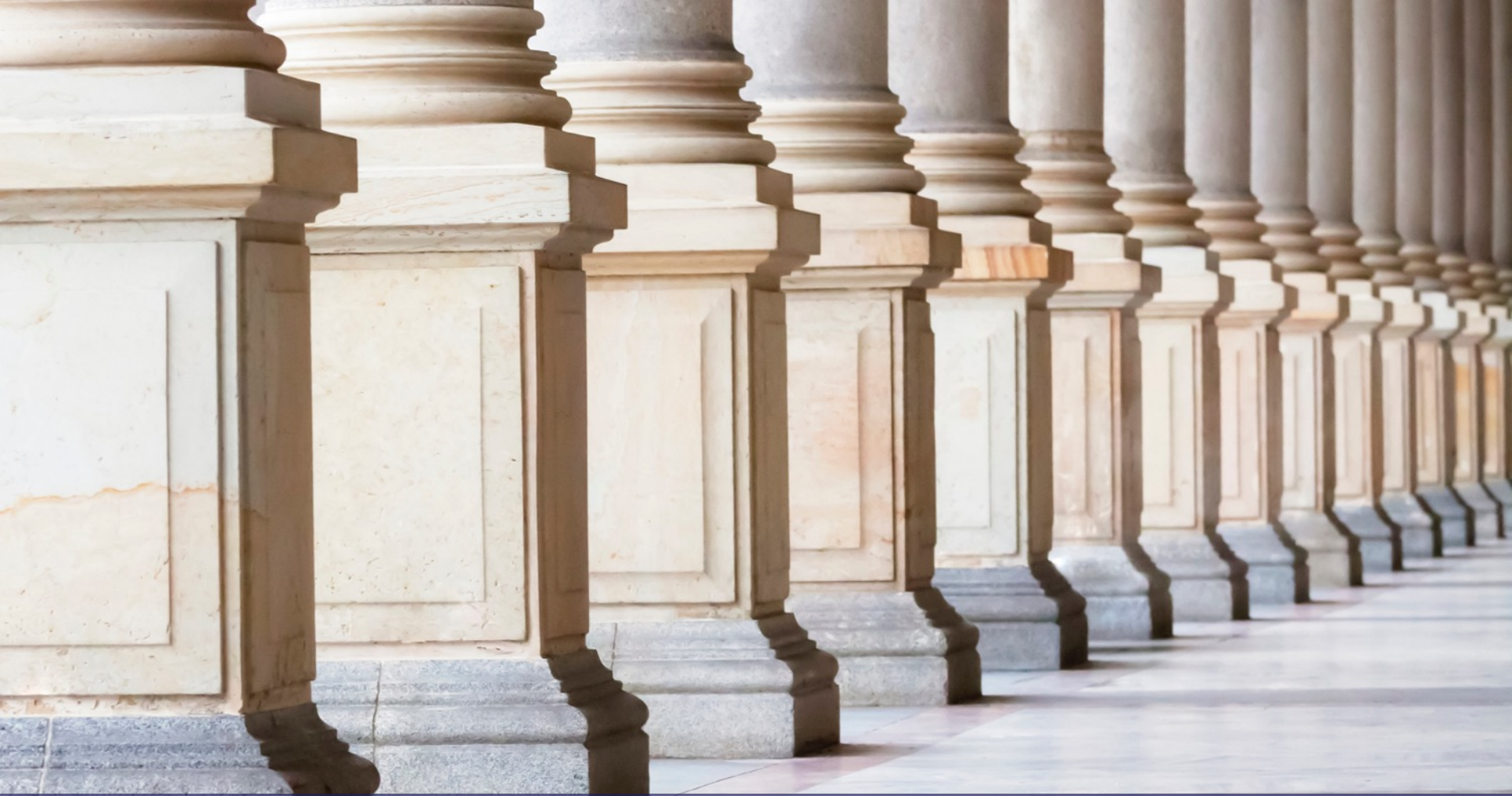

Schedule I Research & Development

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Schedule I Research & Development—It Can be Done!

- Essentially, the steps are the same as for any prescription product (preclinical-Phase 3).
- However, **all** researchers must secure special Schedule I research licenses (registrations) from DEA and **additionally** from the state controlled drugs authority.
  - Special security provisions for handling, storage (safe), recordkeeping, etc.
- After the 2018 Farm Bill, no Schedule I manufacturing/cultivation or research registrations needed for hemp as defined.

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Importing Standardized Cannabis-derived Extracts into the US for Research

- Standardized pharmaceutical-quality cannabis extract preparations may be imported into the US (with a DEA license and if an IND is in place).
- Such preparations are not subject to the “national agency” control requirements of the 1961 Single Convention.
- Since 2006, over 100 clinical research sites around the US have been licensed by DEA to conduct research with such imported preparations.

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Moving Out of Schedule I

- In NDA, sponsor must provide data to FDA from a large package of abuse liability studies.
- At the end of the approval process, FDA will make a scheduling recommendation to DEA.
- Upon FDA approval, a cannabinoid product must be moved to a lower schedule (II-V).
- DEA will issue an interim final rule (IFR) within 90 days of approval, after which time the product can be marketed and dispensed.
  - A full rescheduling administrative process follows
  - Final Rule will be issued if scheduling required by a treaty
  - On September 27, DEA placed the substance CBD, derived from cannabis (i.e., not synthetic), containing **NMT 0.1% THC** and incorporated into an FDA approved product, into Schedule V
    - This amounts to NMT 10mg THC per 100ml bottle or 0.1mg/ml

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Need for State Rescheduling

- Most states also have their own version of the CSA, called the Uniform Controlled Substances Act.
- Marijuana is similarly defined and includes its derivatives and compounds.
  - CBD is in Schedule I under those state laws.
- Even states with medical marijuana or recreational use laws generally have not rescheduled cannabis under state law.

