

Epidiolex in Pediatric Epilepsy

James Brodie - GW Pharmaceuticals

22 May 2014



1. Introduction to GW and our Cannabinoid Platform
2. Rational for the use of cannabinoids in treating epilepsy
3. Epidiolex and our orphan drug development programme
4. Legal and regulatory status of CBD in the United States

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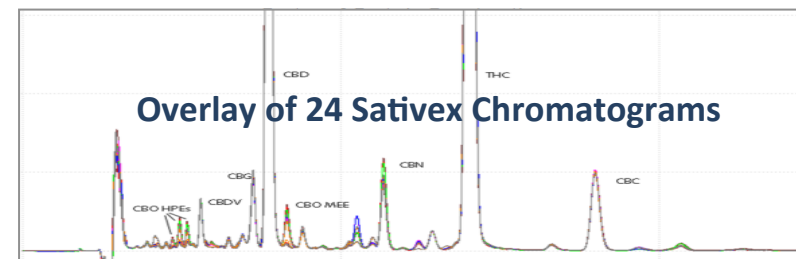
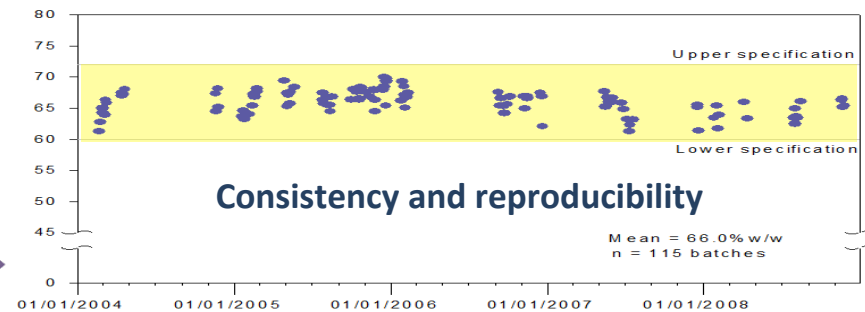
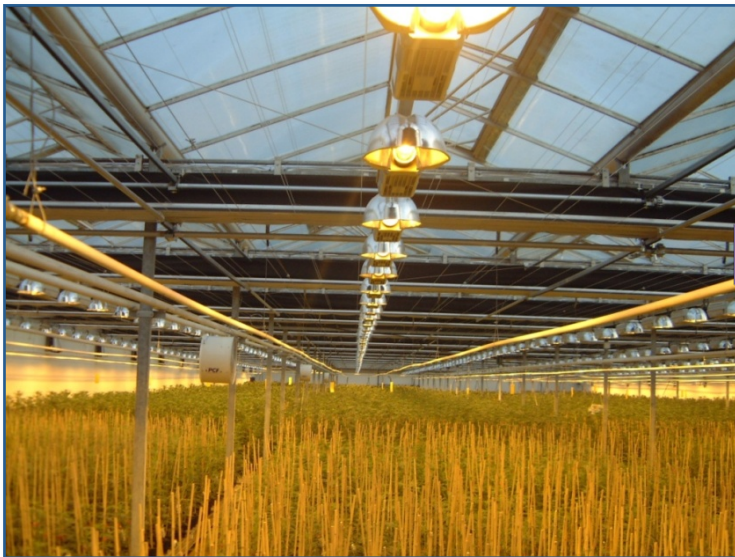


- World leading position in development of plant-derived cannabinoid therapeutics
- Commercialized lead product, Sativex[®]
- New cannabinoid orphan program in pediatric epilepsy
- Promising clinical stage cannabinoid product pipeline
- Collaborations with major pharmaceutical companies
- Listed on NASDAQ: GWPH (May 2013) and AIM (UK)

GW's Cannabinoid Platform



- Cannabis plant is unique source of >70 cannabinoid molecules
- GW's novel proprietary plant "chemotypes" target selected cannabinoids
- In-house formulation, processing, manufacturing and regulatory expertise
- Exclusivity via 46 patent families, know-how, complex formulations



GW's Manufacturing Process



Botanical
Raw Material
(BRM)

GAP

Good agricultural process



Botanical
Drug Substance
(BDS)

GMP

Good manufacturing process



Botanical
Drug Product
(BDP)

Sativex is a standardized extract that contains THC and CBD as well as specific minor cannabinoids and other non-cannabinoid components



- Approved for Spasticity in Multiple Sclerosis
- Global Phase 3 programme in Cancer Pain

Strong pharmacologic rationale: “Endocannabinoid system” modulation by THC combined with polypharmacology of CBD for autoimmune / pain / inflammation

Sativex is a Precise Mixture of 2 BDSs



THC Clones



CBD Clones



Botanical Raw Material (BRM)

THC
BRM

CBD
BRM



Botanical Drug Substance (BDS)

THC
BDS

CBD
BDS



Sativex

Botanical Drug Product (BDP)



