December 8th, 2022

Control and Characterisation of Botanically Derived Cannabis Drugs

The GW Experience

Jazz Pharmaceuticals

AGENDA

Manufacture & Control

Specifications

Complex Botanical Characterisation

Semi-synthetics (isolates)

Synthetic CBD

Epidiolex Manufacturing Process Steps

Growing

Drying & Baling

Pelleting

Milling

Decarboxylation

Extraction

Winterisation

Evaporation

Crystallisation/API

Bulk & Filling/DP

Labelling DP

DP Packaging

Control of Extracts and Intermediates - Testing Points for Epidiolex

Low spec glass growing

Large scale manual harvesting

Pre-Milled BRM – Macroscopic & Microscopic ID, Foreign Matter, Assay, Appearance

Direct drying

Baling

Baled BRM – Assay, Appearance, ID, Loss on Drying

Pelleting

Pelleted BRM - Assay, Appearance, ID, Loss on Drying

Milled Pellets – Assay, Appearance, ID

Decarboxylation

Decarboxylated BRM – Assay, Appearance, ID, decarb efficiency

Extraction

Extract and Spent BRM – Assay, Appearance, ID, extraction efficiency

Winterisation

Refined Extract – Assay, Appearance, ID, Alkanes, Residual ethanol

Crystallisation

CBD API – Comprehensive Specification for assay and impurities

DP Manf/Pack

Finished Product – Comprehensive Specification for assay and impurities

Specifications – Semi-Synthetic v Botanical

Epidiolex CBD API Specification

	Test	Specification
1.	Appearance	White to pale yellow crystals
2.	Identification A: UPLC-UV	Retention time of major peak corresponds to that of certified CBD Reference Standard
3.	Identification B: FT-IR	Conforms to reference spectrum for certified CBD Reference Standard
4.	Identification C: Specific Optical Rotation	-121° to -132° (in ethanol)
5.	CBD Content	98.0-102.0% w/w
6.	Impurities (Other Cannabinoids):	
	- CBDV	NMT 1.0% w/w
	- CBD-C4	NMT 0.5% w/w
	- CBD-C1	NMT 0.15% w/w
	- Δ^9-THC	NMT 0.1% w/w
	- Individual unspecified impurities	NMT 0.1% w/w
	- Total unspecified impurities	NMT 0.5% w/w
7.	Residual Solvents:	
	- Heptane	NMT 0.5% w/w
	- Ethanol	NMT 0.5% w/w
8.	Residual Water	NMT 0.3% w/w
9.	Residue on Ignition	NMT 0.2% w/w

Nabiximols CBD BDS IND Specification*

	Test	Specification
1.	Appearance	Brown viscous semi-solid
2.	Identification A: TLC	Spots have characteristic Rt and colours, compared with CBD standard
3.	Identification B: HPLC	Positive for CBD
4.	CBD Content	60-72% w/w
5.	Total Cannabinoids	68-84% w/w
6.	Other Cannabinoids:	
	-CBD RS 0. 35	NMT 0.2% w/w
	-CBDV	0.8-1.2% w/w
	-CBDA	NMT 0.8% w/w
	-CBG	0.6 -1.7% w/w
	-CBN	NMT 0.1% w/w
	-THC	2.1-3.1% w/w
	-CBC	2.8-3.8% w/w
	-Unspecified Cannabinoids	NMT 3.1% w/w
7.	Residual Solvents: - Ethanol	NMT 3% w/w
8.	Total Aflatoxins (B_1, B_2, G_1 & G_2)	NMT 4 µg/kg
	Aflatoxin B_1	NMT 2 µg/kg
9.	Microbial Quality:	
	- Total Aerobic Microbial Count (TAMC)	NMT10^4 CFU/g
	- Total combined Yeasts/Moulds Count (TYMC)	NMT10^2 CFU/g
	- Bile tolerant gram -ve rods	NMT10^2 CFU/g
	- Salmonella	Absent in 10g
	- Escherichia coli	Absent in 1g
	- Staphylococcus aureus	Absent in 1g
10.	Elemental Impurities:	
	Cadmium	NMT 100ppm
	Lead	NMT 100ppm
	Arsenic	NMT 30ppm
	Mercury	NMT 300ppm
	Cobalt	NMT 1000ppm
	Nickel	NMT 4000ppm
	Vanadium	NMT 2000ppm

