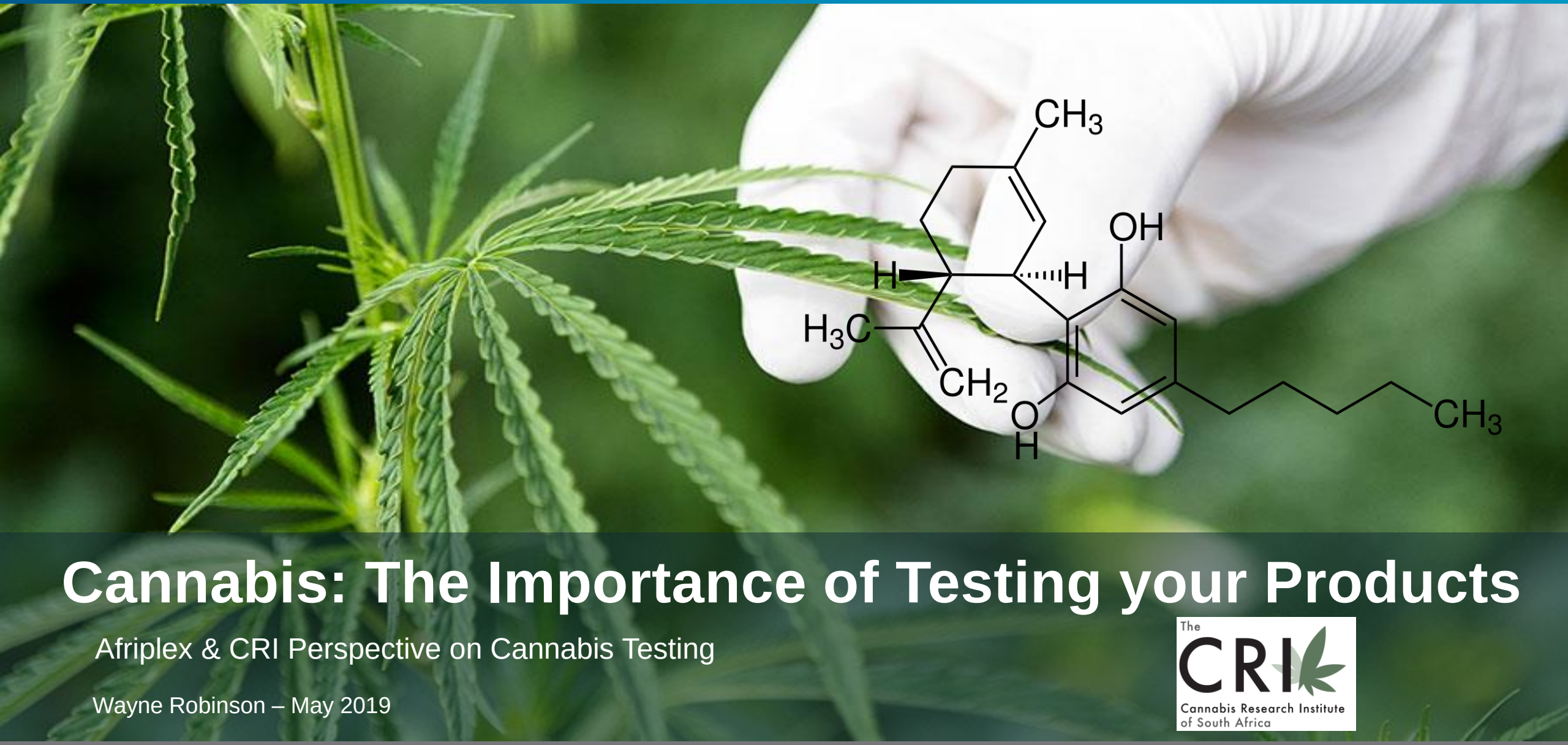


Cannabis: The Importance of Testing your Products

Afriplex & CRI Perspective on Cannabis Testing

Wayne Robinson – May 2019

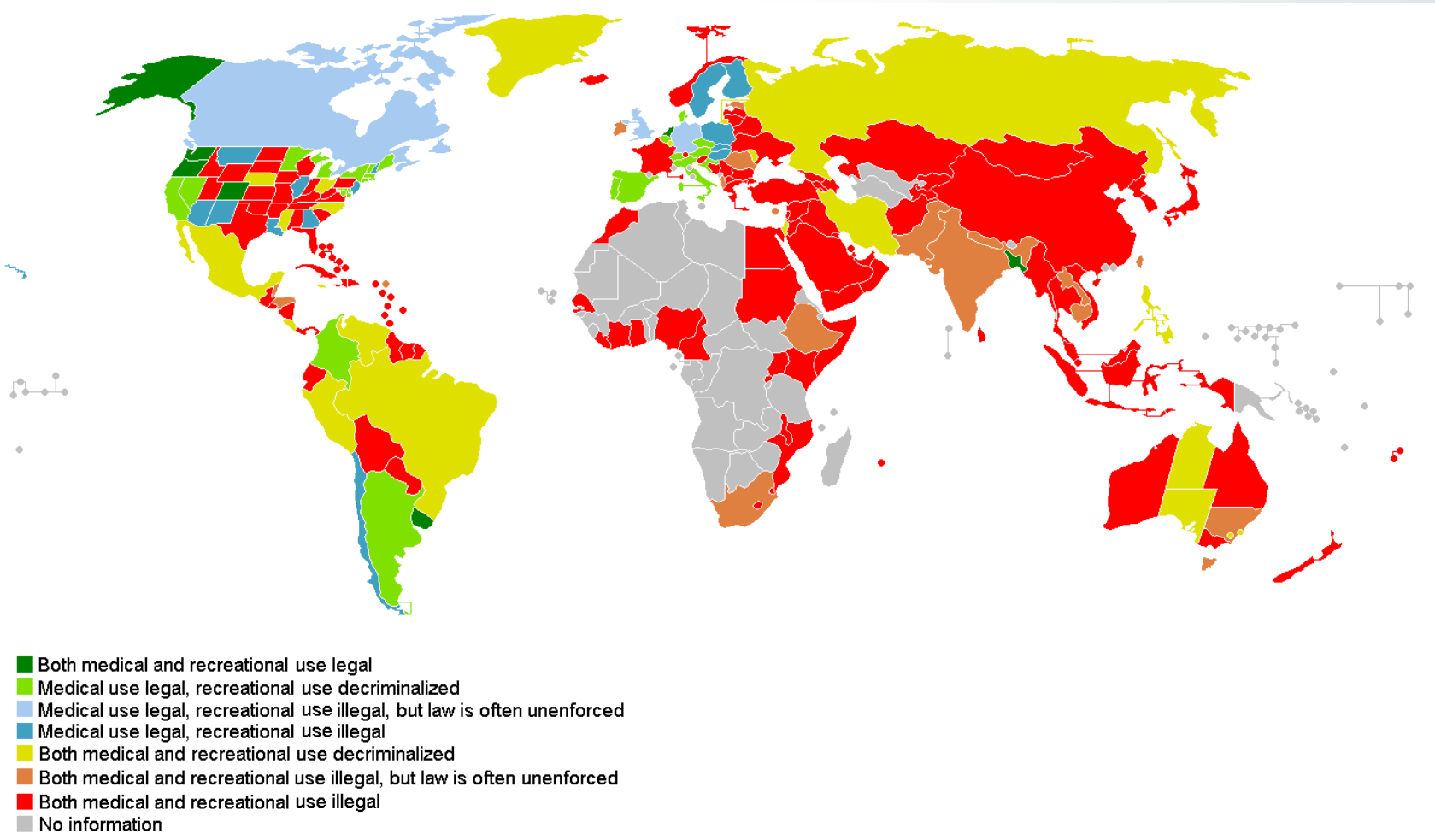
Origins in South Africa

- **dagga** (Afrikaans pronunciation: [/ˈdaχa/]) is commonly used for cannabis; it derives from the Khoikhoi word dacha or dachab in 17th century.

Legislation - Global

Legislation

Global



Legislation - South Africa

Legal status of CANNABIS

Legislation

- The **Medicines and Related Substances Act**

- South Africa is a signatory to various international conventions :-
  - (United Nations Office on Drugs and Crime (**UNODC**)
  - International Narcotics Control Board (**INCB**)
  - United Nations **Single Convention** on Narcotic Drugs (1961)

- SAHPRA – control of Medical Cannabis
- Cannabis is classified as a **Schedule 7** substance in South Africa

» Cannabis is NOT Legal in SA, in ANY Form, yet «

Legal status of CANNABIS

Legislation

- The **Drugs And Drug Trafficking Act. NO. 140 OF 1992:**

Cannabis is listed under "Undesirable Dependence-Producing Substances" and states that "Cannabis (Dagga) (S7), the whole plant or any portion thereof, except dronabinol (S6), is illegal'**.**

