To IND or Not IND
The Basics

FDLI, Legal and Practical Issues in the Evolving World of Cannabis Regulation
December 9, 2020

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OFW Olsson Frank Weeda Terman Matz PC

Disclaimers

- This presentation is not legal advice.
- Refer to FDA regulation and guidance for more information.
- Other interpretations are possible.

Investigational New Drug (IND) Basics
21 C.F.R. Part 312

- Unlawful to ship a "new" drug in interstate commerce.
- IND exemption permits shipment of unapproved product in order to develop conditions for use to support FDA approval.

Purposes Of An IND
21 C.F.R. 312.22

- Assure the safety and rights of subjects in all phases of an investigation.
- In Phase 2 and 3, helps assure quality of the science to permit an evaluation of the drug's effectiveness and safety.

When do you need an IND?

- The research involves a drug;
- The research is a clinical investigation; and
- The clinical investigation is not otherwise exempt from the IND requirements in part 312.

What is a drug?

201(g) of the FDC Act

- "[A]rticles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . ."
- "[A]rticles (other than food) intended to affect the structure or any function of the body of man or other animals."
- Biological products subject to licensure under section 351 of the PHS Act are also considered drugs.

What's not a drug?

- A dietary supplement intended only to affect the structure or function of the body and not intended for a therapeutic purpose.
- A food used primarily for its taste, aroma, or nutritive value and not
  - for a therapeutic purpose, or
  - to affect the structure or function of the body, other than nutrition.

What Is a Clinical Investigation? 21 C.F.R. § 312.3(b)

- "[A]ny experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects."
- "[A]n experiment is any use of a drug except for the use of a marketed drug in the course of medical practice."
- "[A] randomized trial evaluating an unapproved use of a lawfully marketed drug is a clinical investigation and may require an IND."
- "[U]se of a lawfully marketed drug for an unapproved use in the course of medical practice is not a clinical investigation and does not require an IND…"

Source: Guidance for Clinical Investigators, Sponsors, and IRBs Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND (Sept. 2013)

When don't you need an IND?

- BA/BE Studies
- Certain research involving marketed drug products.
  - Drug is lawfully marketed in U.S.
  - The investigation isn't intended to be reported to FDA for a new indication or to support significant labeling change.
  - For an Rx drug, the investigation isn't intended to support a significant change in advertising.
  - The investigation doesn't involve route of administration, dose, patient population, or other factor that significantly increases risk.
  - IRB approval and informed consent obtained.
  - Not promoted or commercialized.

When don't you need an IND?

- Investigations involving products that aren't drugs.
  - Foods and dietary supplements.
  - Depends on intent of the clinical investigation.
- For dietary supplements.
  - "If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required."
  - "However, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312."
- For foods.
  - "[A] clinical investigation intended to evaluate the effect of a food on a disease would require an IND under part 312."

- For more information
  - 21 C.F.R. Part 312
  - Guidance for Clinical Investigators, Sponsors, and IRBs Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND (Sept. 2013)

Tish Pahl

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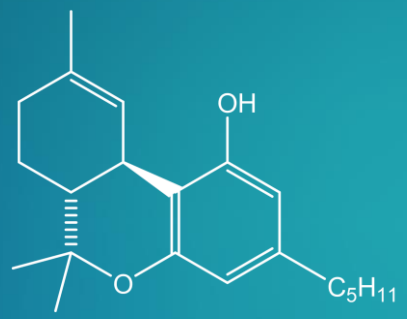
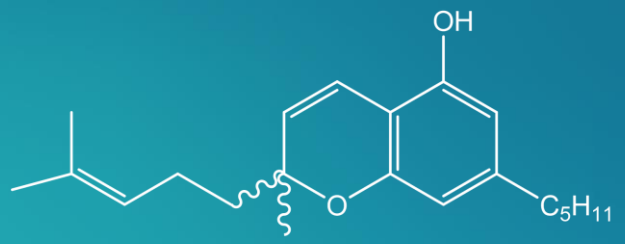


Δ9-THC



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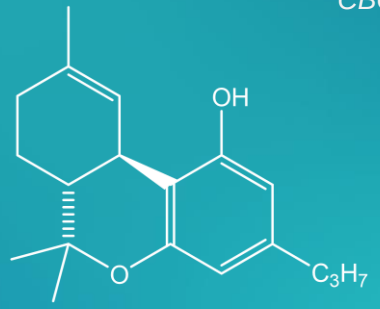