*Partial Specification – Non-Cannabinoids not included

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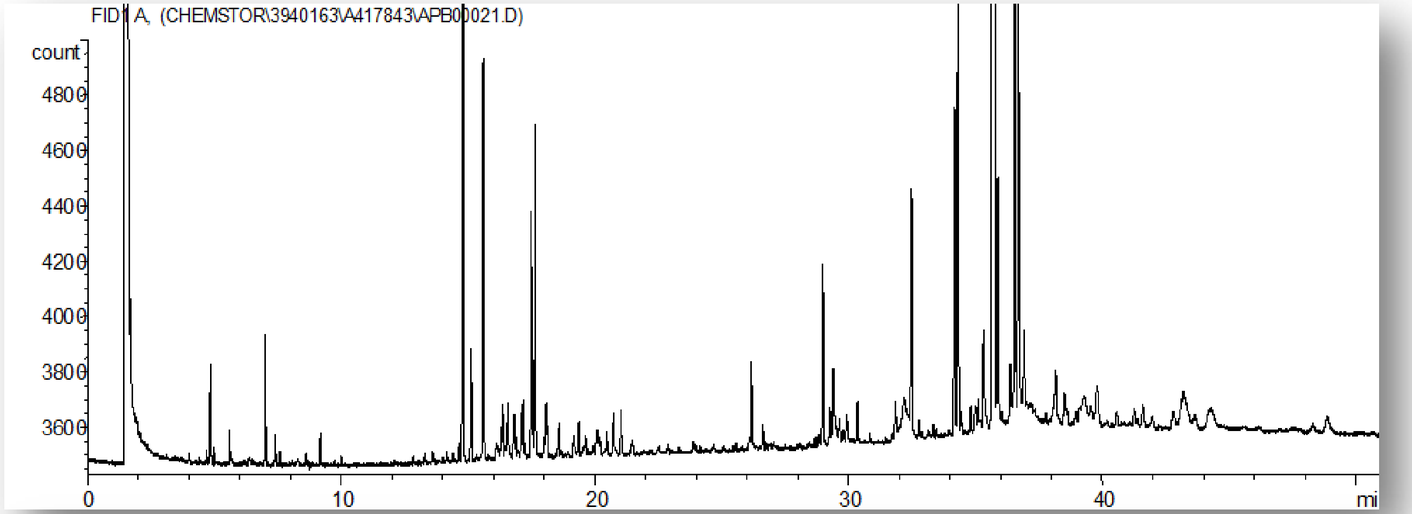
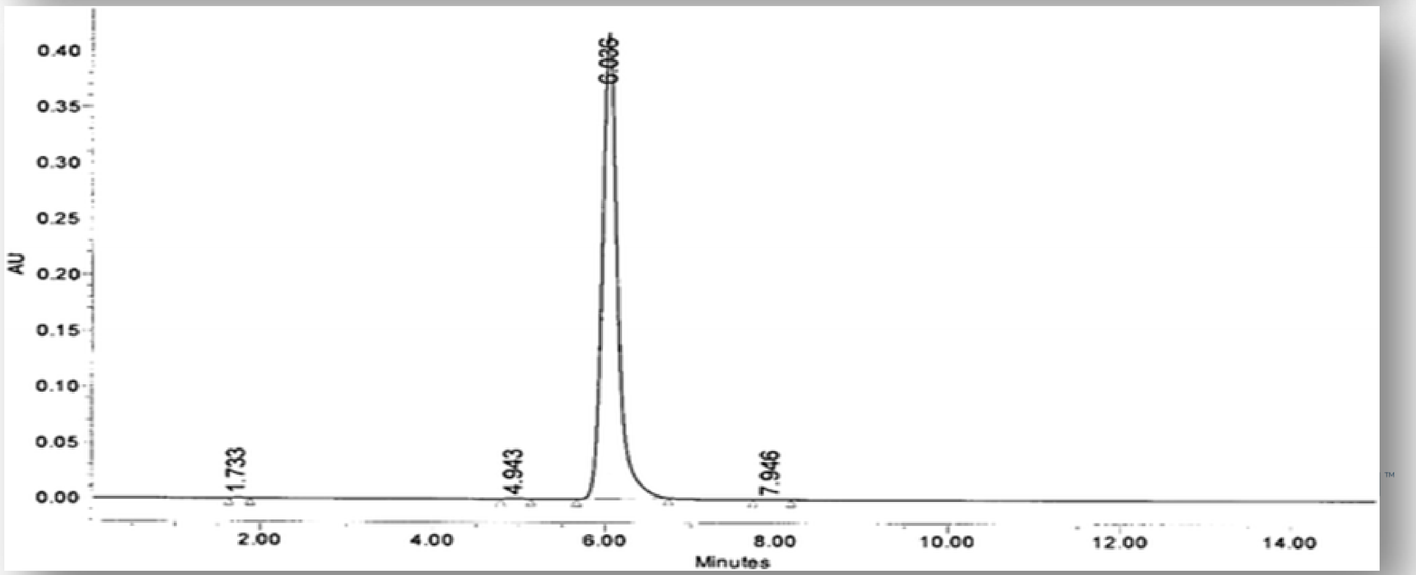
FDA comments….on Characterisation of Botanical Extracts