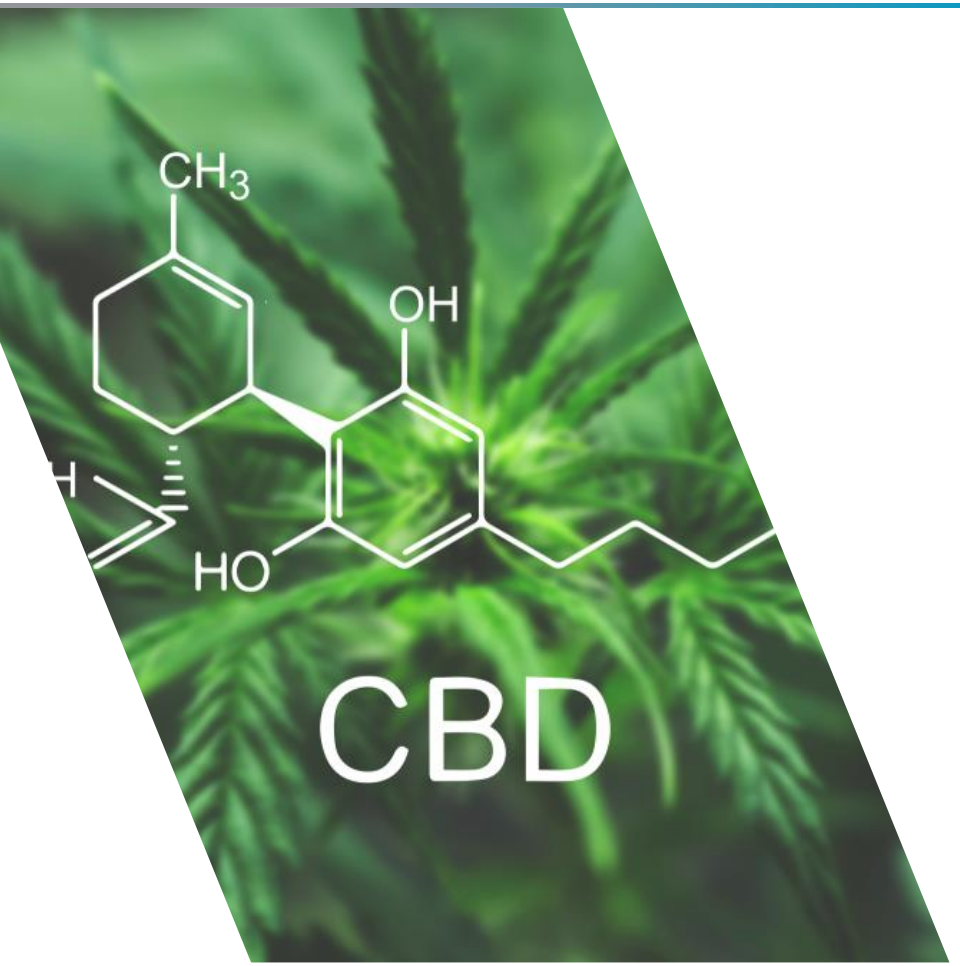
"Dagga still illegal in SA" – SAPS

- The **legislative framework**:
  - **Authorisation of Cannabis cultivation**
  - **The Single Convention**
  - **Aligning** the access of Cannabis-containing products for medicinal purposes with that of other **controlled medicines**
- Under this Act, medical practitioners can apply to the Council for **permission to access and prescribe unregistered medicines**

Cannabis Legislation is still pending

Legal status of CANNABIS

Legislation



Communication to industry *Scheduling matters*

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

SCHEDULING MATTERS
RESCHEDULING OF CANNABIDIOL

TO ALL APPLICANTS

Kindly be advised that at a recent meeting of the Medicines Control Council, Council resolved to down-schedule cannabidiol from Schedule 6 to Schedule 4.

Words in **[bold and in square brackets]** indicate omission from a Schedule.

Words underlined with a solid line indicate insertions in a Schedule.

Schedule 4

Cannabidiol.

Schedule 6

[Cannabidiol, when intended for therapeutic purposes.]

Further be advised that cannabidiol is excluded from Schedule 4 to the Medicines and Related Substances Act, 1965 (Act 101 of 1965), when specifically packed, labelled, sold and used for –

(i) industrial purposes **including** the manufacture or compounding of consumer items or products which have no pharmacological action or medicinal purpose; and

(ii) analytical laboratory purposes.

Kindly note that the office of the Registrar is in the process of drafting an amendment to the published Schedules, for consideration by the Minister of Health and publication in the Government *Gazette*.

DR JC GOUWS
REGISTRAR OF MEDICINES

9.99_Rescheduling_cannabidiol_Jul17_v2 *August 2017* Page 1 of 1

The down-scheduling cannabis-oil (CBD) from Schedule 6 to Schedule 4 (9.99_Rescheduling_cannabidiol_Jul17_v2)

Cultivation of cannabis for medicinal use

Guidelines

- **MCC Guideline -**
  - CULTIVATION OF CANNABIS AND MANUFACTURE OF CANNABIS-RELATED PHARMACEUTICAL PRODUCTS FOR MEDICINAL AND RESEARCH PURPOSES (2.44_Cannabis_growth_Feb2017_v1_for_comment.doc March 2017)

- **APPLICATIONS FOR CULTIVATION OF CANNABIS FOR MEDICINAL PURPOSES published -** 2.44_Cannabis_cultivation_Sept17_v2.doc November 2017

Cultivation of Cannabis

Cultivation of cannabis for medicinal use

Guidelines

- **An applicant** may apply to the MCC for a licence in terms of the provisions of Section 22C(1)(b) of the Medicines Act for any or all of the following activities:
- **Cultivate/grow** and produce Cannabis and Cannabis resin**;**
- **Extract and test** Cannabis, Cannabis resin and/or cannabinoids**;**
- **Manufacture** a Cannabis-containing or cannabinoid-containing medicine;
- **Import** a Cannabis-containing medicine;
- **Export** a Cannabis-containing medicine;
- **Distribute** a Cannabis-containing medicine.