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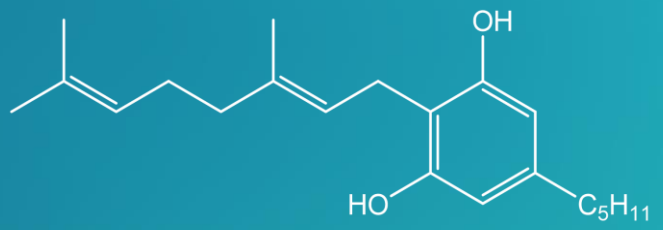

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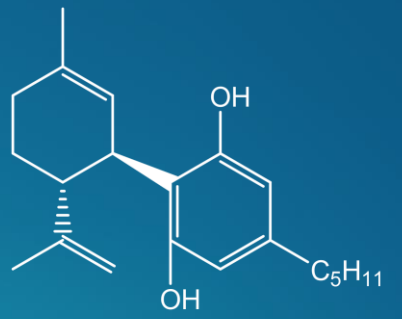
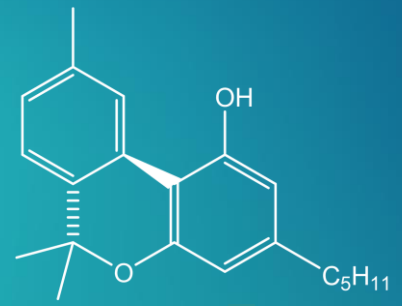


CBD



CBN

Developing Cannabis-Based Medicines Through the FDA Process

Alice Mead, J.D., LL.M.

GREENWICH™ BIOSCIENCES

Greenwich Biosciences

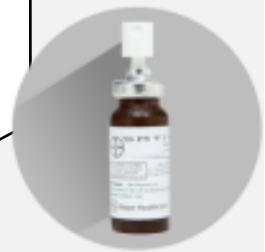
RESEARCH

20+ years experience in researching and developing novel Rx cannabinoid medicines

- 14 cannabinoids evaluated in pre-clinical research
- >100 peer-reviewed publications
- Cannabinoids exported to >35 countries for research

DEVELOPMENT

1000+ person in-house team with expertise in bringing drugs to regulatory approval in US and ROW



- >60 Phase 2/3 clinical trials
- >135,000 pt-years of human safety data
- Sativex® (nabiximols) approved in >25 countries (ex-US) for relief of MS spasticity*
  - Complex Botanical Mixture
  - *Not approved in US for any indication
  - Clinical trials underway in US

COMMERCIALIZATION

- Epidiolex® (cannabidiol) approved by FDA for seizures associated with Dravet syndrome, Lennox Gastaut syndrome and tuberous sclerosis complex in patients 1 year or older
  - Active ingredient is highly purified CBD
  - Oral liquid 100 mg/ml

World Leader in Cannabinoid Science

FDA approval answers critical questions important for all, but especially for vulnerable patients

Vulnerable populations
and patients with
serious illnesses

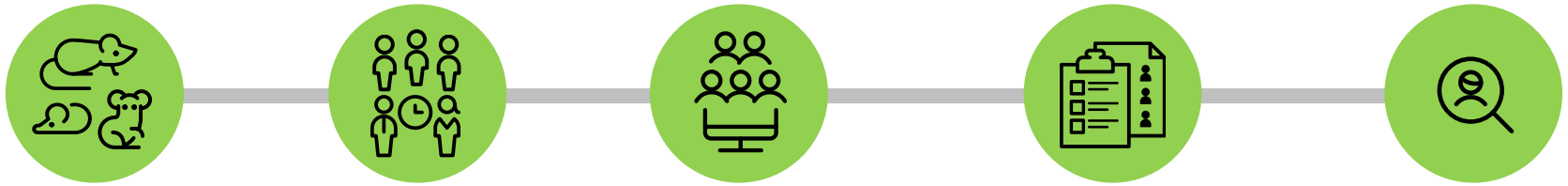
+ DOES THE DRUG WORK?

- What does it work for?
- What doesn't it work for?
- How well does it work?
- Does something else work better?
- How long does it take to work?
- Will it stop working?
- How much should I take?
- How long should I take it for?
- Should I take it with or without food?