- Sativex
  - Produced from 2 Botanical Drug Substances - Originally 5 THC and 4 CBD Genotypes
  - EU/RotW - Specification based on cannabinoids, Some characterisation data on non-cannabinoids provided with submission
  - FDA EOP2 meeting in 2010 – Different approach - Hold on phase 3.
- *"provide total amounts of each class of non-cannabinoid compounds, as needed, for mass balance calculations."*
- *"…a minimum of **90%** of the components of the drug substances should be monitored as either individual amounts or total fractions."*
- *"The proposed tests…in the BDS specification are insufficient to assure the quality and safety of each lot. You **must include chromatographic fingerprint data and chemometric peak analyses for each major chemical class of the components of the BDS**, including both cannabinoids and non-cannabinoid fractions. The fingerprint data are crucial to ensuring that minor components of the cannabinoid and other fractions, which may present safety and other concerns, are consistent from batch to batch. Your must expand your multivariate analysis to include non-cannabinoid and additional minor cannabinoid components, as appropriate."*
- *FDA also wanted evidence of similarity between pre-clinical, clinical and commercial BDSs.*

Challenges for Botanical Extracts

- Botanicals
  - Comparatively low Principal content
  - Complex – typically hundreds of components
    - Other cannabinoids
    - Plant compound classes
  - Medicine is the whole extract
    - Impurities only non-plant derived
      - Pesticides, aflatoxins, micro, heavy metals
  - Mass Balance/Characterisation
    - Quantitative assessment
    - FDA demand for >90% w/w
  - Fingerprinting
    - Qualitative assessment





Characterisation – Initial Response

Compound Classes

- Methods in place for many non-cannabinoids
  - Terpenes
  - Triglycerides
  - Sterols/Triterpenes and Fat Soluble Vitamins
  - Carotenoids
- New methods developed
  - Free fatty acids
  - Cannabinoid Esters/Ethers (new class of compounds)
  - Total polar fraction
- Class Totals approach applied for mass balance