Cultivation of Cannabis

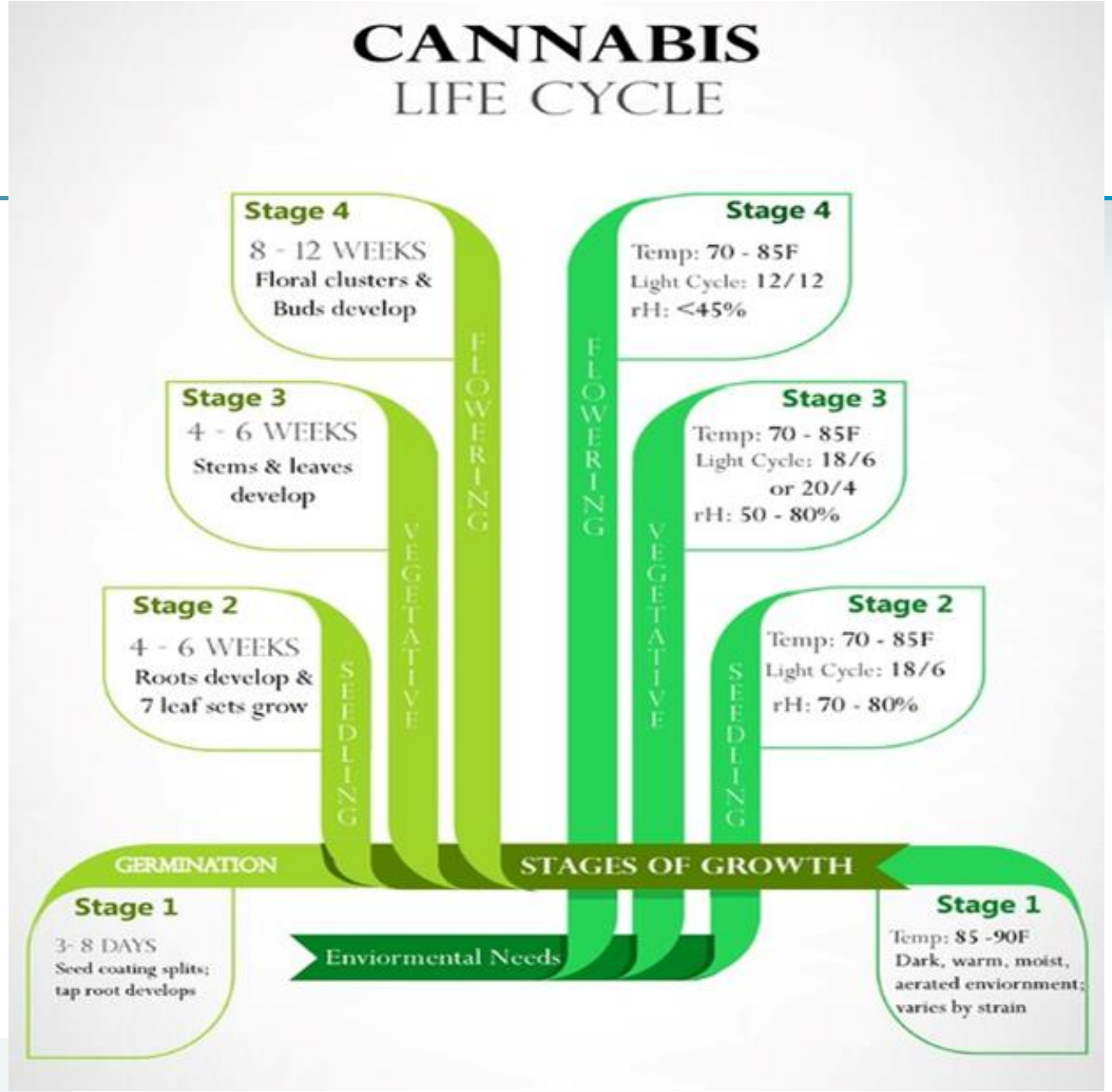
Cannabis Cultivation

Cultivation Methods

Cannabis Grow medium and lifecycle

Plant Life Cycle

Cannabis cultivation



Seedling Cultivation

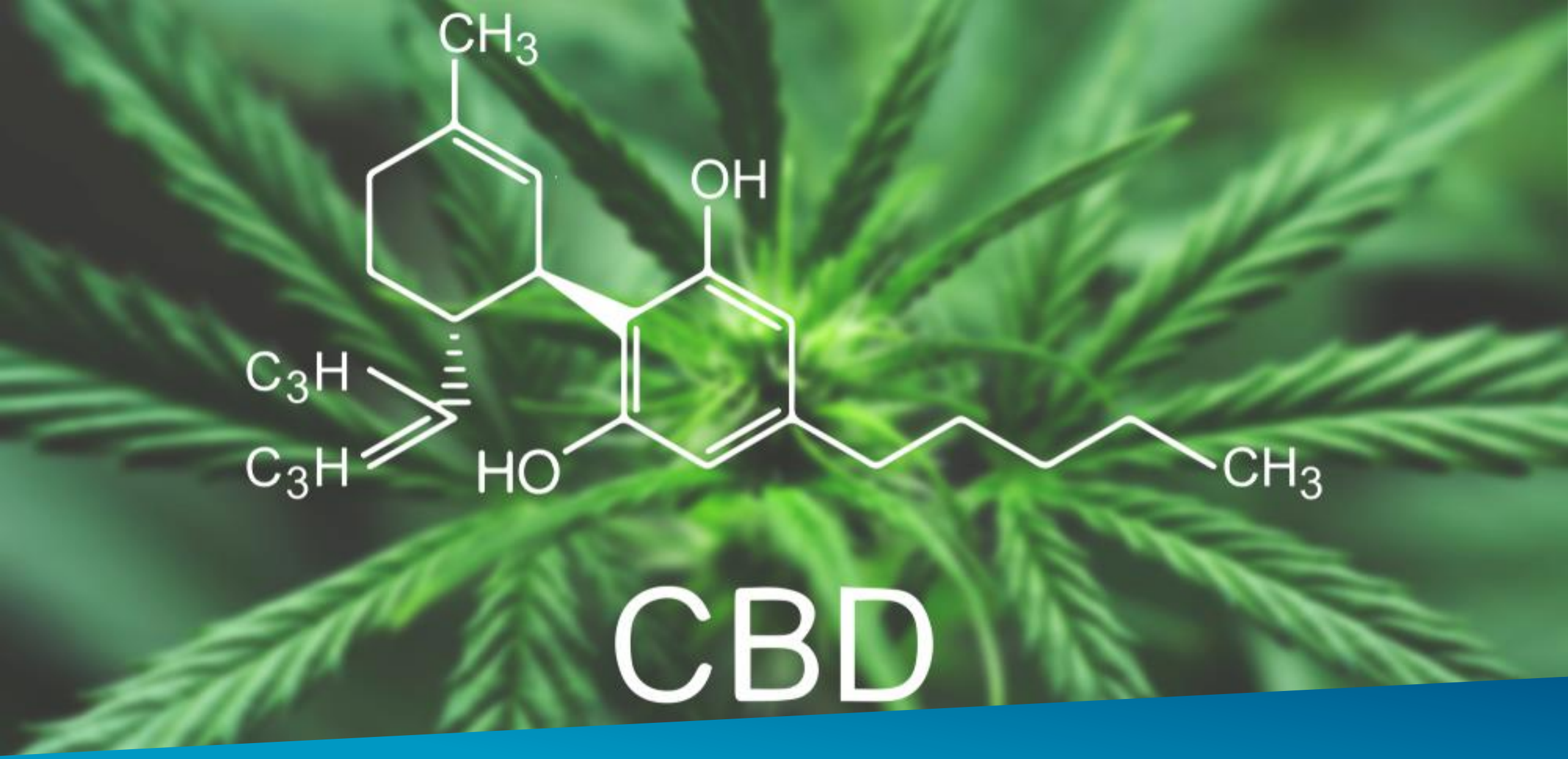
Plant Cultivation

Processing

Cannabis cultivation

Drying

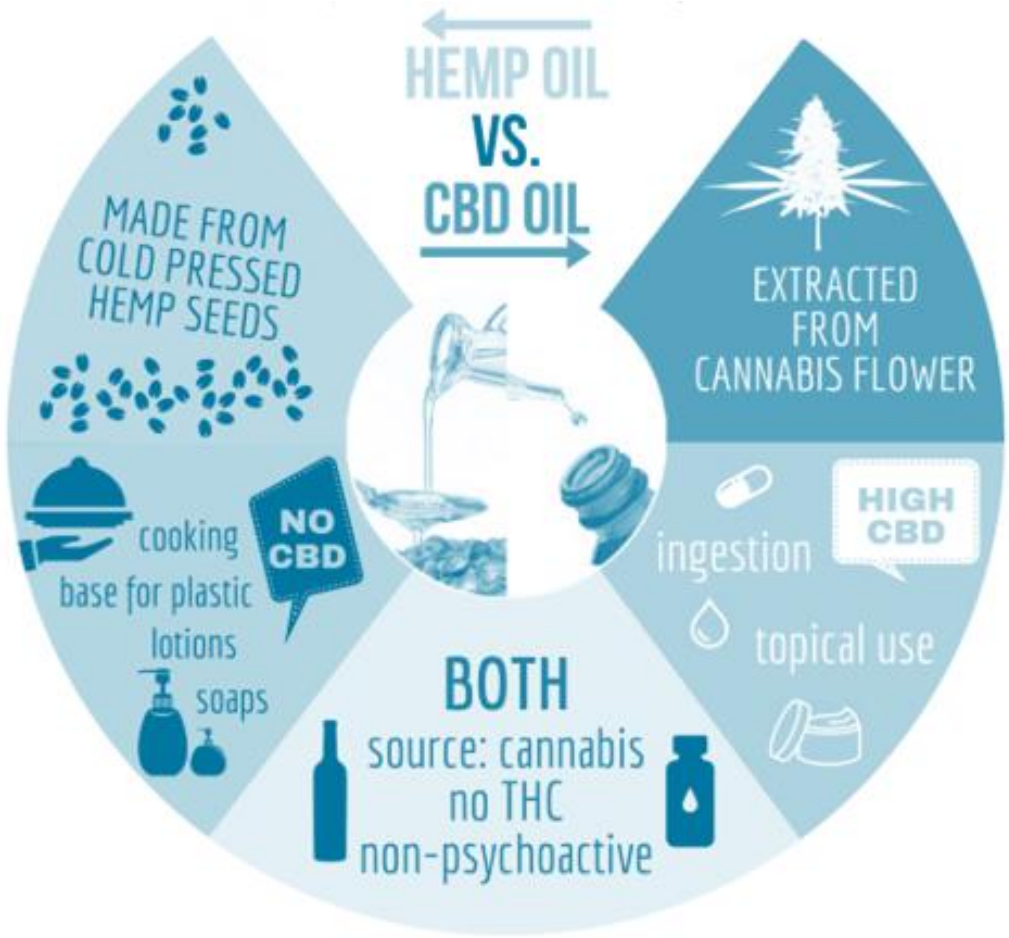
Ground Plant Material



Cannabis Extraction

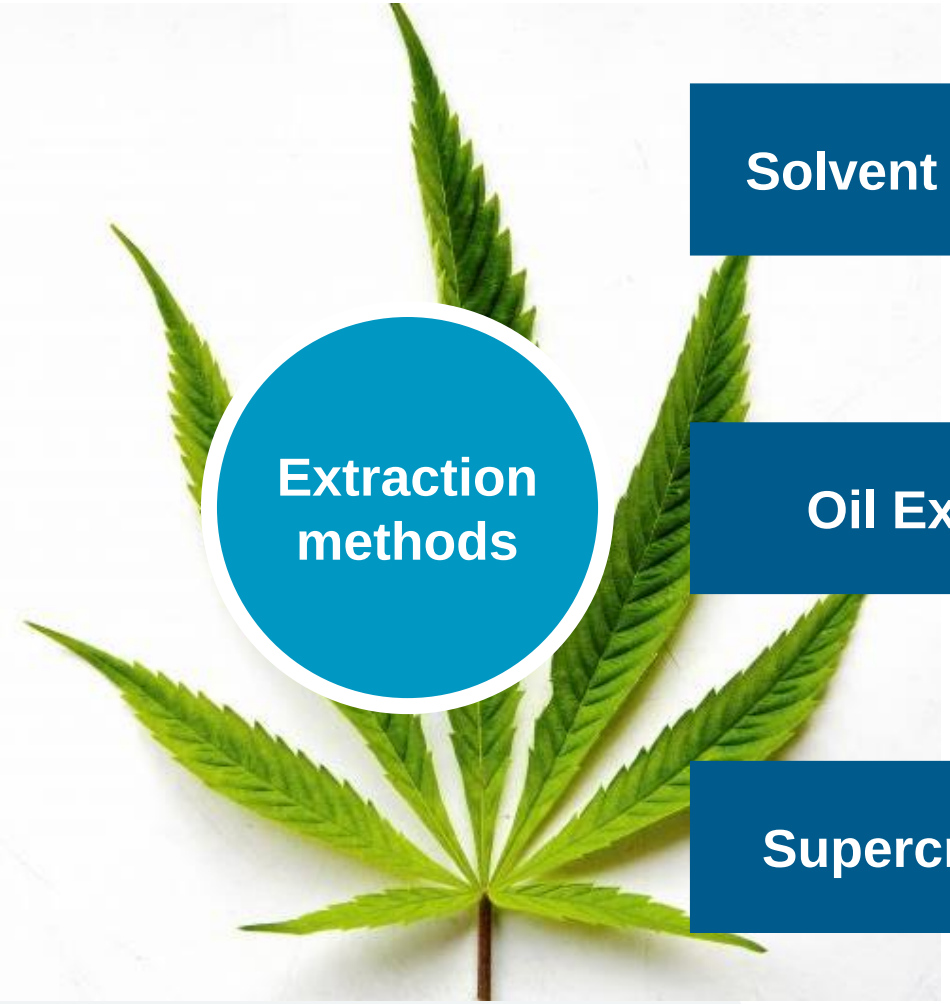
Difference between Hemp seed and Cannabis