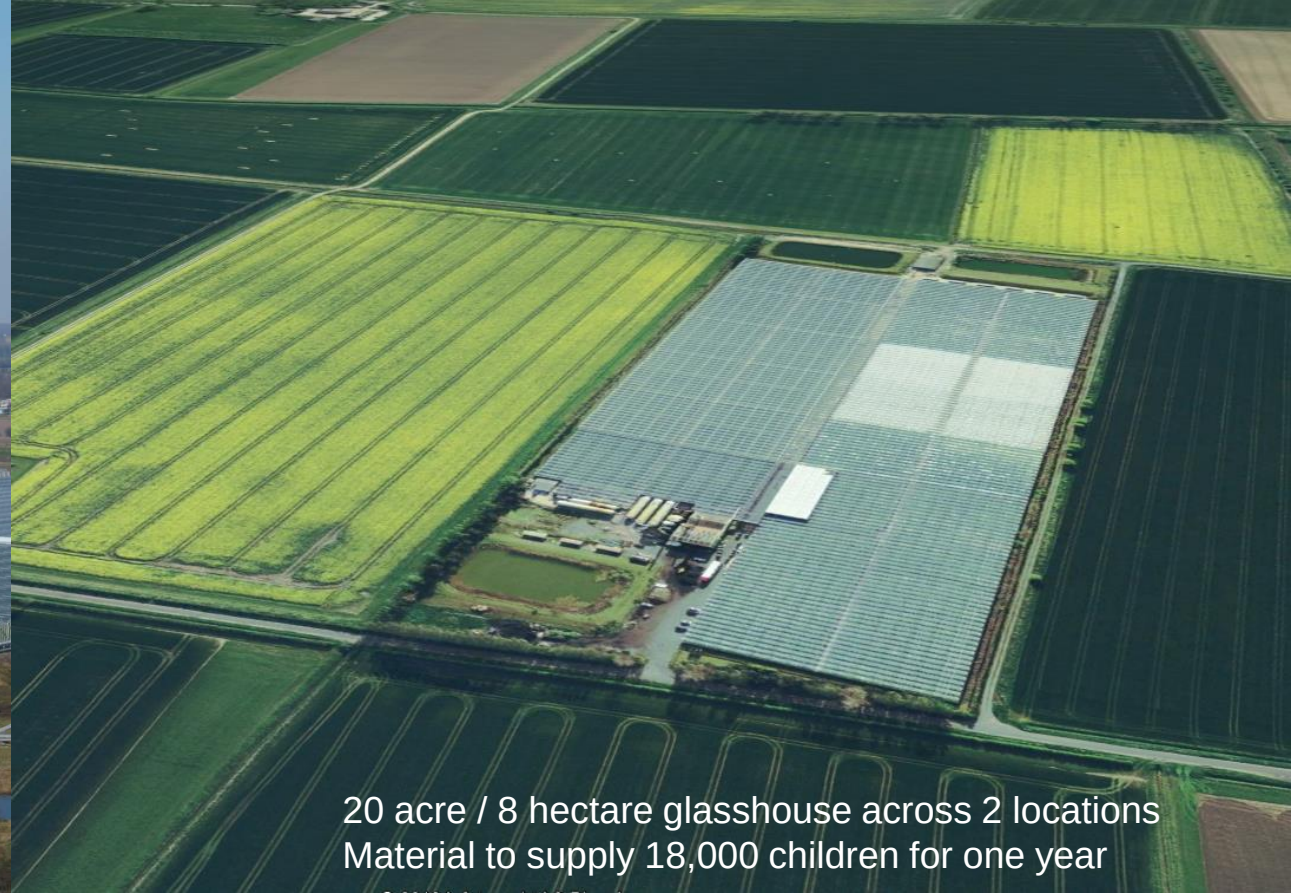
− IS THE DRUG SAFE?

- What are the side effects?
- How closely should I be monitored?
- Can I take it if I'm pregnant or trying?
- Can the elderly take it?
- Is it free of contaminants?
- Will it conflict with my other drugs?
- How is it manufactured?
- Is it consistently manufactured?
- Is each dose the same?

What additional studies must be done to show that medicines are safe?