Final product =
precise 1:1 ratio
of THC to CBD

Sativex[®] License Agreements



UK and Canada

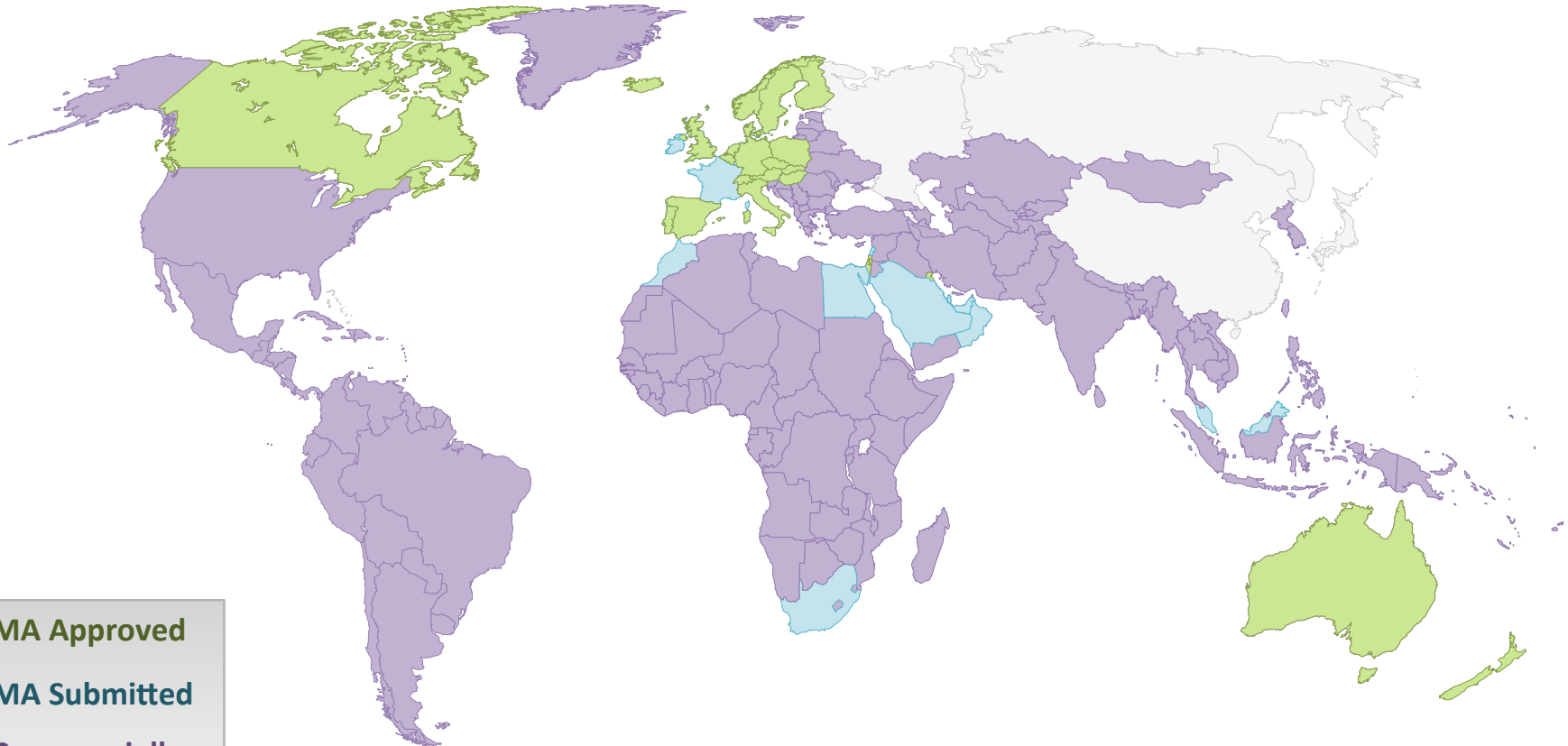
EU and Mexico

United States

Israel

Africa, Middle East, Asia

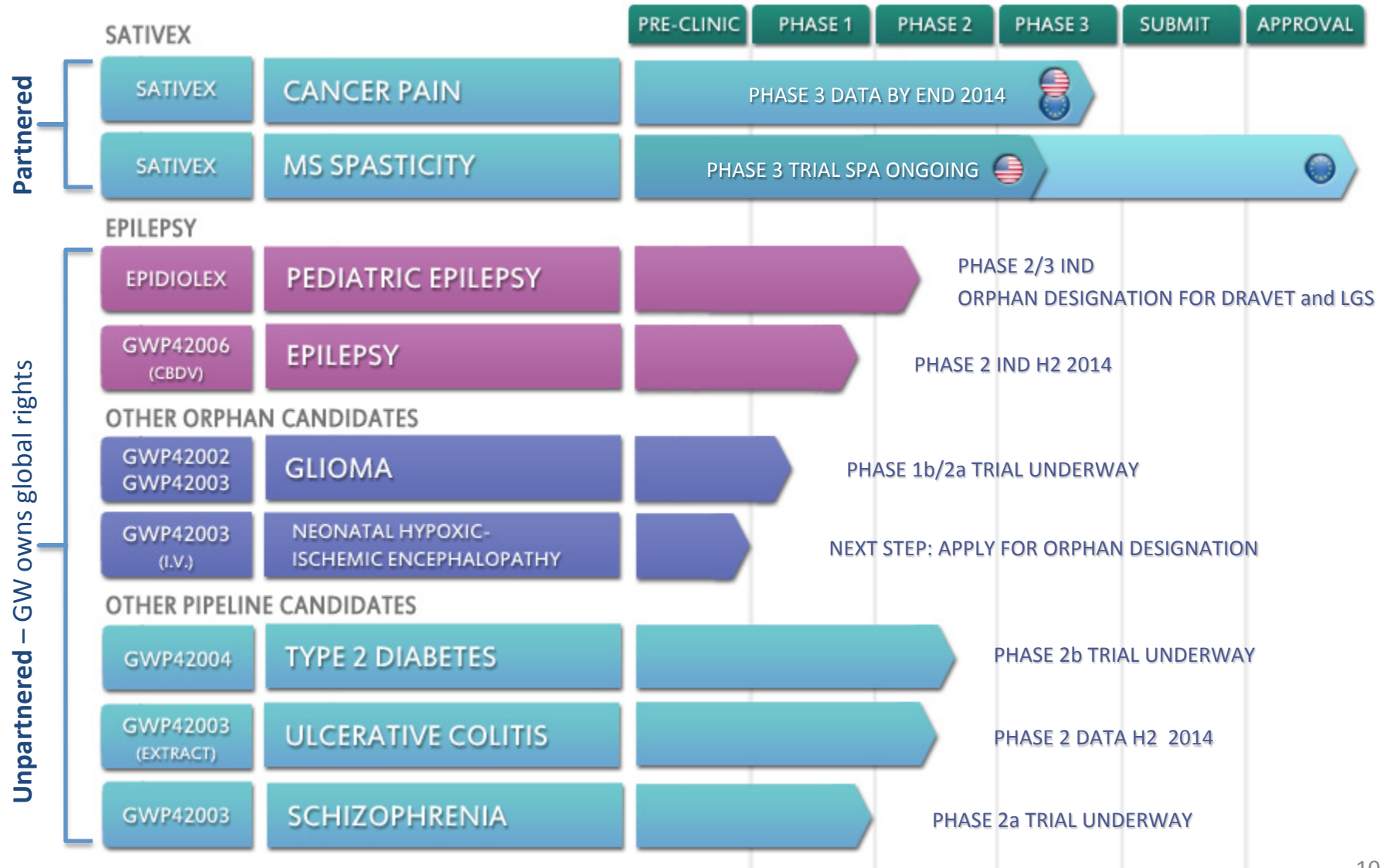
Latin America



- MA Approved
- MA Submitted
- Commercially Partnered

Approved in Europe, Israel, New Zealand, Australia and Canada

Our Pipeline

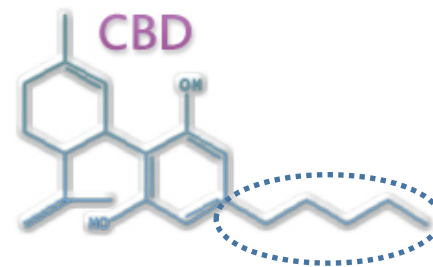


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- 2. Rational for the use of cannabinoids in treating epilepsy**
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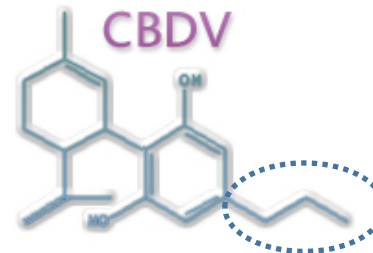
Cannabinoids in Epilepsy