Process

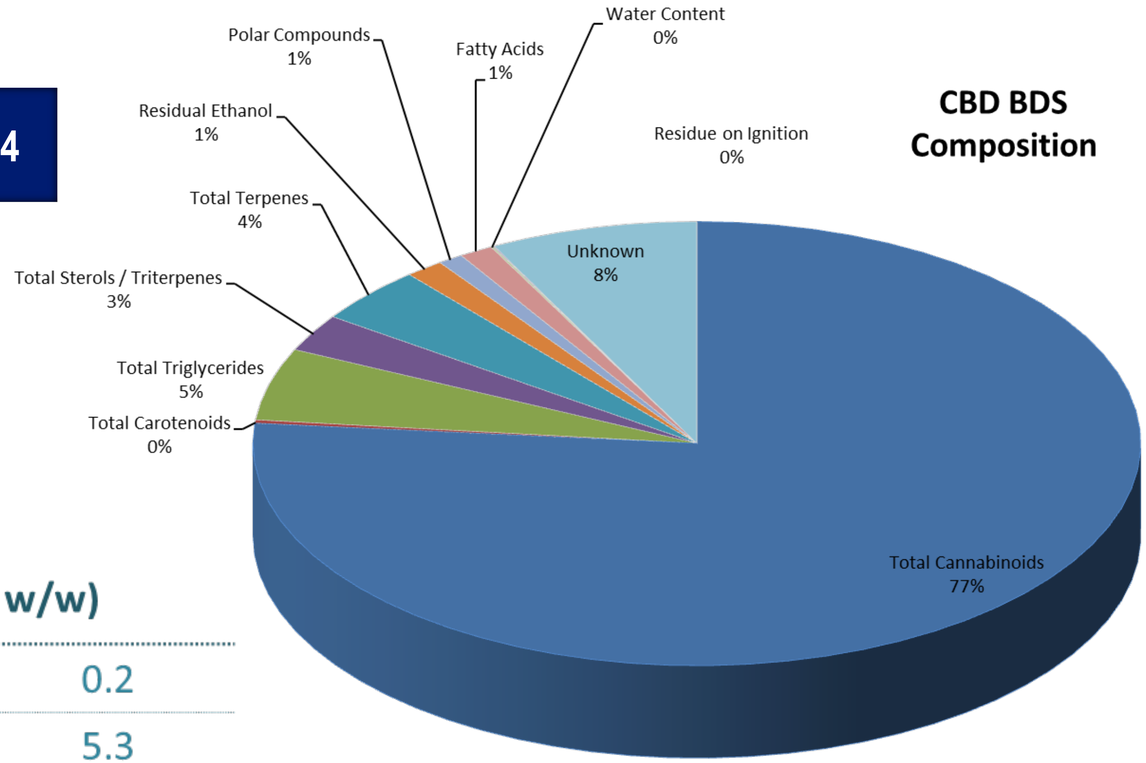
- BDS very stable at -20°C – retained samples available
- Comprehensive analytical program
  - 73 batches of THC BDS
  - 79 batches of CBD BDS
- Every year from 2004 to 2012 including…
  - Pre-clinical tox
  - Phase 2 clinical trial
  - Phase 3 clinical trial
  - Commercial
  - High and low cannabinoid content
  - Selected extreme non-cannabinoid

Characterisation – CBD BDS (n=79)

Cannabinoids (% w/w)

CBD	65.83
THC	2.53
CBDA	0.29
CBG	1.07
CBC	3.24
CBDV	0.89
CBN	0.07
Cis-THC	0.72
CBD RS 0.35	0.08
Others	1.73
Total	**76.4**

Total characterised 92.4



Non-cannabinoids (% w/w)

Carotenoids	0.2
Triglycerides	5.3
Sterols	2.7
Terpenes	4.1
Residual ethanol	1.4
Polar fraction	0.9
Free fatty acids	1.2
Total	**16.0**

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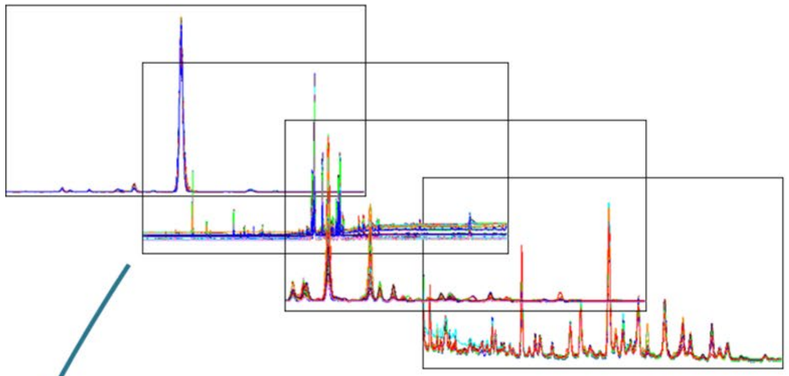
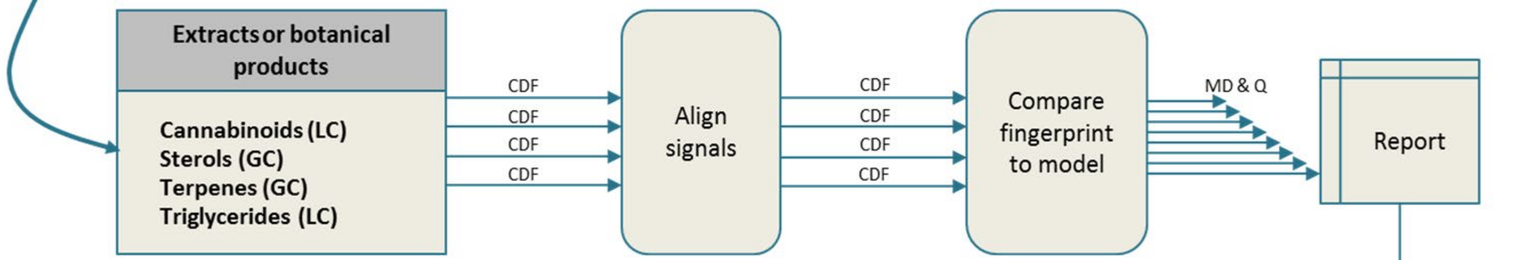
Qualitative Fingerprinting for QC Analysis