Cannabis extraction



Cannabis Extraction Methods

Cannabis extraction



Extraction methods

Solvent Extraction

- butane, isopropyl alcohol, hexane, or ethanol
  - Trace impurities

Oil Extraction

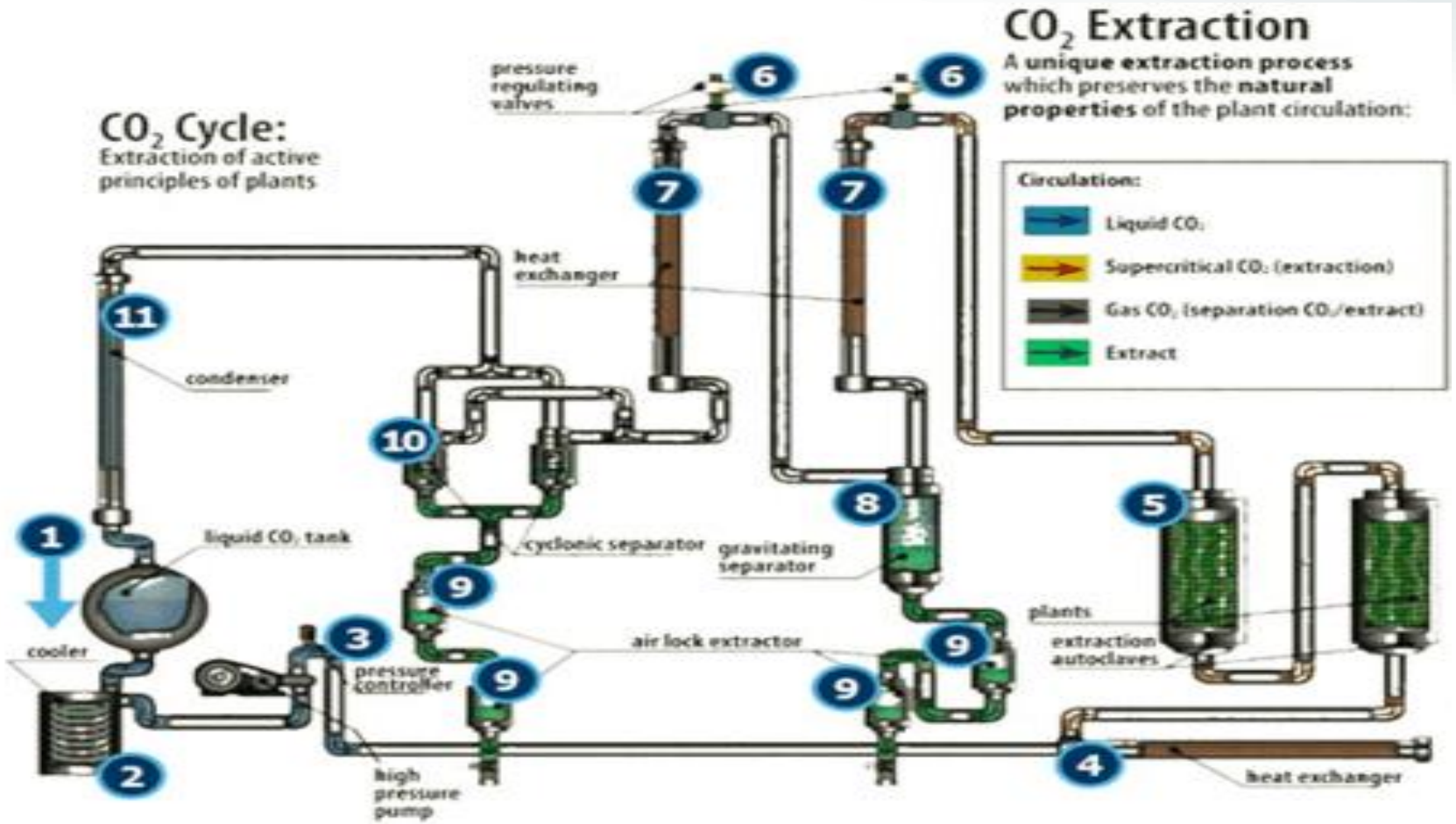
- olive oil
  - olive oil cannot be evaporated away after the processes

Supercritical C02

- Carbon Dioxide (C02) is a unique molecule that can function as any state of matter

Processing of cannabis for medicinal use – SUPERCRITICAL CO_2

Cannabis extraction – SUPERCRITICAL EXTRACTION PROCESS



1. CO_2 Storage
2. Cooling
3. Pressurization
4. Reheating
5. Extraction
6. Relaxation
7. Reheating
8. Separation
9. Decompression
10. Cyclonic separation
11. Liquefaction

Separation & Collection

General processing steps

Separation Collection 1 & 2

Terpene Collection

Processing of cannabis for medicinal use

General processing steps

- Dried & milled hemp plant material received as feedstock;
- Verify quality including moisture, CBD &THC content;
- Extract delivers raw hemp oil, including Cannabis resin and/or cannabinoids; may be a product as is.
- Purification to separate solids by filtration; THC isolated via chromatographic process;
- Process further to an Isolate product if required.

Processing Cannabis

Cannabis extraction

Post Extraction Isolation

General processing steps

Final Cannabis Products

Research and Development

Where we bring your product to life

There are no finished product registered in the SA market, yet.

Although the industry is still new it is expanding very quickly and therefore many companies are working on developing these products.

Our reputation is backed by more than 20 years of scientific research into Botanical Extractions and final product development

- We have a state of the art Research & Development Department equipped with onsite microbiology & instrument laboratories
- In-house stability chambers to facilitate accelerated shelf life studies in order to provide client confidence with their products
- Nominated by CRI as their dedicated Cannabis Laboratory

Our professional team of experts with industry leading expertise can provide excellent advice on a wide variety of products

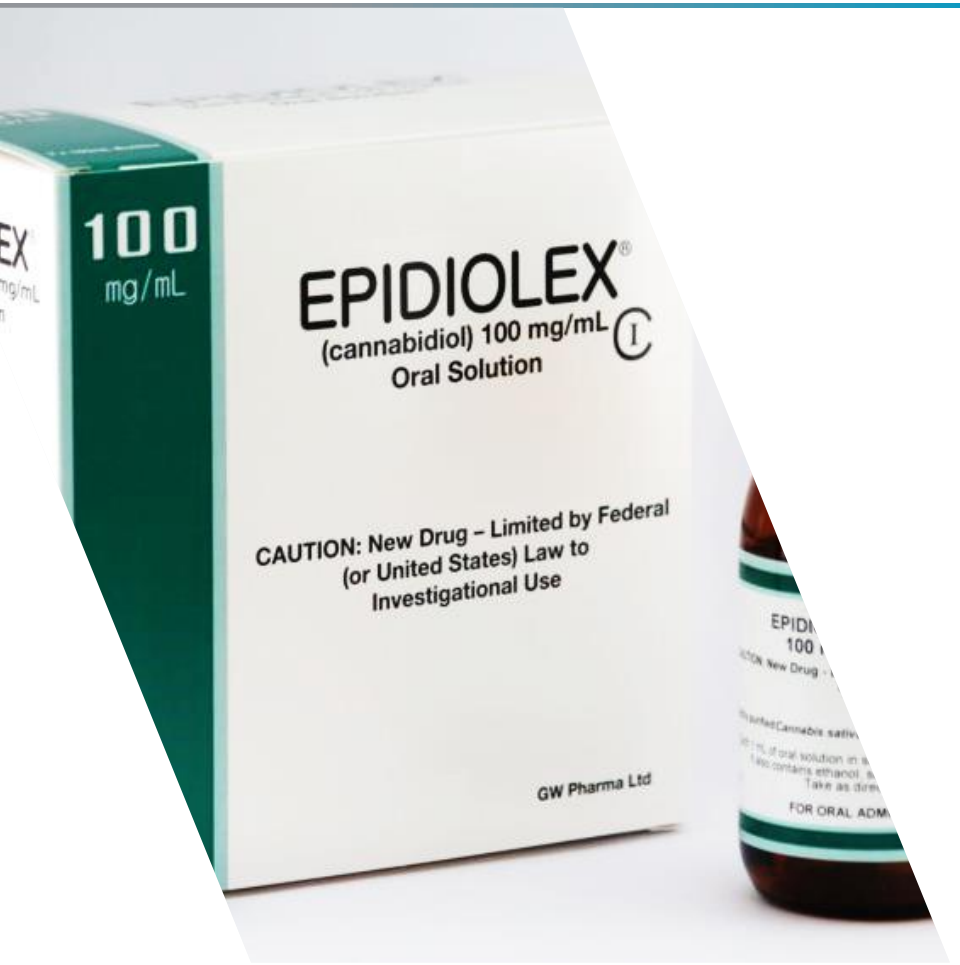
Cannabis Product Development

Discovery | Early development | Formulation development | Scale-up | Commercial scale supply fill / finish

Active pharmaceutical ingredient | Molecule | Medicine | Product | Mass production | Commercial packaging

Marketing Authorizations (as a Medicinal Product)

Outcomes from 40th ECDD WHO Meeting



- **There are currently no authorized or registered pure CBD products.**

However, there are several in development.

- Epidiolex® is a liquid oral formulation of pure plant-derived CBD
- Arvisol® is an oral tablet containing pure CBD.

PHARMA CANNABIS

40th ECDD WHO Meeting

Marketing Authorizations (as a Medicinal Product)

Outcomes from 40th ECDD WHO Meeting

- Zynerba® Pharmaceuticals is developing a CBD gel (ZYN002) that is designed for transdermal use.
- Bionorica® (Germany) has developed a pure CBD product that is extracted from hemp plants through a multi-stage process into a crystalline powder (production completed by THC Pharm).