- GW has conducted 7 years research into cannabinoids in epilepsy, leading to two product candidates:

- **Epidiolex[®]** (CBD - cannabidiol)



- **GWP42006** (CBDV - cannabidivarin)



- Historical evidence supporting cannabinoids as anticonvulsants
- Anecdotal evidence and case reports in US media of effects of CBD-enriched marijuana in childhood epilepsy

Possible cannabinoid targets:

Endocannabinoids inhibit release of excitatory neurotransmitters ^[1]

Role for inflammation in epilepsy^[2]

Many different ion channels influence epileptogenesis^[3]

Cannabinoid actions:

Target both endocannabinoid system (ECS) and non-ECS targets

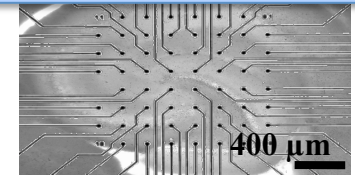
Cannabinoids are potent anti-inflammatories and anti-oxidants

Cannabinoids have cation modulatory actions

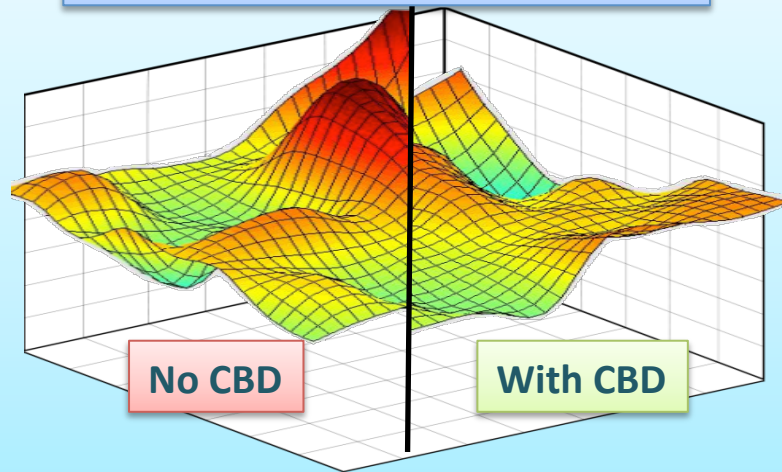
in vitro Screening of CBD

- Anti-seizure activity demonstrated on brain slices
 - ▶ Sheets of confluent hippocampal neurons

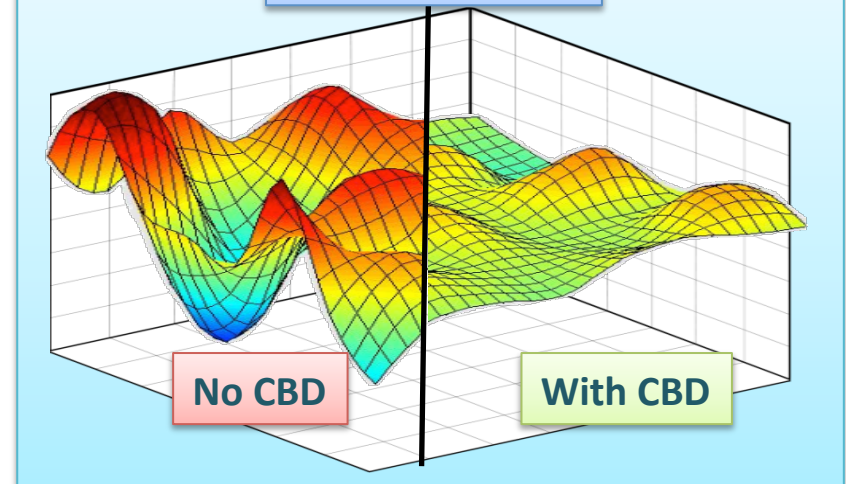
Hippocampal slice



4-aminopyridine induced wave



Mg²⁺ free wave



- Mg²⁺-free and 4-AP models induce recurrent discharges that possess the same properties as seizures *in vivo*

- CBD exerted significant anti-convulsant effects in five acute *in vivo* models of seizure
 - ▶ Maximal Electroshock:
 - ▶ Audiogenic
 - ▶ Pentylentetrazole-induced
 - ▶ Pilocarpine-induced
 - ▶ Penicillin-induced

- Numerous positive measures:

- ▶ Seizure severity
- ▶ % seizure free
- ▶ Onset latency
- ▶ Seizure duration
- ▶ Mortality

Summary of CBD preclinical findings:

<i>in vitro</i>		<i>in vivo</i> Acute Models of Seizure				
Cellular activity		PTZ	MES	Pilocarpine	Penicillin	Audiogenic
4-AP	Mg ²⁺ -free	Generalised	Generalised	Temporal Lobe	Partial	Generalised
Anti-epileptiform/anti-convulsant	Anti-epileptiform/anti-convulsant	Anti-epileptiform/anti-convulsant	Minor anti-convulsant effect	Anti-epileptiform/anti-convulsant	Anti-epileptiform/anti-convulsant	Anti-epileptiform/anti-convulsant