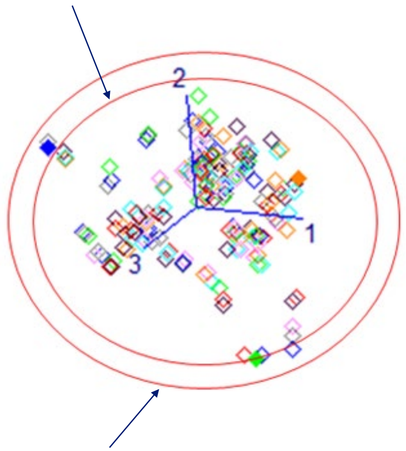
- PCA Model Comparison
  - 4 Separate Assays
  - Peak Markers
  - 2 Outlier Diagnostics
  - Primary & Secondary Scores



- Verified ID test with power to distinguish…
  - Chemotypes (CBG, CBDV, THCV)
  - Genotypes (Epidiolex CBD)
  - Contamination
  - Stability (aged degraded samples)
  - Process Change
  - Counterfeit samples

GC, gas chromatography; LC, liquid chromatography; QC, quality control

Warning limit (95% confidence interval)



Failure limit (99% confidence interval)

Fundamental Design Point…

Models must satisfy the Goldilocks criteria

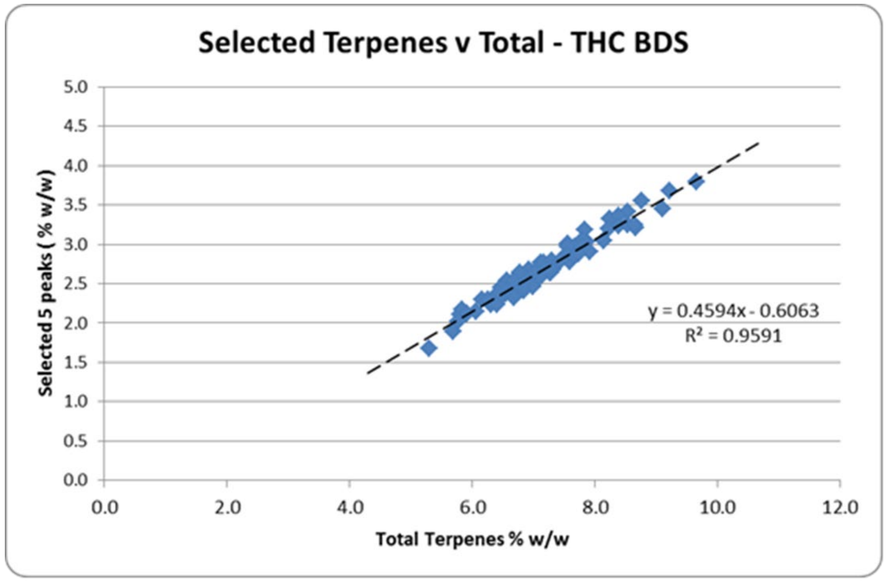
Not too sensitive, not insensitive but "just right"

Build expected variation into the models

Proposed Non-Cannabinoid Specifications (US)