PHARMA CANNABIS

Marketing Authorizations (as a Medicinal Product)

Outcomes from 40th ECDD WHO Meeting

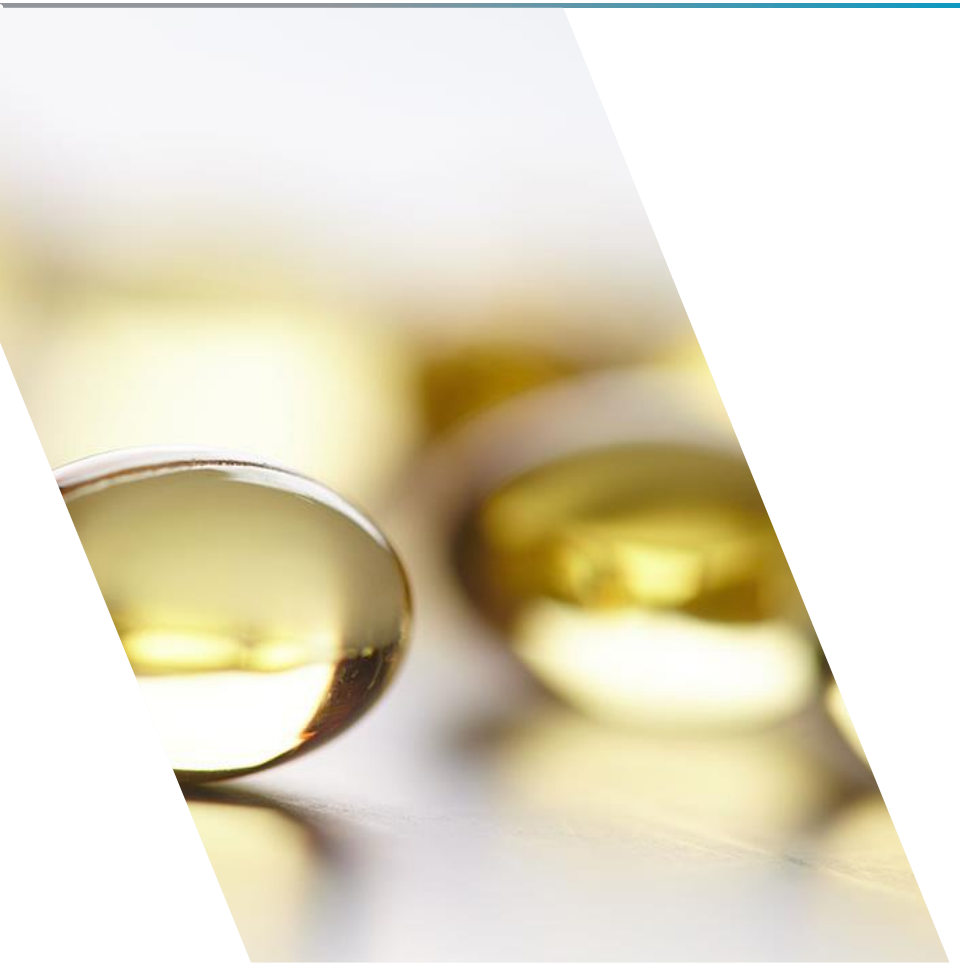
- STI Pharmaceuticals (Essex, United Kingdom) has developed a crystalline powder of pure synthetic CBD with multiple doses.

- INSYS Pharmaceuticals (United States) has developed an oral solution of pure CBD. It is currently in Phase 2 trials for childhood absence seizures (20-40 mg) and in a Phase 3 trial as an adjunctive therapy in conjunction with vigabatrin for infantile spasm-type seizures.

PHARMA CANNABIS

Marketing Authorizations (as a Medicinal Product)

Outcomes from 40th ECDD WHO Meeting



- PhytoTech Therapeutics (Tel Aviv, Israel) is developing an oral formulation (PTL101) that contains purified CBD embedded in gelatine matrix pellets.

- Ananda Scientific (Israel) is producing pure CBD for medicinal purposes and reports having their Phase 1 pharmacokinetics studies underway presently in Israel, with numerous other trials planned in Israel and China.

PHARMA CANNABIS

Cannabis Research Institure

CRI Focus Points

ESTABLISHING THE **MEDICAL STANDARD** FOR CANNABIS IN SOUTH AFRICA

The Cannabis Research Institute (CRI) is the first Centre of Excellence in the field of cannabis and cannabinoid therapy management in Africa. The SACRI incorporates the use of multidisciplinary approaches to further advance cannabis medicinal, veterinary and complementary drug development utilising clinical research and data analytical trials as well as developing cutting-edge methodology and utilizing state of the art equipment and technology.

The CRI is partnered with South African and international research organisations. The CRI works with universities, high-tech innovative companies and other corporations to provide research-based proven approaches to cannabis and cannabinoid therapy management. The combined services and capabilities of the CRI sets the industry standards for Southern African industries for the application of best practice and good governance in cannabis producing facilities. The CRI partners with government and other local and international regulatory bodies to develop and help implement policies pertaining to Good Agricultural and Cultivation Practice (GACP), Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP).

The CRI co-ordination of parties invested in cannabis production for medicinal use creates a synergy between: shareholders, trained and informed personnel, innovative research and development, LIMS and data analysis, and most importantly from the medical professional to the patient.

Services:

- Research and Development
- QC Testing and Compliance
- University partnerships
- Advisory Panel assistance, workshops and training
- Research projects
- Investments and expansion for the SA market

CRI Stakeholders

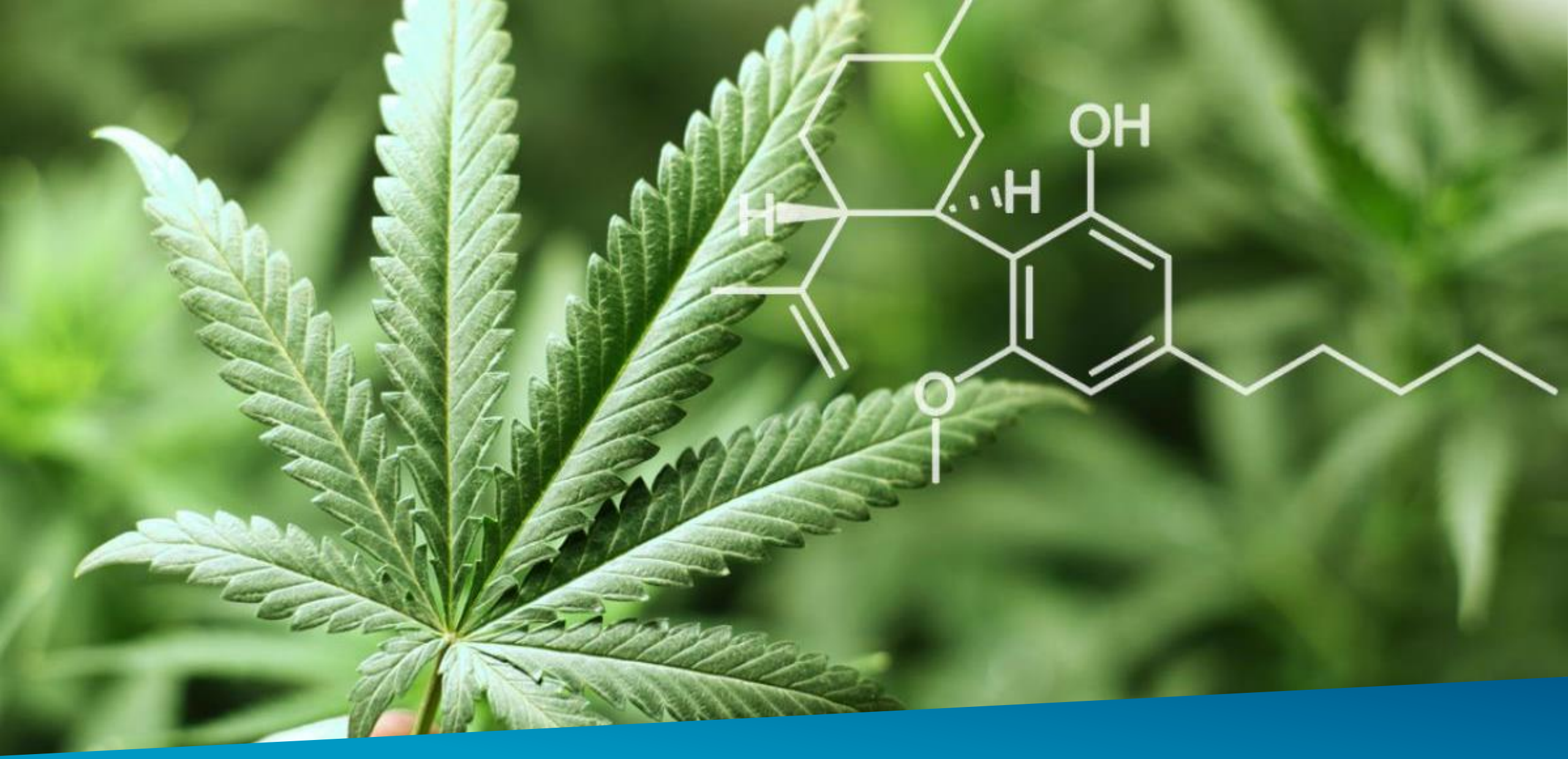
Cape Bio Pharms
Proteins made in plants. Just better.