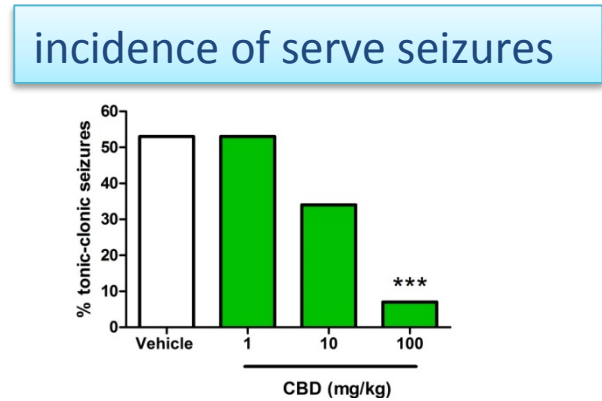
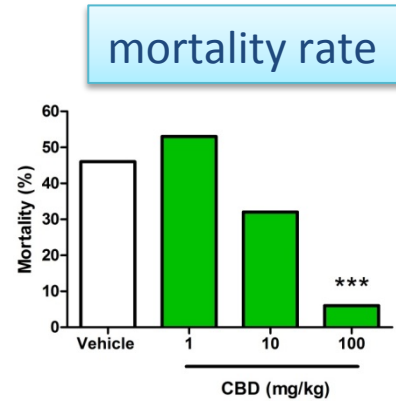
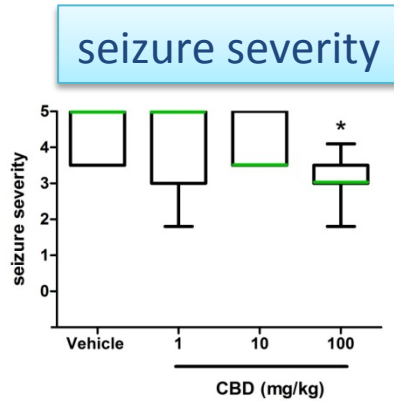
No effects
 Minor anti-convulsant effect
 Anti-epileptiform/anti-convulsant

- CBD proven to be as efficacious as standard AEDs (e.g. valproate)

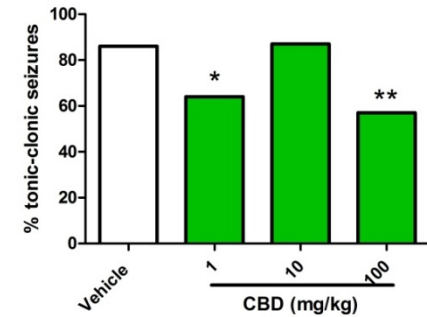
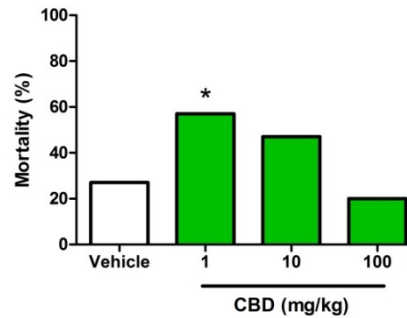
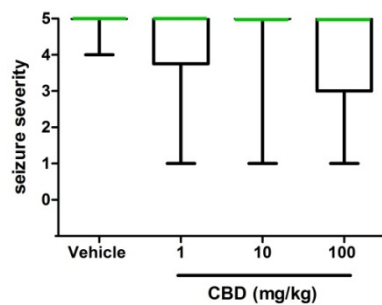
in vivo Evaluation of CBD



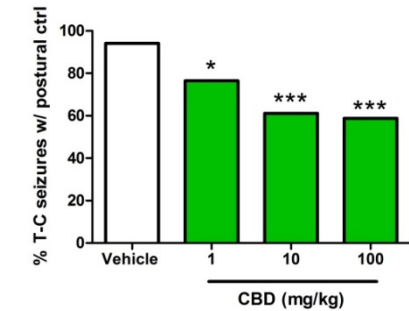
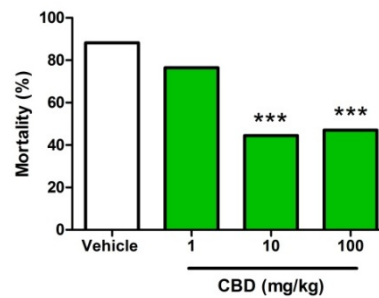
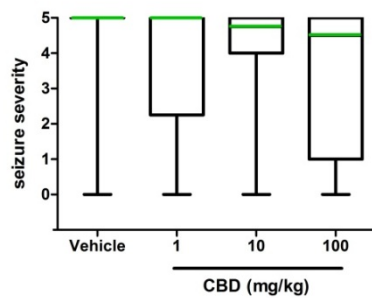
Pentylenetetrazole