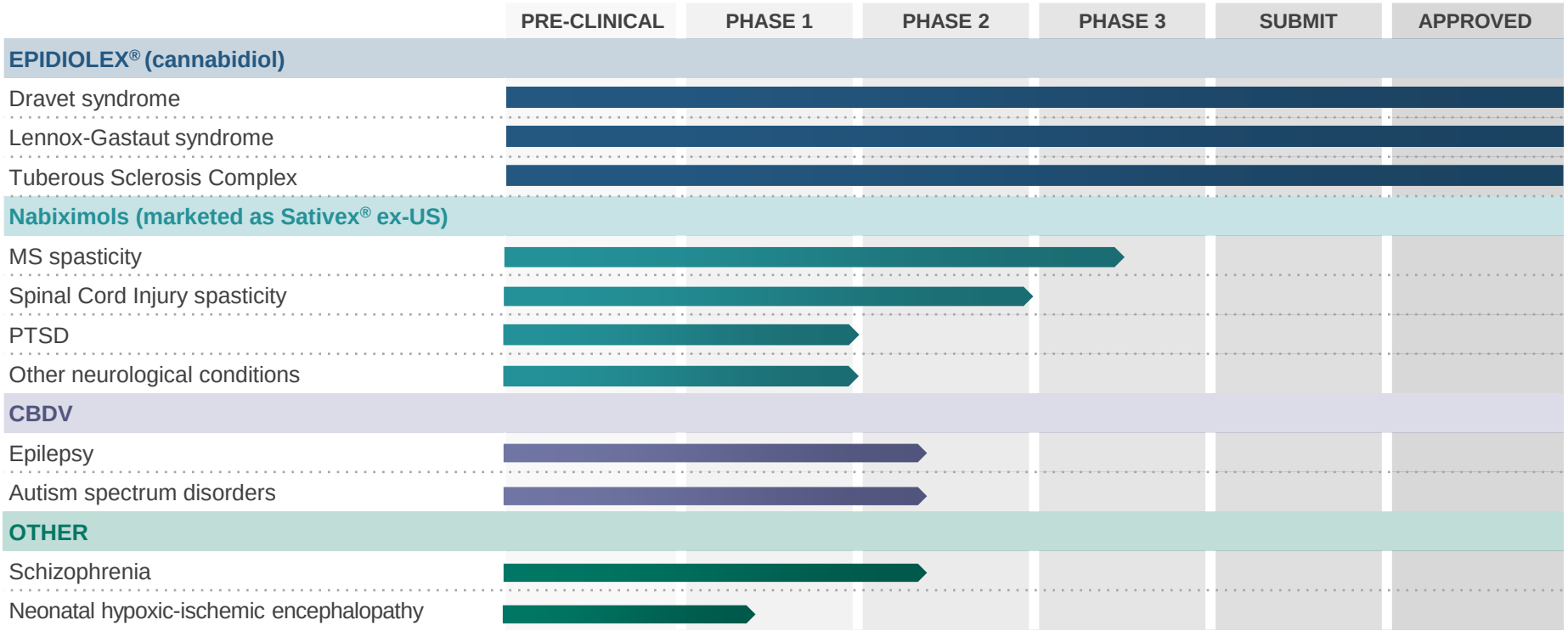


- ✓ Multiple animal toxicology studies
- ✓ At least one hundred patient-years of data required
- ✓ Collection of all adverse events (side effects)
  - **Mild/moderate/severe**
  - **Related and unrelated**
- ✓ Studies… studies… and more studies
  - **Drug/drug interaction**
  - **Food/drug interaction**
  - **Abuse potential**
  - **Renal or hepatic impairment**
  - **QT (cardiac)**
- ✓ Monitoring of all adverse events indicative of abuse or dependence



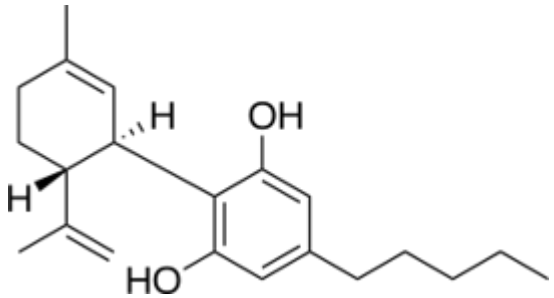
Epidiolex commercial growing site Norfolk/East and Yorkshire/North

GW is exploring a range of investigational cannabinoids for serious conditions



Early GW CBD Research

Cannabidiol



Project CBD

WWW.PROJECTCBD.ORG

GREENWICH™ BIOSCIENCES

Listening To Patients

In the summer of 2012, a California family reached out to us.

They had a son with intractable epilepsy

They desperately needed help.

Epidiolex Development Program

- IND opened with FDA in 2014 to conduct clinical trials.
- Expanded access sites joined as clinical trial sites.
- Patient recruitment was swift.
- FDA approval in record time in June 2018.
- DEA rescheduled to Schedule V 3 months later.