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State Rescheduling cont.

- Even once a cannabis product has been approved by FDA and rescheduled by DEA, it cannot be distributed in pharmacies in states which control it in Schedule I until it is rescheduled in those states.
- This is different from most medications comprised of synthetic molecules;
  - These are initially scheduled by DEA after NDA approval but are not yet scheduled under state law and so can be dispensed while the state (eventually) puts the medication in the appropriate schedule.

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Need for State Rescheduling

- States employ one of three processes to schedule, reschedule, or deschedule a substance
  - Automatic: 30 days after DEA action
    - A few states are automatic
  - Administrative
    - A state agency is authorized or mandated to conduct an administrative process to schedule a substance.
    - In many cases, this process requires that the public be given notice and an opportunity to comment or object.
    - If an objection is made, the process becomes very prolonged. This can take up to two years to complete.
  - Legislative
    - Legislature must pass a bill to schedule a substance.
    - Many state legislative sessions are quite short, e.g., 4 months, and some legislatures meet only every other year.

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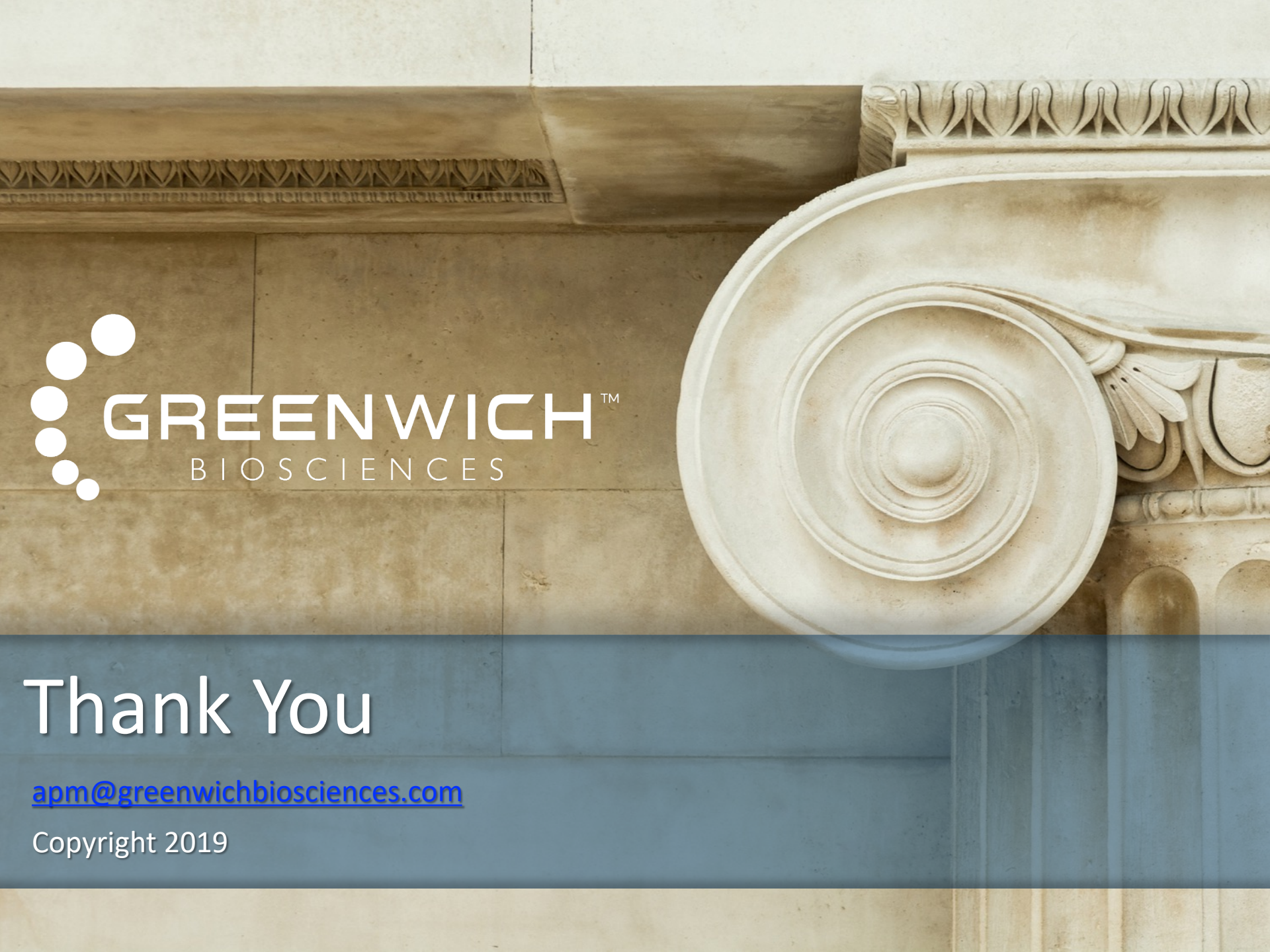

Thank You

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