Pilocarpine



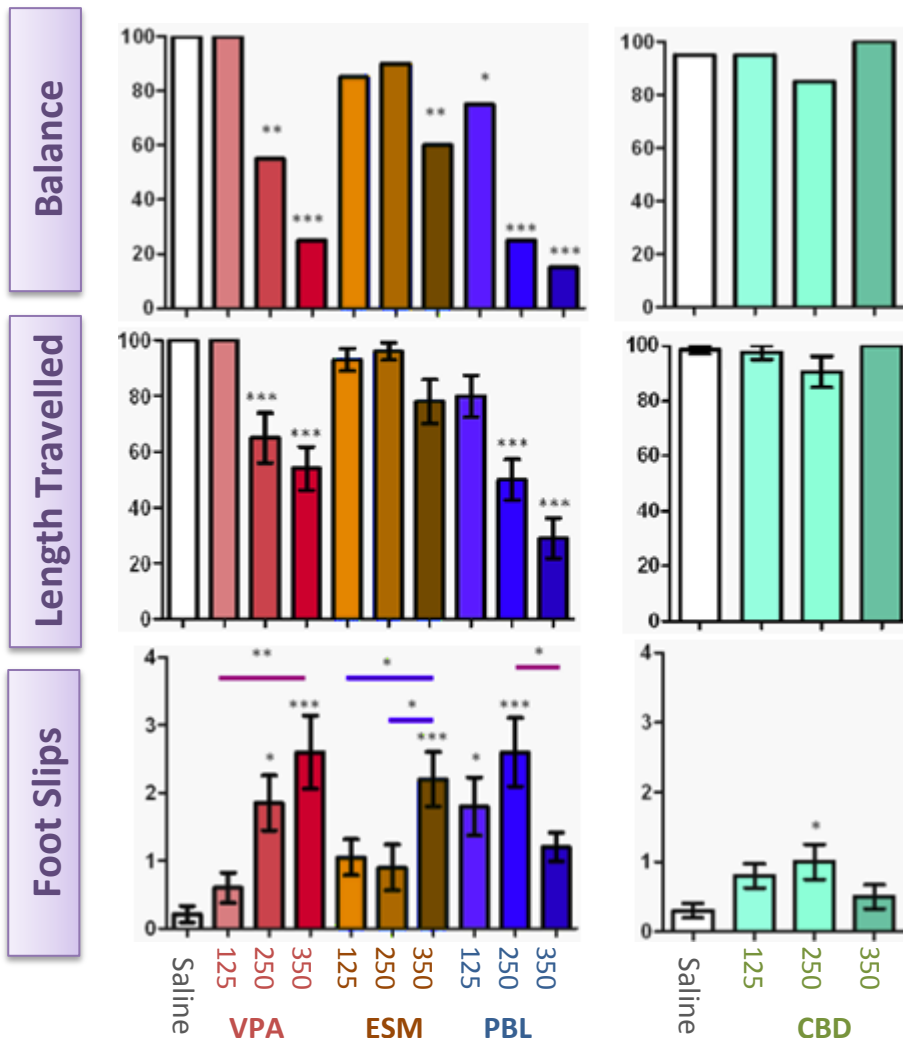
Penicillin



Reduced Side Effects Compared to AEDs



CBD vs. AEDs on motor coordination assessed: static beam assay



- Comparator AEDs:

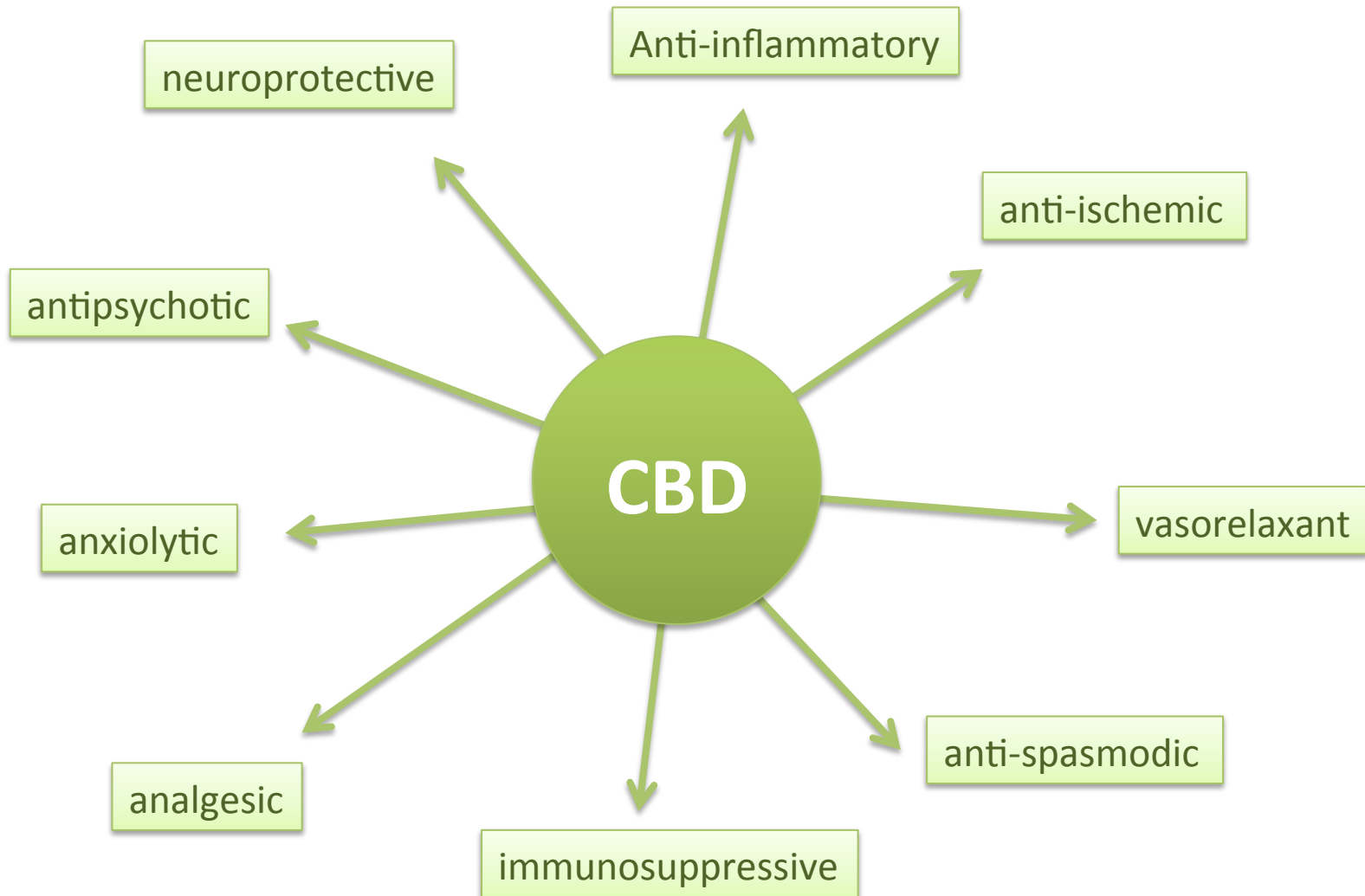
- ▶ Valproate (VPA)
- ▶ Ethosuximide (ESM)
- ▶ Phenobarbital (PBL)

- Doses used based on ED25, ED50 & ED75 in PTZ model

- Significant drug effects in assay reflect poor tolerability

- Neither CBDV nor CBD caused any detectable deficits unlike all standard AEDs tested

Additional Beneficial Effects of CBD



Why Do We Exclude THC?