Epidiolex®
(cannabidiol) CV

GREENWICH™
BIOSCIENCES

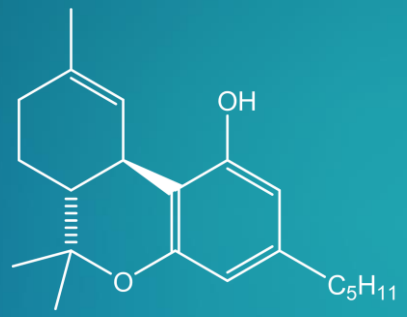
Work toward innovative cannabis medicines has just begun

CANNABINOID POTENTIAL

GW studying cannabinoids **for 8 serious illnesses** with unmet need

Research needed in many other indications with significant unmet need

GREENWICH BIOSCIENCES
A GW Pharmaceuticals PLC Company



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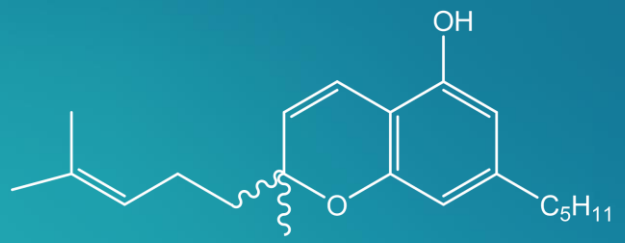

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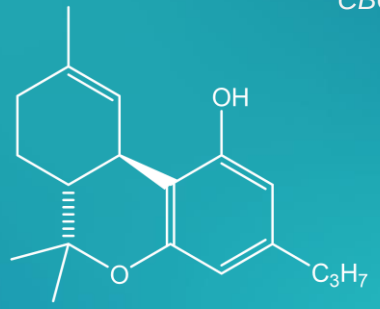

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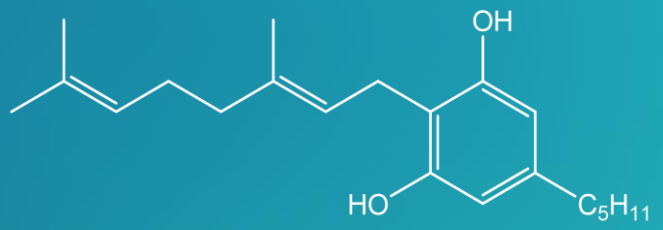

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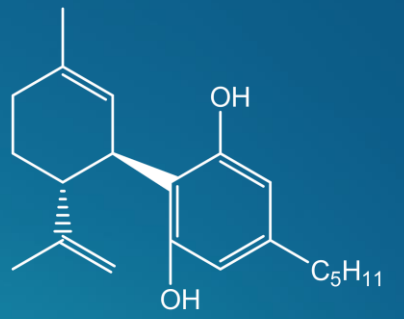

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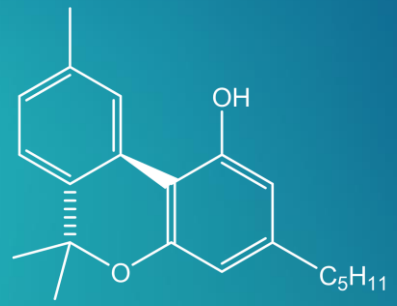

CBN3

Thank You!

GREENWICH™ BIOSCIENCES


CANOPY GROWTH
CORPORATION

Lead F22 New Product Ideas: New formats, higher dosing

Back to asks

Packaging being Tested

	Deep Space Flavour Extension(s)	Houseplant Flavour Extension	(Loose Leaf) Iced Tea	(Tweed) Cannabis Seltzers	Multipacks	Quatreau (USA)
Dosage	10mg THC	2.5mg THC	5mg THC	5mg THC	THC & CBD	20 mg CBD
Primary Need State	Enhance	Unwind / Connect	Connect	Connect	Connect	Mind & Body Wellness
Competitive Analog	Cannabis Edibles	Bev Alc RTD	Twisted Tea	White Claw	Bev Alc Multi-Packs	Enhanced Waters
Competitive Difference	Rapid Onset	Alcohol Free; Low Cal	Alc Free; No hangover	Alc Free; Low Sugar	Alcohol Free	CBD