Test	CBD BDS
Total Terpenes	2.8 – 5.4% w/w
Beta-Myrcene	NMT 0.7% w/w
Trans-Caryophyllene	0.7 – 1.7% w/w
Alpha-Caryophyllene	0.2 - 0.5% w/w
Trans-Nerolidol	0.1 – 0.4% w/w
Phytol	NMT 0.6% w/w
Total Sterols/Triterpenes/Vitamins	1.2 – 4.4% w/w
Squalene	NMT 0.4% w/w
Alpha-Tocopherol	0.1 – 0.7% w/w
Beta-Sitosterol	0.2 – 1.0% w/w
Total Carotenoids	NMT 0.5% w/w
Trans-Beta-Carotene	NMT 0.3% w/w
Total Triglycerides	2.0 – 8.5% w/w
LnLnL	NMT 1.5% w/w
Total Fatty Acids	0.8 – 1.7% w/w
Total Polar Fraction	0.5 – 1.3% w/w

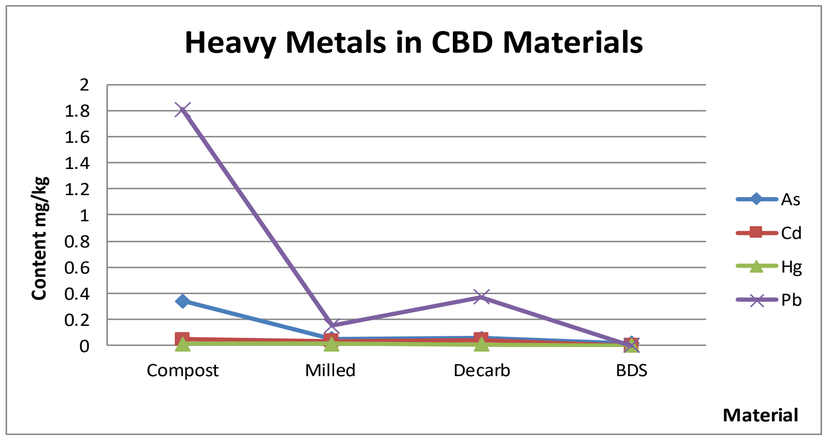
- Representative compounds from specific compound classes plus class totals
- Impossible to get standards for all compounds - content determined using representative peaks
- Possible to simplify by showing linear relationship between subset of compounds and total