Afrigen
Biologics & Vaccines
An Avacare Health & IDC Company

Afriplex
SOURCE TO SHELF

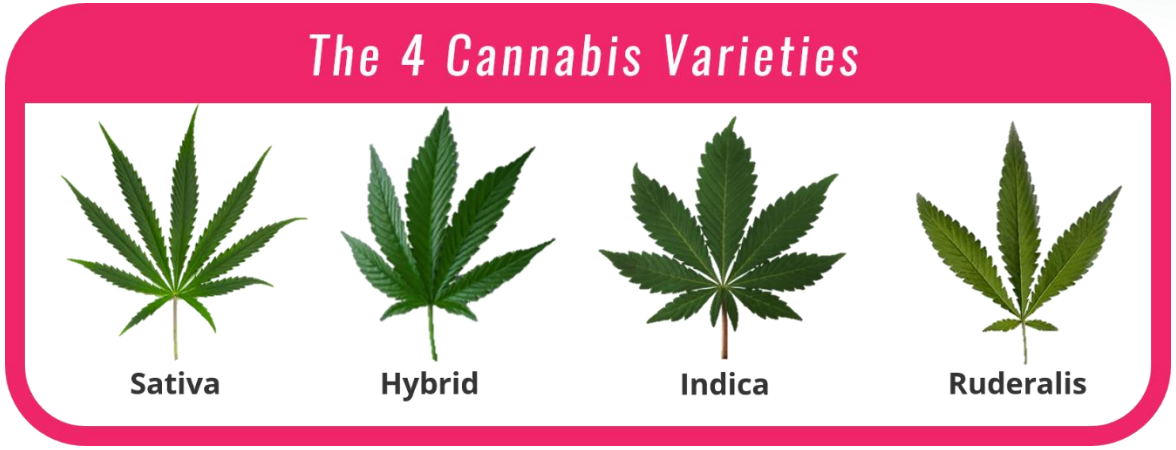
MEDRELEAF
THE MEDICAL STANDARD

RELEAF
PHARMACEUTICALS

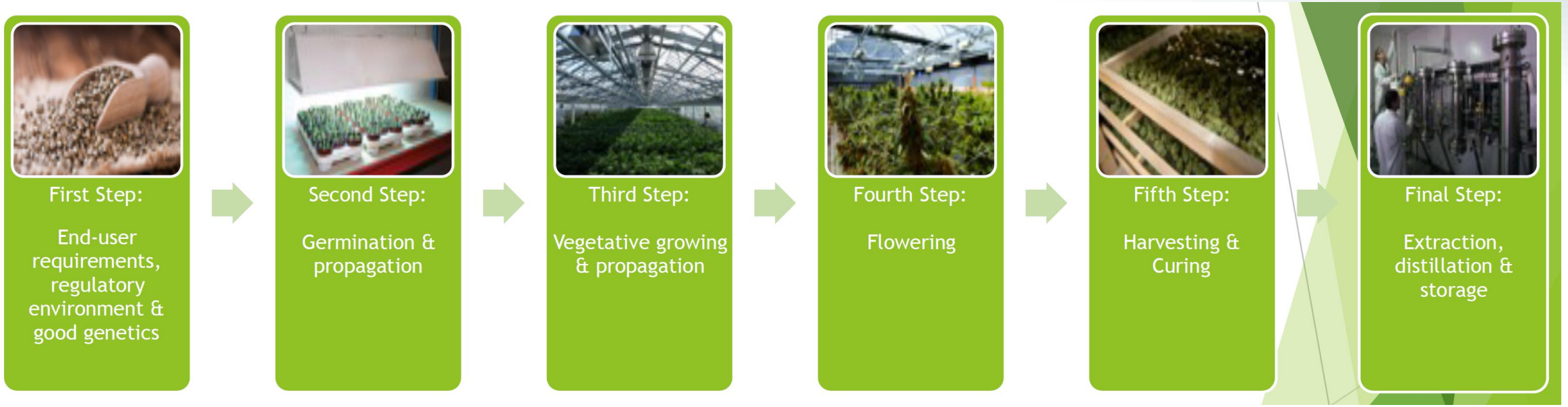


Cannabis Testing

Cannabis Types



Where do we test?



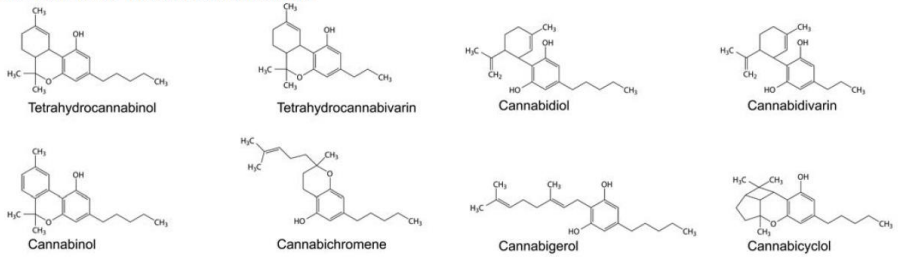
What is Quality?

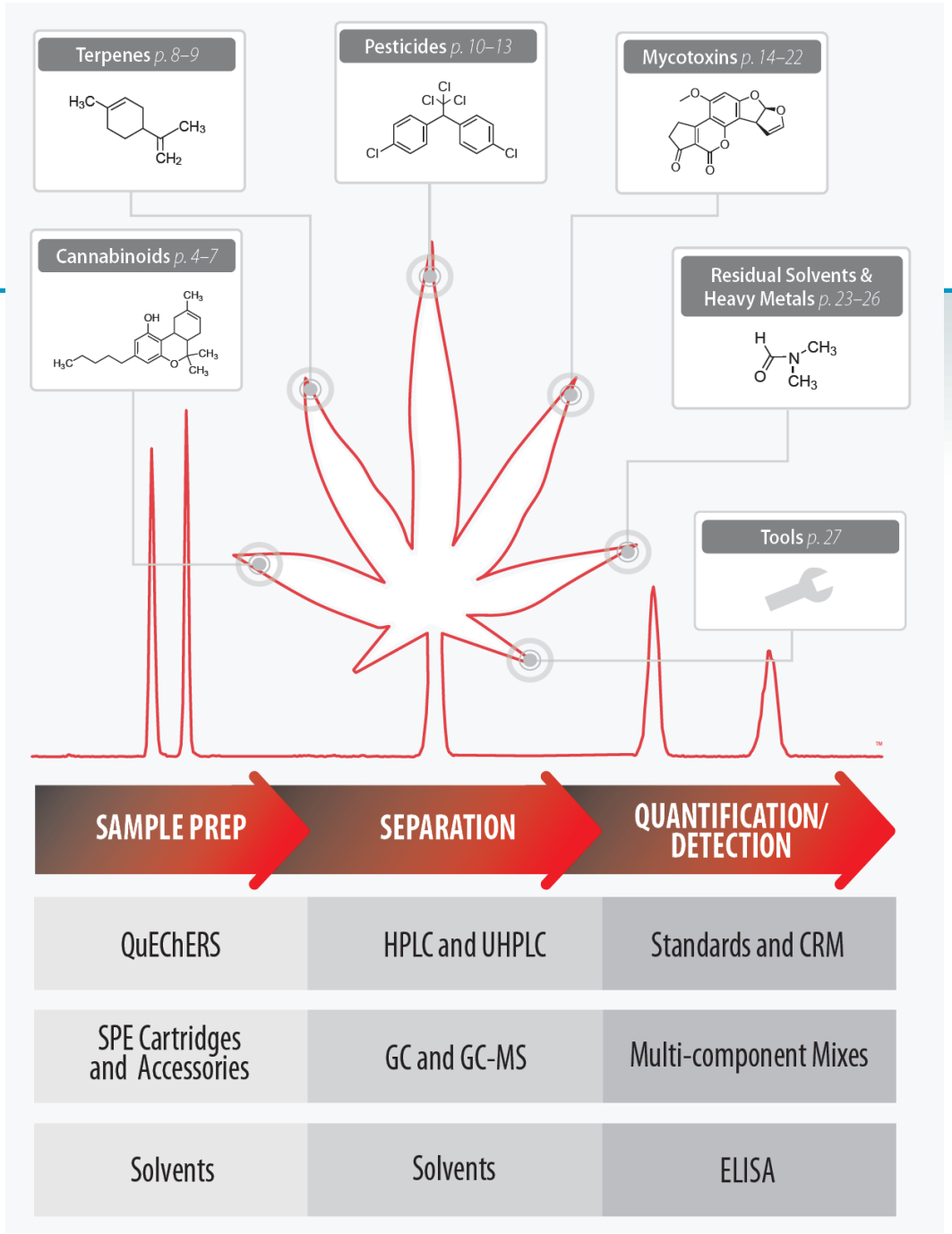
- Goal to produce medicine that is consistent, batch to batch, lot to lot.
- Growers and processors encouraged to produce cannabis in a range of means and routes of administration
- Growers and processors to also produce varieties and products containing high CBD levels
- No batch or lot may be released unless it meets the specification set forth for it
- Producers must do stability testing
- Producers must retain samples sufficient for follow-up testing

Cannabinoid Testing

CANNABINOID STANDARDS AND CRMS

Structural formulas of main natural cannabinoids

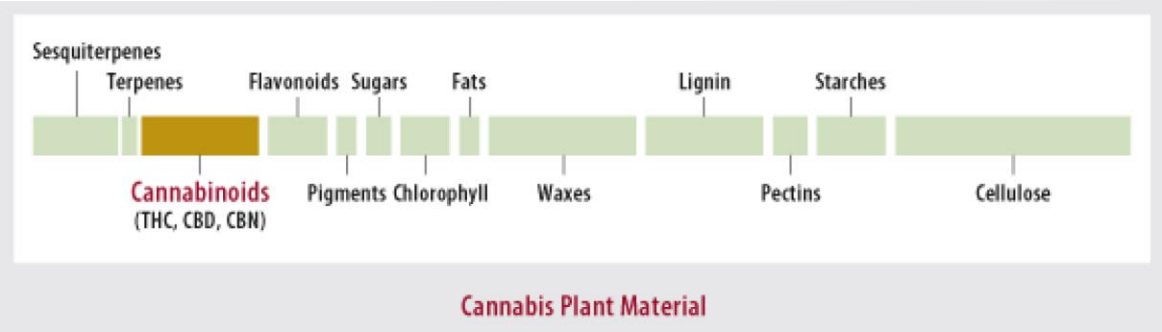




Common Testing Requirements

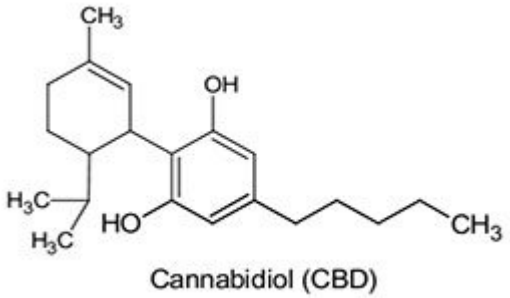
COMPOUNDS TESTED	ANALYTICAL TECHNIQUE
Cannabinoids	HPLC and UPLC
Pesticides	LC/GC-MS/MS
Residual Solvent	GC-FID, GC-MS
Heavy Metals	ICP, AA, TXRF
Mycotoxins	LC, LC-MS, Affinity
Microbiological	Cultures, qPCR