Competitive Landscape - Beverage

	everie	DEEP SPACE	Tweed	HOUSEPLANT	THE GREEN ORGANIC DUTCHMAN	HAVEN ST. PREMIUM CANNABIS
Share Position	#1	#2	#3	#4	#5	#6
LP	Tilray Canada LTD	Canopy Growth Corp	Canopy Growth Corp	Canopy Growth Corp	The Green Organic Dutchman	Terrascend
SKU Portfolio	5 SKUs	1 SKUs	2 SKUs	2 SKUs	4 SKUs	5 SKUs
Top SKUs	Lemon & Lime CBD - 269 ml 	Deep Space 222ml 	Bakerstreet - 355ml 	Graperfruit - 355ml 	Dissolvable Powder - 1 x 0.45g 	No.550 Rise Tea - 1pk 
F21 YTD Sales	$1,261,700	$1,200,843	$1,010,242	$1,001,524	$780,585	$568,333

Source: Provincial Data (ON+NB+NS+PEI+BC+AB), FY21 YTD (April - Nov)

Competitive Landscape - Edible Extracts

	REDECAN	Solei	EDISON CANNABIS CO	verywell.	COVE	Twd.
Share Position	#1	#2	#3	#4	#5	#6
LP	Redecan Pharm	Aphria Inc	Organigram		Peace Naturals Product	Canopy Growth Company
SKU Portfolio	4 SKUs	7 SKUs	5 SKUs	4 SKUs	3 SKUs	3 SKUs
Top SKUs	Reign Drops - 30:0 - Oils - 30ml 	Free - Oils - 30ml 	CBD - Oils - 25ml 	Yawn Drops - 27ml 	CBD - Oils - 20ml 	Indica - Oils - 20ml 
F21 YTD Sales	$6,069,701	$5,500,560	$1,337,442	$1,083,591	$1,014,062	$965,791

Source: Provincial Data (ON+NB+NS+PEI+BC+AB), FY21 YTD (April - Nov)

Confectionary Portfolio on a Page

US CBD Portfolio

CAD THC Portfolio

Product:						
	Martha Stewart CBD Gummies, Citrus Medley	**Martha Stewart CBD Gummies, Berry Medley**	**Tweed Bakerstreet + Peppermint, Milk Chocolate**	**Tweed Houndstooth + Mocha, Milk Chocolate**	**Tokyo Smoke Pause, Dark-Milk Chocolate**	**Tokyo Smoke Go, Dark-Milk Chocolate**
Portfolio Role: *Demand Space*	***Proactive Mind + Body Wellness***		***Mood Modulation***			
Needstate	***Long term health***		***Unwind with a Reward***		***Enhance***	
Consumer	**CBD intenders**	**CBD intenders**	**Practical Value Seekers**	**Practical Value Seekers**	**Explorers, Quality Seekers**	**Explorers, Quality Seekers**
Price to Consumer*:	**USD $34.99**	**USD $34.99**	**CAD $7.79 (wavg)**	**CAD $7.97 (wavg)**	**CAD $9.51 (wavg)**	**CAD $9.31 (wavg)**
Points of Difference:	• Martha-inspired flavors (Meyer lemon, blood orange, kumquat) • Martha 'normalization' factor • Pate-de-fruits style texture	• Martha-inspired flavors (Black raspberry, huckleberry, raspberry) • Martha 'normalization' factor • Pate-de-fruits style texture	• Milk chocolate + favorite flavors • Indica dominant	• Milk Chocolate + favorite flavors • Sativa dominant	• Peruvian + Colombian cacao beans • 'Clean' label – organic cane sugar, organic cacao butter • 60% cacao	• Peruvian + Colombian cacao beans • 'Clean' label – organic cane sugar, organic cacao butter • 60% cacao
Competitors:	CHARLOTTE'S WEB STANLEY BROTHERS 	chowie 	Foray 		AURORA drift 	EDISON CANNABIS CO 

*Variance in CAD driven by provincial mix

SPECTRUM FLOWER PRODUCT PORTFOLIO

Spectrum Red accounts for 80% of F21 YTD flower Sales in Canada

Red No 1

Red No 2

Orange

Purple

Blue

Green

Yellow

Size / Price	2g - $16 5g - $34 15g - $98						5g - $34 15g - $98
THC: CBD Ratio	High THC, No CBD		Med. THC, No CBD	Low THC, Low CBD	Balanced Med. THC: CBD	Balanced Low THC: CBD	No THC, High CBD
Phenotype	Indica	Sativa	Indica	Hybrid	Hybrid	Hybrid	Hybrid
FY21 YTD Share of Sales % (Canada)	51%	29%	3%	2%	7%	3%	6%
Direct Competitors (top 1-3)	Canada: Shopper's Drug Mart, Aurora, Aphria, Tilray, Organigram Germany: Bedrocan, Tilray, Aurora						