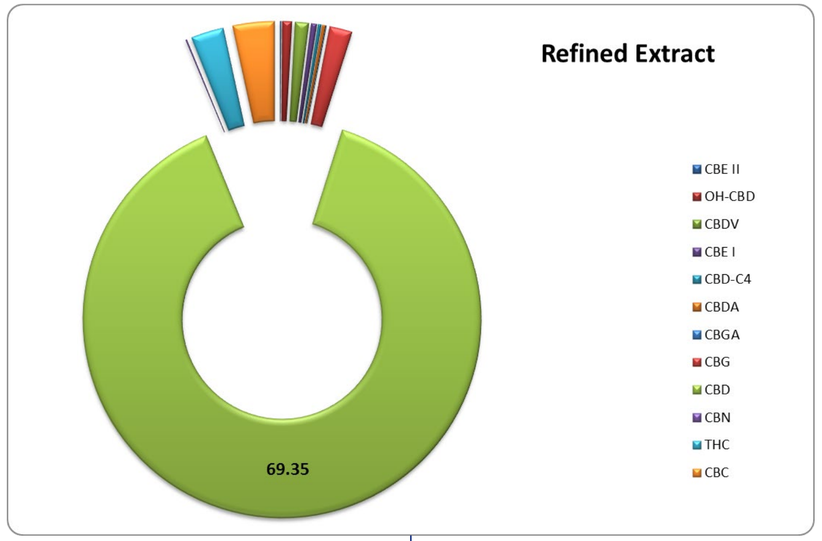


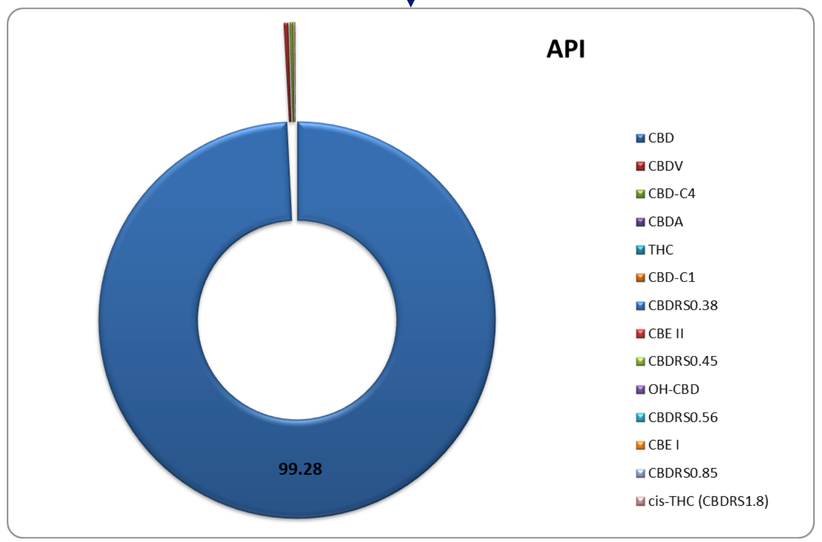
Semi-synthetics (Isolates)

- Much simpler than complex botanicals – but principles similar
- Understand fate/purge of compounds through processing
- Characterise what remains in the isolate – cannabinoids and non-cannabinoids
- Contaminants e.g. elemental impurities also tracked through the process
  - Risk assessments performed (ICH Q3D)
  - Confirmed absence in API by analysis of commercial batches
  - Same concept applied to residual solvents, aflatoxins, micro etc

Compound	% purged
beta-Myrcene	100.0
trans-Caryophyllene	100.0
trans-Nerolidol	100.0
Phytol	100.0
Squalene	100.0
LLL	99.5
PPP	100.0
Stigmasterol	100.0
alpha-Tocopherol	99.8
Nonacosane	100.0
Total Alkanes	99.8
Palmitic Acid	89.8
beta-Carotene	100.0