Cannabinoid Test Markers

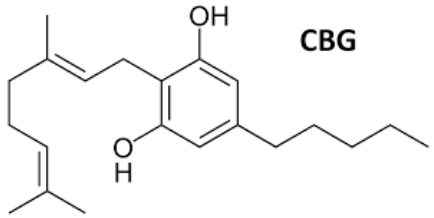


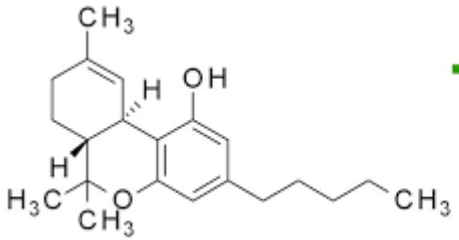
Every batch and lot must be analyzed and labeled with cannabinoid ingredients:

- CBD
- CBDA
- THC
- THCA
- Certain terpenes
- CBG
- CBN



Cannabidiol (CBD)





THC
Tetrahydrocannabinol

Quality

Analysis must detect any microbiological impurity:

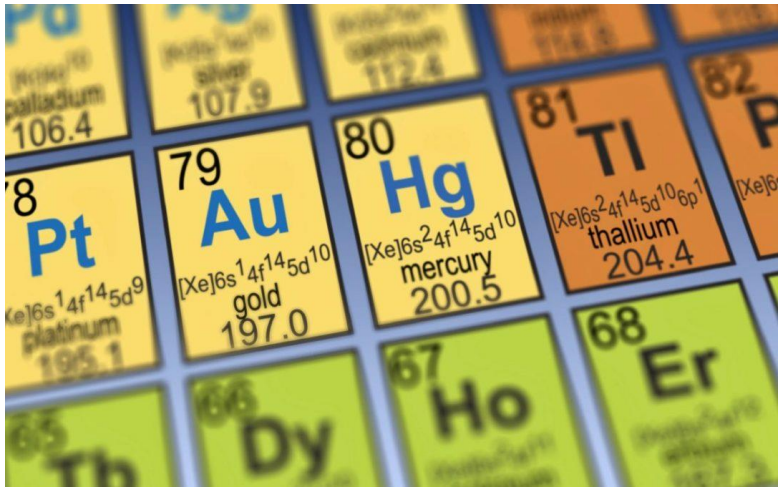
- Total aerobic microbial count (TAMC)
- Total yeast mold count (TYMC)
- P. aeruginosa
- Aspergillus spp.
- S. aureau
- Aflatoxin B1, B2, G1 & G2
- Ochratoxin A.
- Pesticide residue

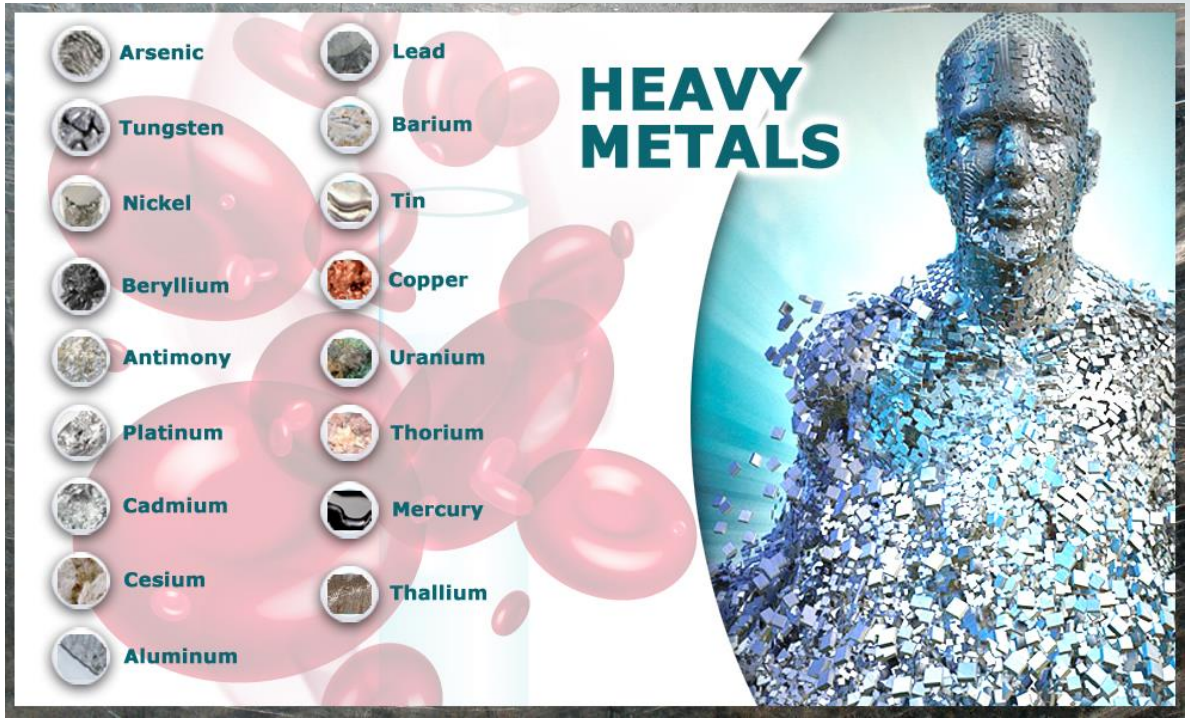
Quality

PREVENTION OF CONTAMINATION

Analysis must look for:

- Heavy metals, mercury, lead, arsenic, cadmium
- Foreign matter (insects, hair, other adulterants)





Pesticide Testing

Table 1: Pesticide analytes and their action levels in OR

Analyte	Chemical Abstract Services (CAS) Registry Number	Action Level ppm
Abamectin	71751-41-2	0.5
Acephate	30560-19-1	0.4
Acequinocyl	57960-19-7	2
Acetamiprid	135410-20-7	0.2
Aldicarb	116-06-3	0.4
Azoxystrobin	131860-33-8	0.2
Bifenazate	149877-41-8	0.2
Bifenthrin	82657-04-3	0.2
Boscalid	188425-85-6	0.4
Carbaryl	63-25-2	0.2
Carbofuran	1563-66-2	0.2
Chlorantraniliprole	500008-45-7	0.2
Chlorfenapyr	122453-73-0	1
Chlorpyrifos	2921-88-2	0.2
Clofentezine	74115-24-5	0.2
Cyfluthrin	68359-37-5	1
Cypermethrin	52315-07-8	1
Daminozide	1596-84-5	1
DDVP (Dichlorvos)	62-73-7	0.1
Diazinon	333-41-5	0.2
Dimethoate	60-51-5	0.2
Ethoprophos	13194-48-4	0.2
Etofenprox	80844-07-1	0.4
Etoxazole	153233-91-1	0.2
Fenoxycarb	72490-01-8	0.2
Fenpyroximate	134098-61-6	0.4
Fipronil	120068-37-3	0.4
Flonicamid	158062-67-0	1
Fludioxonil	131341-86-1	0.4
Hexythiazox	78587-05-0	1
Imazalil	35554-44-0	0.2
Imidacloprid	138261-41-3	0.4
Kresoxim-methyl	143390-89-0	0.4
Malathion	121-75-5	0.2
Metalaxyl	57837-19-1	0.2
Methiocarb	2032-65-7	0.2
Methomyl	16752-77-5	0.4
Methyl parathion	298-00-0	0.2
MGK-264	113-48-4	0.2
Myclobutanil	88671-89-0	0.2
Naled	300-76-5	0.5
Oxamyl	23135-22-0	1
Paclobutrazol	76738-62-0	0.4
Permethrins[16]	52645-53-1	0.2
Phosmet	732-11-6	0.2
Piperonyl_butoxide	51-03-6	2
Prallethrin	23031-36-9	0.2
Propiconazole	60207-90-1	0.4
Propoxur	114-26-1	0.2
Pyrethrins[17]	8003-34-7	1
Pyridaben	96489-71-3	0.2
Spinosad	168316-95-8	0.2
Spiromesifen	283594-90-1	0.2
Spirotetramat	203313-25-1	0.2
Spiroxamine	118134-30-8	0.4
Tebuconazole	80443-41-0	0.4
Thiacloprid	111988-49-9	0.2
Thiamethoxam	153719-23-4	0.2
Trifloxystrobin	141517-21-7	0.2