Regarding development:

- The CB₁ receptor (activated by THC) contributes to the directional **growth of neurons**
- **THC interferes** with cell **structure and protein** turnover in neurons (Tortoriello *et al* 2014)
- THC exposure **alters connections** fetal brain of mice and humans
- In human fetuses cannabis exposure also **reduces neuron growth** in the brain

Regarding epilepsy:

- THC modulation fetal nervous system may lead to unexpected outcomes (as opposed to adults)
- Low dose THC increases amplitude of electrically evoked cortical potentials (Turkanis *et al* 1981)

Regarding behavior:

- Deficient social behaviour in chronic CB1 agonist treated animals
 - ▶ Schneider *et al*, 2005 – social play, social behaviour, self grooming – juvenile and adult

Chronic exposure of the pre- and postnatal brain to THC might impact brain development in at least two different ways:

1. Unwanted activation of CB₁ in neurons can be detrimental as it interferes with the time and space specific developmentally-ordered (i.e. endogenous) activation of CB₁
2. Down-regulating CB₁ expression (which occurs after prolonged activation of a receptor) will create a phenotype functionally similar to CB₁ knock-out

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Intractable Childhood Epilepsy



74 MILLION US CHILDREN

US CHILDREN WITH EPILEPSY

PREVALENCE OF 6.3/1000 DIAGNOSED¹

466,000

PHARMACORESISTANT EPILEPTICS²

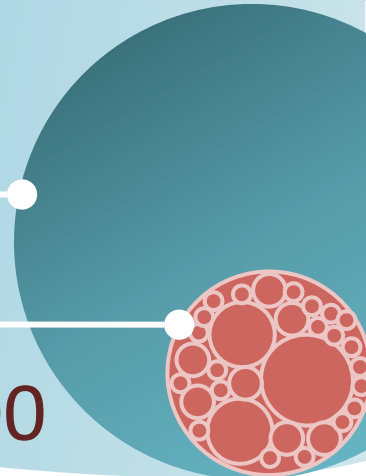
SEIZURES THAT PERSIST, DESPITE MULTIPLE AED TREATMENT³

20%

TARGET US POPULATION

REFRACTORY EPILEPSY COMPOSED OF CLUSTER OF ELECTROCLINICAL SYNDROMES

93,000



- Most syndromes have orphan sized populations
- Strategy is initially to target NDAs in Dravet and L-G syndromes
 - Severe infantile-onset, drug-resistant syndromes
- Expanded access IND patients include range of syndromes

DRAVET SYNDROME

UP TO 5% OF ALL CHILDHOOD EPILEPSIES IN THE FIRST YEAR OF LIFE⁴

5,440 US and **6,710 EU** patients

LENNOX-GASTAUT SYNDROME

3 TO 4% OF CHILDHOOD EPILEPSY⁵

14-18.5k US and **23-31k EU** patients

ADDITIONAL RELATED REFRACTORY EPILEPSIES²

- Intractable childhood epilepsy with generalized tonic-clonic seizures
 - Infantile seizures with variable foci
 - Doose syndrome
 - Infantile spasms

[1] Russ et al, 2012 [2] Wirrel 2013 [3] Picot et al, 2008
[4] Dravet et al, 2012 [5] Trevathan et al, 1997

“unadopted” by the pharmaceutical industry because it provides little financial incentive

- No single, widely accepted definition for rare diseases
- Affects Less than 200,000 in the US, less than 1 in 2000 in the EU
- 7000 known rare diseases
- 8% of population diagnosed with rare disease
- 85 to 90% are chronic, serious or life threatening
- Treatments are almost always unavailable

Orphan Drug Act (1983) promotes rare disease drug development

Why Orphan Indications?