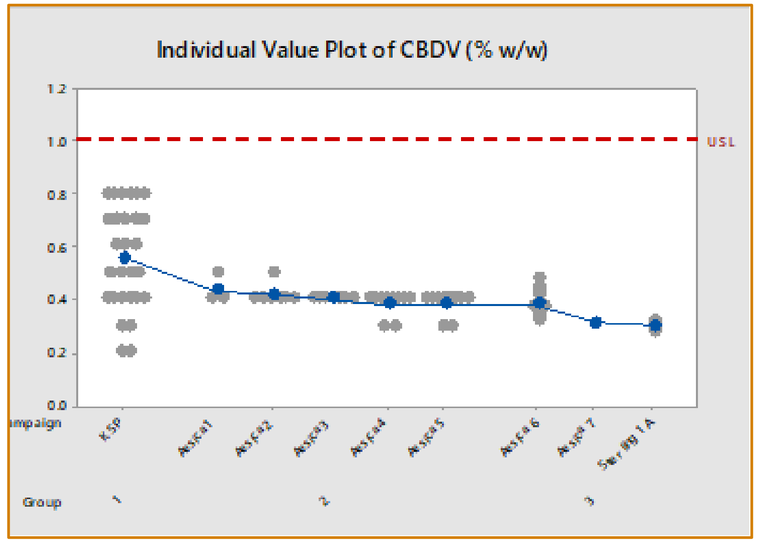


Elemental Impurities in Isolate

Element		ICH Q3D Class	Reporting Limit (mcg/kg)*	Mean Results (mcg/kg)						Permitted Oral Conc. (mcg/kg)**	Permitted Parenteral Conc. (mcg/kg)**	Pass
				800299030	800300060	800300070	6066919	6066920	6067091			
Cadmium	Cd	1	10	ND	ND	ND	ND	ND	0.32	500	200	Yes
Lead	Pb	1	10	5.75	2.90	5.90	29.65	4.65	5.45	500	500	Yes
Arsenic	As	1	10	23.50	14.50	12.10	4.80	6.45	3.38	1500	1500	Yes
Mercury	Hg	1	10	0.54	0.25	1.35	ND	0.01	ND	3000	300	Yes
Cobalt	Co	2A	100	ND	ND	ND	ND	ND	ND	5000	500	Yes
Vanadium	V	2A	100	ND	ND	0.08	0.46	0.01	1.13	10000	1000	Yes
Nickel	Ni	2A	100	40.00	70.50	10.60	1.98	28.95	20.50	20000	2000	Yes
Thallium	Tl	2B	100	ND	ND	ND	ND	ND	ND	800	800	Yes
Gold	Au	2B	10	2.35	1.60	1.75	2.05	1.32	0.60	10000	10000	Yes
Palladium	Pd	2B	100	0.33	0.21	ND	ND	ND	ND	10000	1000	Yes
Iridium	Ir	2B	100	1.05	0.70	0.53	0.60	0.47	0.52	10000	1000	Yes
Osmium	Os	2B	100	1.50	1.07	1.45	1.21	0.73	1.09	10000	1000	Yes
Rhodium	Rh	2B	100	0.15	ND	ND	ND	ND	ND	10000	1000	Yes
Ruthenium	Ru	2B	100	ND	ND	ND	0.05	0.11	0.11	10000	1000	Yes
Selenium	Se	2B	100	ND	1.91	2.75	0.65	1.40	2.05	15000	8000	Yes
Silver	Ag	2B	100	1.52	0.45	0.47	2.66	1.38	0.81	15000	1000	Yes
Platinum	Pt	2B	100	0.02	0.23	ND	0.12	0.11	0.17	10000	1000	Yes
Lithium	Li	3	100	1.90	1.30	2.81	1.40	1.20	1.75	55000	25000	Yes
Antimony	Sb	3	100	0.72	1.10	0.75	2.10	0.95	3.10	120000	9000	Yes
Barium	Ba	3	100	7.00	0.60	ND	0.43	1.25	0.75	140000	70000	Yes
Molybdenum	Mo	3	100	ND	15.50	ND	101.70	60.00	3.00	300000	150000	Yes
Copper	Cu	3	100	19.90	25.50	46.50	259.00	22.00	58.00	300000	30000	Yes
Tin	Sn	3	100	73.50	8.00	135.50	21.50	134.50	8.25	600000	60000	Yes
Chromium	Cr	3	100	36.00	28.00	39.50	16.95	44.00	37.50	1100000	110000	Yes

Synthetic CBD

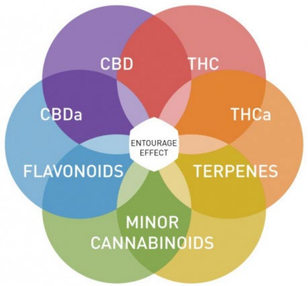
- Epidiolex is botanically derived
  - Has an impurity* profile indicative of plant origins (e.g. CBD homologues)
- Proposed USP monograph for botanically derived CBD has controls around synthetic intermediates
  - Limitations - there are multiple synthetic routes to CBD
  - Methods need to be developed to detect them all
  - New routes could be developed with different intermediates
- Batch data from a decade of production of CBD API
  - CBDV and CBD-C4 always present
  - always between a range of values that can be defined by 3xsd around the mean
- If presence of CBDV, CBD-C4 is required to confirm botanical origin
  - No need to test for synthetic intermediates
- Does anyone produce CBD isolate by a method that removes all other cannabinoids?



* Personally, I don't like calling the natural compounds impurities! They are botanically derived related substances.

Final Considerations for Botanically Derived Cannabis Drugs

- Three main elements for drug products
  - Quality, Safety, Efficacy
  - Clinical Trials are expensive – efficacy can be difficult to demonstrate, patients often have an expectation of success based on anecdotal evidence
  - But for any product aimed at people with a medical condition, Quality and Safety should be fundamental.
- Structural Alerts
  - Identified components above specific thresholds as defined in ICH Q3A should be evaluated by structural alerts software e.g. DEREK for Windows, Leadscope
    - Toxicology risk assessment required
    - For Sativex we screened over 100 compounds through both packages
- Understand your product
  - If you claim full or broad spectrum and want to make favorable claims about the entourage effect, about terpenes or flavonoids then you need to…
    - Know the concentration ranges for those components from genotype to genotype, batch to batch, season to season, year to year, facility to facility etc
    - Know what affects levels in your manufacturing process
    - Know what the stability is of those components over the likely storage times for API and/or in-use times for product
    - Know if there is interaction with excipients in finished products
    - Are there extractables and leachables concerns with packaging?
  - Use the guidelines for impurities (USP/Ph.Eur/ICH)
    - Risk assess you process, and test appropriately based on those assessments



ENTOURAGE EFFECT

Thank You