Solvent Testing

Table 2: USP Chapter 467 Solvents and their concentration limit

Solvent	Concentration Limit (ppm)	Category
Benzene	2	1
Carbon tetrachloride	4	1
1,2-Dichloroethane	5	1
1,1-Dichloroethene	8	1
1,1,1-Trichloroethane	1500	1
Acetonitrile	410	2
Chlorobenzene	360	2
Chloroform	60	2
Cyclohexane	3880	2
1,2-Dichloroethene	1870	2
1,2-Dimethoxyethane	100	2
N,N-Dimethylacetamide	1090	2
N,N-Dimethylformamide	880	2
1,4-Dioxane	380	2
2-Ethoxyethanol	160	2
Ethylene glycol	620	2
Formamide	220	2
Hexane	290	2
Methanol	3000	2
2-Methoxyethanol	50	2
Methylbutylketone	50	2
Methylcyclohexane	1180	2
Methylene chloride	600	2
N-Methylpyrrolidone	530	2
Nitromethane	50	2
Pyridine	200	2
Sulfolane	160	2
Tetrahydrofuran	720	2
Tetralin	100	2
Toluene	890	2
Trichloroethylene	80	2
Xylene	2170	2
Acetic acid		3
Acetone		3
Anisole		3
1-Butanol		3
2-Butanol		3
Butyl acetate		3
tert-Butylmethyl ether		3
Cumene		3
Dimethyl sulfoxide		3
Ethanol		3
Ethyl acetate		3
Ethyl ether		3
Ethyl formate		3
Formic acid		3
Heptane		3
Isobutyl acetate		3
Isopropyl acetate		3
Methyl acetate		3
3-Methyl-1-butanol		3
Methylethylketone		3
Methylisobutylketone		3
2-Methyl-l-propanol		3
Pentane		3
1-Pentanol		3
1-Propanol		3
2-Propanol		3
Propyl acetate		3

Testing Options

Afriplex SOURCE TO SHELF

LABORATORY PRICE LIST 2019

Parameter	Specification	Test Method	Price
FT-IR	≥ 95.00 % similarity to reference	SOP-QC023	R150.00
Identification of Actives by TLC **CBD+CBDA** **THC+THCA** **Terpines**	The chromatogram Rf measurement of the sample bands corresponds to the Rf time of the reference standard bands.	Ph. Eur. 2.2.27	R1250.00
Identification of Actives by GC: Terpenoid Assay **β-Caryophyllene** **α-Humulene** **Caryophyllene oxide** **α-Pinene** **Limonene** **β-Pinene** **Linalool**	Batch specific	SOP-QC117	R2500.00
Identification of Actives by HPLC: Cannabinoid Assay	Total CBD+CBDA Total THC+THCA	SOP-QC116	R2500.00
Aflatoxin B1	≤ 2 µg/ kg	Ph. Eur. 2.8.18	R2000.00
Total Aflatoxins (B1, B2, G1 and G2)	≤ 4 µg/ kg	Ph. Eur. 2.8.18	

Parameter	Specification	Test Method	Price
Pesticides	Meets Ph. Eur. requirements	Ph. Eur. 2.8.13	R1800.00
Heavy Metals-Lead	< 5.00 mg/ kg	Ph. Eur. 2.4.8	R400.00
Heavy Metals-Cadmium	< 1.00 mg/ kg	Ph. Eur. 2.4.8	R400.00
Heavy Metals-Mercury	< 0.10 mg/ kg	Ph. Eur. 2.4.8	R400.00
Heavy Metals-Arsenic	< 1.00 mg/ kg	Ph. Eur. 2.4.8	R400.00
Residual Solvent – Methanol, Ethanol, Acetone, Isopropyl alcohol, Heptane, Pentane	< 0.5% m/m	Ph. Eur. 2.4.21	R500.00
Total aerobic count	< 2 000 cfu/ g	Ph. Eur. Method 2.6.31; 2.6.12-13	R100,00
Total combined Yeast and Mould	< 100 cfu/ g	Ph. Eur. Method 2.6.31; 2.6.12-13	R100,00
Bile tolerant gram-negative bacteria	< 100 cfu/ g	Ph. Eur. Method 2.6.12-13	R100,00
Escherichia coli	Absent/ g	Ph. Eur. Method 2.6.31; 2.6.12-13	R180,00
Staphylococcus aureus	Absent/ g	Ph. Eur. Method 2.6.12-13	R130,00
Salmonella	Absent/ 25 g	Ph. Eur. Method 2.6.31; 2.6.12-13	R140,00

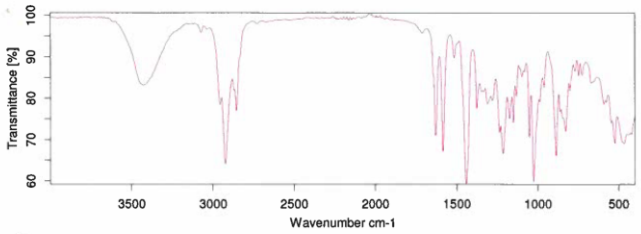
Test Results

Afriplex SOURCE TO SHELF

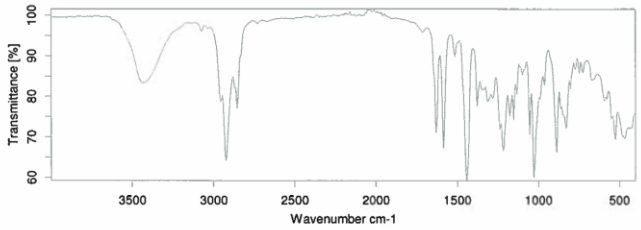
Spectra Comparison

BRUKER

Sample: EXTRACT 1 ALL FRAC WINTERIZED FSD A



Reference Library



Result: OK

Correlation: 99.96 %
Threshold: 95.00 %

Sample: EXTRACT 1 ALL FRAC WINTERIZED FSD A.1
Compared with Reference: EXTRACT 1 ALL FRAC WINTERIZED FSD A.0

Method file:
Operator: Pamelah
Date and time (measurement): 08/03/2019 14:50:38.300 (GMT+2)
Comment:

Signature (Operator) Signature (Release)

Page 1 of 1

Afriplex SOURCE TO SHELF

10 De Vreugde crescent
Paarl
021 872 4976

Microbiology report

Date received	Date reported
07 MAR 2019	13 MAR 2019

Sample name: EXTRACT 1, 2, 4 LIGHT FRAC-D VOL

Internal identification: MIP 2019/388

Test performed:	Result:	Method used:
Total plate count:	No growth/g	SOP-QC029
Total yeast count:	No growth/g	SOP-QC029
Total mould count:	No growth/g	SOP-QC029
Bile tolerant gram negative bacteria	No growth/g	SOP-QC029

***

R Thompson --- Microbiologist

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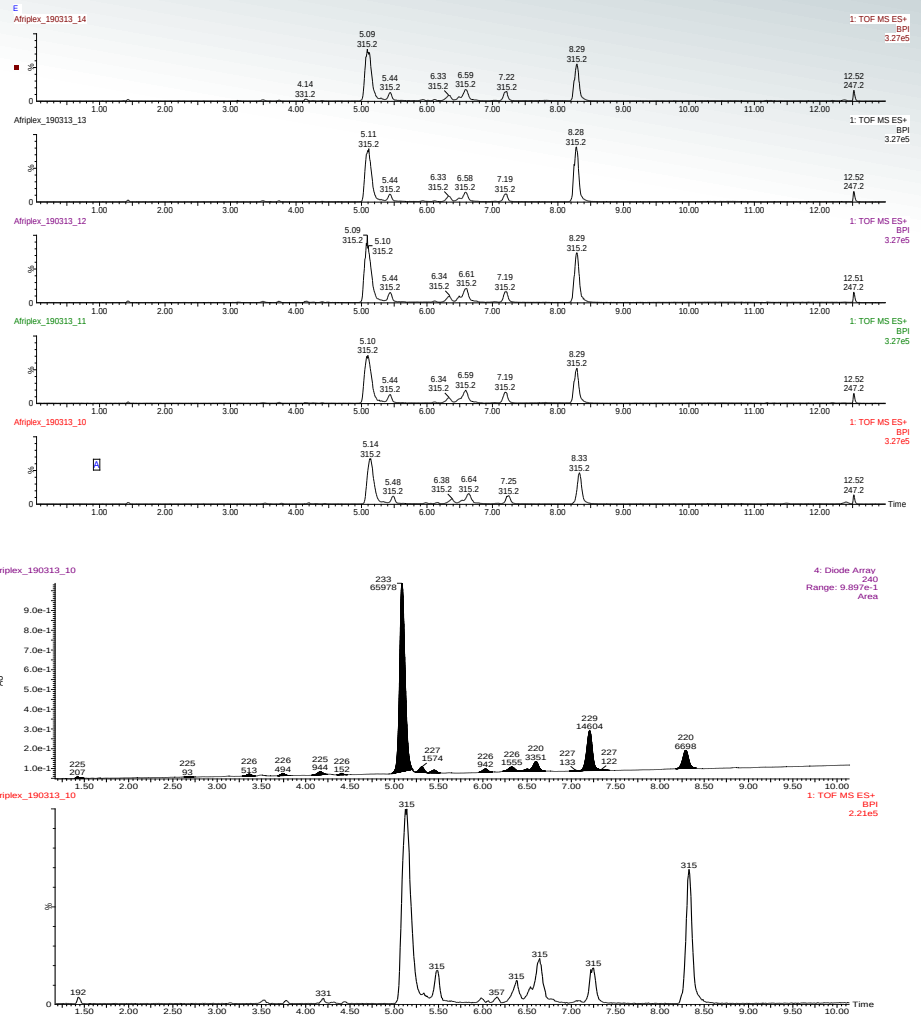

Importance of Testing

Protecting consumer safety

- Ensuring products are free from contaminants
- Ensuring products are labelled properly

Product consistency and potency

- Monitoring extraction and manufacturing processes
- Optimization of cultivation practices
- Testing levels of CBD, THC etc

Patient confidence

Remember …

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Afriplex

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