R&D DRIVERS/INCENTIVES

Waived FDA fees

R&D Grants

Tax Credits

Financial

Development

Greater regulatory success

Lower approval hurdles

Shorter developments

Faster uptake

Longer exclusivity

Lower marketing costs

The Market

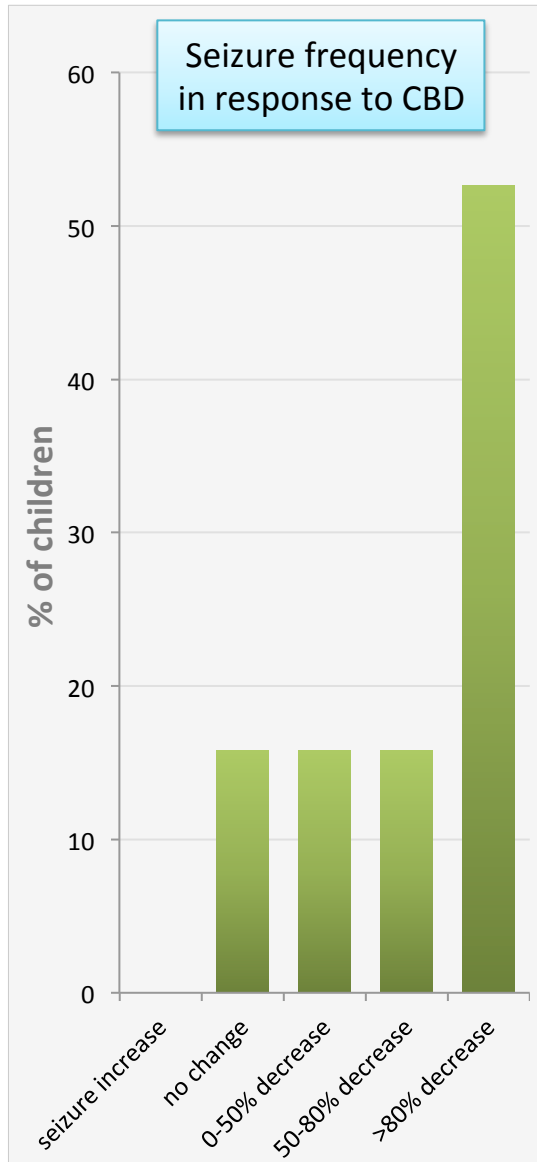
Returns

Premium pricing

Likely reimbursement

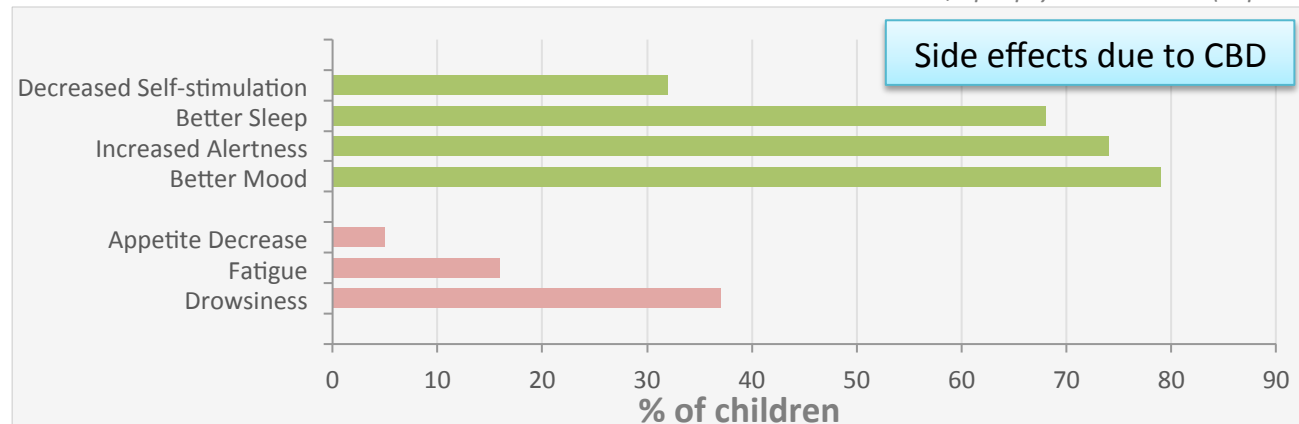
COMMERCIAL DRIVERS/INCENTIVES

CBD Survey in US Pediatric Epilepsy

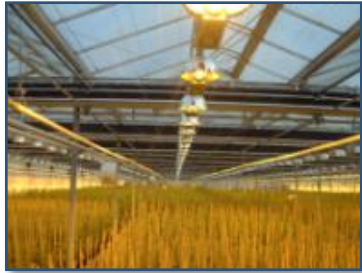


- **19 children** on CBD-enriched medical marijuana
 - ▶ 13x Dravet syndrome
 - ▶ 4x Doose syndrome
 - ▶ 1x Lennox-Gastaut syndrome
 - ▶ 1x idiopathic epilepsy
- 24 questions including: clinical factors; CBD effect on child's seizure frequency; side effects etc.
- **CBD reduced seizure frequency in majority of cases**
- **CBD had an excellent side effect profile**
 - ▶ better mood; increased alertness; better sleep; drowsiness
 - ▶ Common negative side effects often associated with other AEDs notably absent after CBD exposure

Jacobson and Porter, *Epilepsy Behav.* 2013 (in press)



Epidiolex Manufacturing Process



CBD BRM



Processing of plant material
into CBD extract



CO₂ Extraction



CBD BDS



Purification Process



Pure CBD



Bulk Solution Production



Filling, Capping & Labelling



Epidiolex



Epidiolex[®] Orphan Program Overview

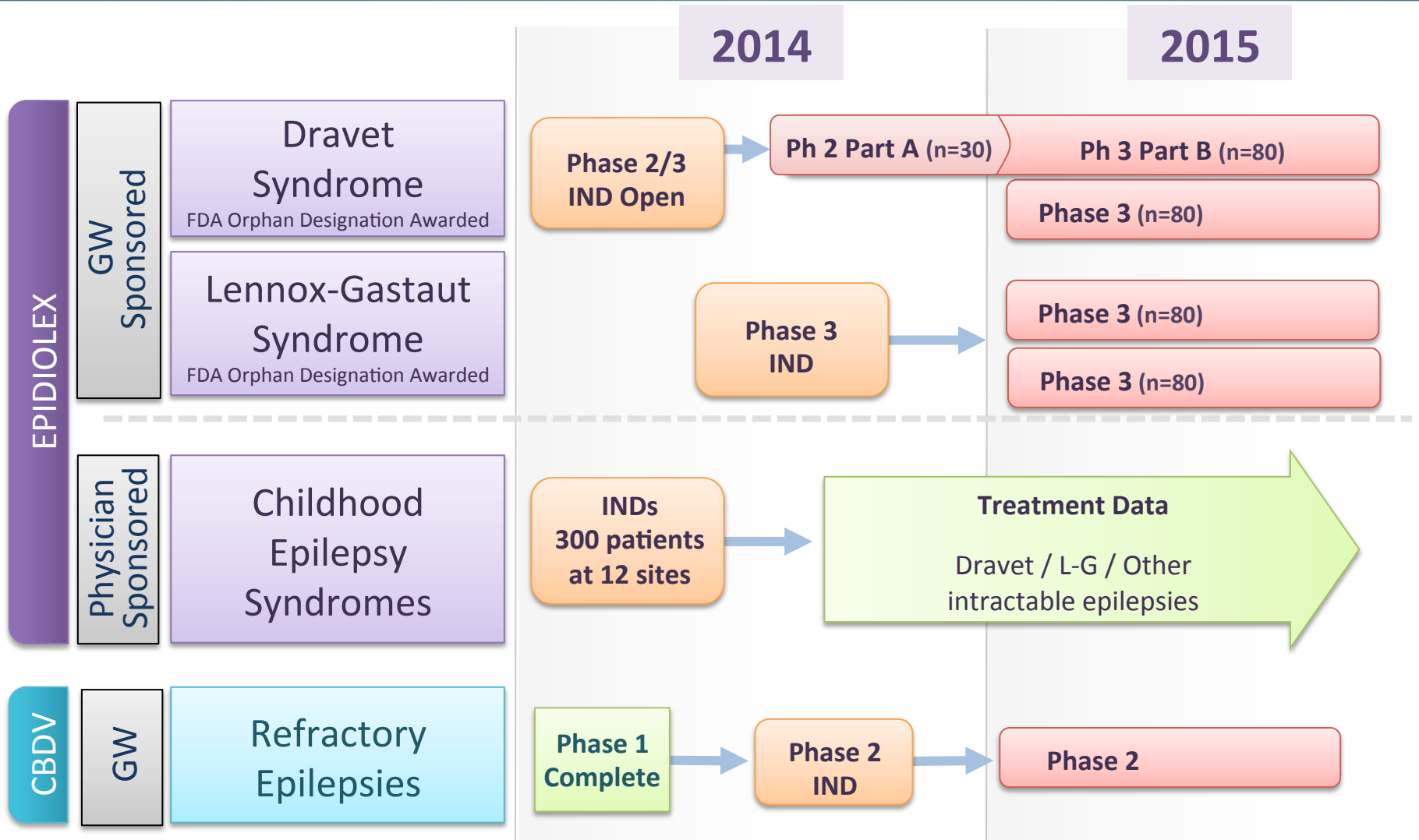


- 3 Individual INDs - Initial Patient treated by Dr Cilio
 - Programme started with Child S (late 2012)
- 12 FDA “expanded access” INDs
 - 300 patients at 12 U.S. sites suffering from range of pediatric epilepsy syndromes
 - Initial patients started treatment in January 2014 - data from mid-2014 onwards
 - FDA have extended one site from 25 patients to 60 patients
- 5 emergency INDs (e.g. FIRES)
- FDA orphan development program
 - Orphan designation granted in both Dravet and Lennox-Gastaut syndromes (LGS)
 - Company sponsored IND received May 2014, Phase 2/3 trial commences in H2
 - Phase 3 trials in both Dravet and LGS during 2015
- CBD is a Schedule I substance under federal Controlled Substances Act
 - Regardless of whether it is derived from “hemp” or other higher THC strain
 - DEA registration (licence) and state controlled drug licenses obtained

What is needed for artisanal preparation use in clinical research?