U.S. Portfolio Introduction

A Firm Grasp on Existing & Future Consumers

Therapeutic CBD

Today's Focus

- Martha Stewart
- First & Free

Lifestyle CBD

Today's Focus

- whisl
- Tweed
- Storz & Bickel

Sports Nutrition & Beverages

- BioSteel

Today's Focus

- Quatreau

Wellness / Beauty

- thisworks 24HR SKIN SOLUTIONS

Animal Health

- Martha Stewart
- canopy animal health

Martha Stewart CBD: Brand Introduction


whisl
CBD
Tune In
Intermission
Fade Out
Starter Kit
Deep Blue Vaporizer
Warm Grey Vaporizer
CBD the difference.

Cannabis and the IND Pathway

Why bother?

I know cannabis works……

FDLI

Conventional Drug Development

Receptor / Targets

Candidate Screening

Manufacturing

Test article evaluation

Non-clinical

Human

Phase III

NDA

Controlled Data:

- Formulation,
- In vitro characteristics,
- Drug-drug interactions,
- In vivo characteristics,
- Safety profile,
- Efficacy profile

Peri / Post Registration Research

Academic / Business

Clinical Program Design

Manufacturing

Blinding

Alternate formulation

Test article evaluation

Phase III- like

New indication / changes to Label

ICH harmonisation for better health

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

Controlled Data:

- Formulation,
- In vitro characteristics,
- Drug-drug interactions,
- In vivo characteristics,
- Safety profile,
- Efficacy profile

…The agency recently updated the public on concerns about potential harm from CBD products……

- potential liver injury,
- interactions with other drugs and
- male reproductive toxicity,
- side effects such as drowsiness.
- potential effects of sustained and/or cumulative use,
- co-administration with other medicines,
- risks to vulnerable populations.

FDA STATEMENT

FDA Advances Work Related to Cannabidiol Products with Focus on Protecting Public Health, Providing Market Clarity

Share Tweet Linkedin Email Print

For Immediate Release: March 05, 2020

Statement From: Commissioner of Food and Drugs - Food and Drug Administration
Stephen M. Hahn M.D.

Over the past year, the U.S. Food and Drug Administration has embarked on a comprehensive evaluation of cannabidiol (CBD) products, with a focus on educating the public about the risks and unknowns of these products, gathering the science needed to better understand both these safety concerns and potential benefits to inform our regulatory approach, as well as taking steps when necessary to address products that violate the law in ways that raise a variety of public health concerns.

Today, we are providing updates on our efforts in this area, including several new steps in areas of education, research and enforcement with the ultimate goal of continuing to protect the public health and working to provide market clarity.

https://www.fda.gov/news-events/press-announcements/fda-advances-work-related-cannabidiol-products-focus-protecting-public-health-providing-market

FDA Guidance (draft)

20 July 2020

Cannabis and Cannabis-Derived Compounds:

Quality Considerations for Clinical Research Guidance for Industry

Focus – ***manufacturing***

https://www.fda.gov/media/140319/download

https://cannabis.net/blog/opinion/the-fda-releases-their-cannabis-research-playbook

Definitions Matter

cGMP

21 CFR Part 111 vs. Part 211

Raw Materials

[111.75(a)(2)] There is no requirement for the dietary supplement manufacturer to confirm the identity of non-dietary ingredients used in the finished dietary supplement product if the supplier has been previously qualified by the manufacturer.

vs.

[211.84(d)(1)] There is a requirement that at least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

21 CFR Part 111 vs. Part 211

Finished Product Testing

[111.75(c) and 111.75(d)] There is an option of testing a subset of finished batches based on a sound statistical sampling plan or testing all finished product batches. Manufacturers may also exempt one or more finished product specifications from verification prior to release of the batch for good cause and with appropriate documentation.

vs.

[211.165(a)] There is a requirement to test each active pharmaceutical ingredient in each finished drug product batch.

So why file an IND?

… “**drug**” ..by reference to its intended use…
“in the *diagnosis, cure, mitigation, treatment, or prevention of disease*”