- Sufficient pharmacological evidence
 - ▶ Support proposition and indication requested by the IND
 - ▶ Safety pharmacology
- *(Sufficient pharmacokinetic evidence) – not necessary, only helpful*
 - ▶ *(Absorption, distribution, metabolism, excretion, drug interactions etc)*
- Sufficient toxicology data
 - ▶ To show safety at doses and study duration proposed
- Clinical summaries
 - ▶ Abuse-liability studies
- Well controlled investigational product, manufactured under GMP
 - ▶ Well controlled growing conditions to produce a consistent product
 - ▶ A team of scientists able to prove a consistent product suitable for use in clinical trials with appropriate analytical techniques, agreed by the FDA

GW Epilepsy Program – Expected Next Steps



GW expects to apply to FDA for breakthrough designation and seek to minimize timelines for initial orphan NDA

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Typical (sequential) Steps Required for CBD Research in the U.S.

1 Submission of IND to FDA, including all preclinical safety and chemistry, manufacturing and control (CMC) data

2 Receipt of IND number from FDA

3 Submission to institutional review board (IRB)

4 Application to state controlled drugs agency for a Schedule I license

5 Application to DEA headquarters (HQ) for Schedule I research registration

6 Inspection and subsequent approval by state controlled drugs agency

7 Inspection by DEA field office; report written and sent to DEA HQ

8 IRB approval

9 Issuance of state license

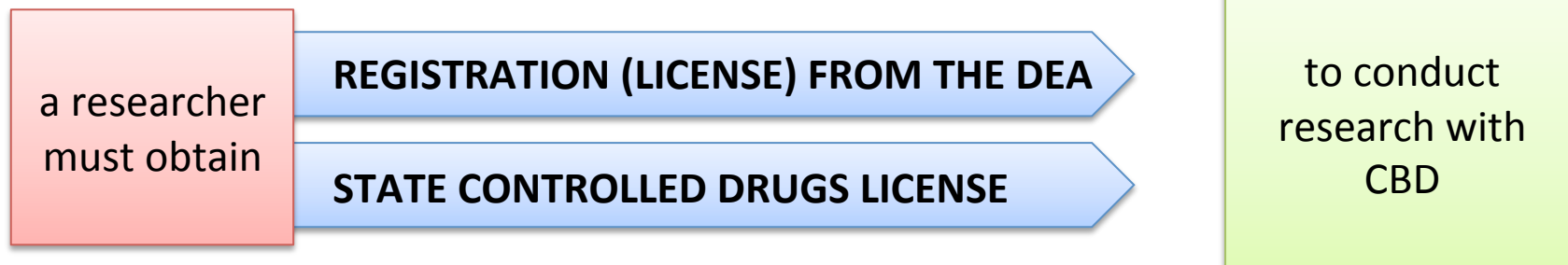
10 Issuance of DEA research registration

The system works
but time consuming

Legal Status of CBD in the U.S.



- CBD = natural component of cannabis/marijuana plant = **Schedule I** substance under the federal Controlled Substances Act (CSA)
 - ▶ regardless whether it is derived from “hemp” or other higher THC strain
- Most states also have their own version of the CSA, and CBD is in Schedule I under **all state laws**



- ▶ Often, both agencies will inspect site
 - ▶ In some cases, a safe must be installed
 - ▶ Entire process can take 4-6 months +
- The existence (or absence) of a state “medical marijuana” law, and its provisions, are irrelevant to the need for DEA and FDA approval
 - ▶ unclear whether they would facilitate obtaining a state license

What About Hemp?



- The Controlled Substances Act does not define hemp
 - ▶ merely exempts all marijuana stalk, fiber, seeds and oil/cake made from seeds
 - ▶ **Hemp seeds (and therefore hemp seed oil) contain no cannabinoids**
 - ▶ **This exemption does not include hemp flowers**
- **However**, if CBD or any other cannabinoids are extracted from the stalk, fiber and seeds, those cannabinoids (“resin”) are in **Schedule I**
 - ▶ Particularly true if the cannabinoids are extracted from the hemp flowers
 - ▶ Schedule I substance can be used only for FDA- and DEA-approved research under an IND; it **cannot lawfully be sold commercially**
- Agricultural Act of 2014 (farm bill) authorizes institutions and State departments to grow industrial hemp for research purposes:
 - ▶ **Only if** state law permits the growth and cultivation of the plant
 - ▶ Industrial hemp defined as no more than **0.3% THC** on a dry weight basis
 - ▶ “Research purposes” is not defined but would still **require approval/licensure**

Summary

- Sativex validated our cannabinoid platform and approach to development meeting same rigorous standards of modern pharmaceuticals (regulatory, manufacturing and clinical)
- Cannabinoids have proven their utility as a treatment for seizure
 - ▶ Extensive CBD preclinical, clinical and safety data already in place
 - ▶ Along the way we have found THC to have deleterious effects
 - ▶ Other cannabinoids present in the extract have different pharmacologies; some of which may be good and some of which may be bad
- Orphan drug development programme in epilepsy underway
- All GW research is conducted in accordance with all local/global laws

- Stalk, stem, oil/cake from seeds (and non-cannabinoid preparations made from them) and sterilized seeds = not controlled, may be imported to U.S.
 - ▶ Opinion of our ex-DEA consultants, that when CBD is extracted from any part of the plant, it is considered “resin” that is an exception to the exception of the Controlled Substances Act – i.e. establishes an **“exception to the exception”**
 - ▶ Note: exempted plant material containing tiny amounts of THC are allowed so long as they are not used or intended for use by human consumption
- Therefore extracted CBD (even if diluted with hemp oil) imported into the U.S. need to be licensed as a Schedule I importer by DEA
 - ▶ It is very rare for DEA to license the importation of a Schedule I product for commercial (rather than research) purposes
- If intended to be used for human consumption, FDA inspectors at the port of entry would need to sign off on it
- Once in the U.S., a Schedule I substance can be used only for FDA- and DEA-approved research under an IND; it cannot lawfully be sold commercially