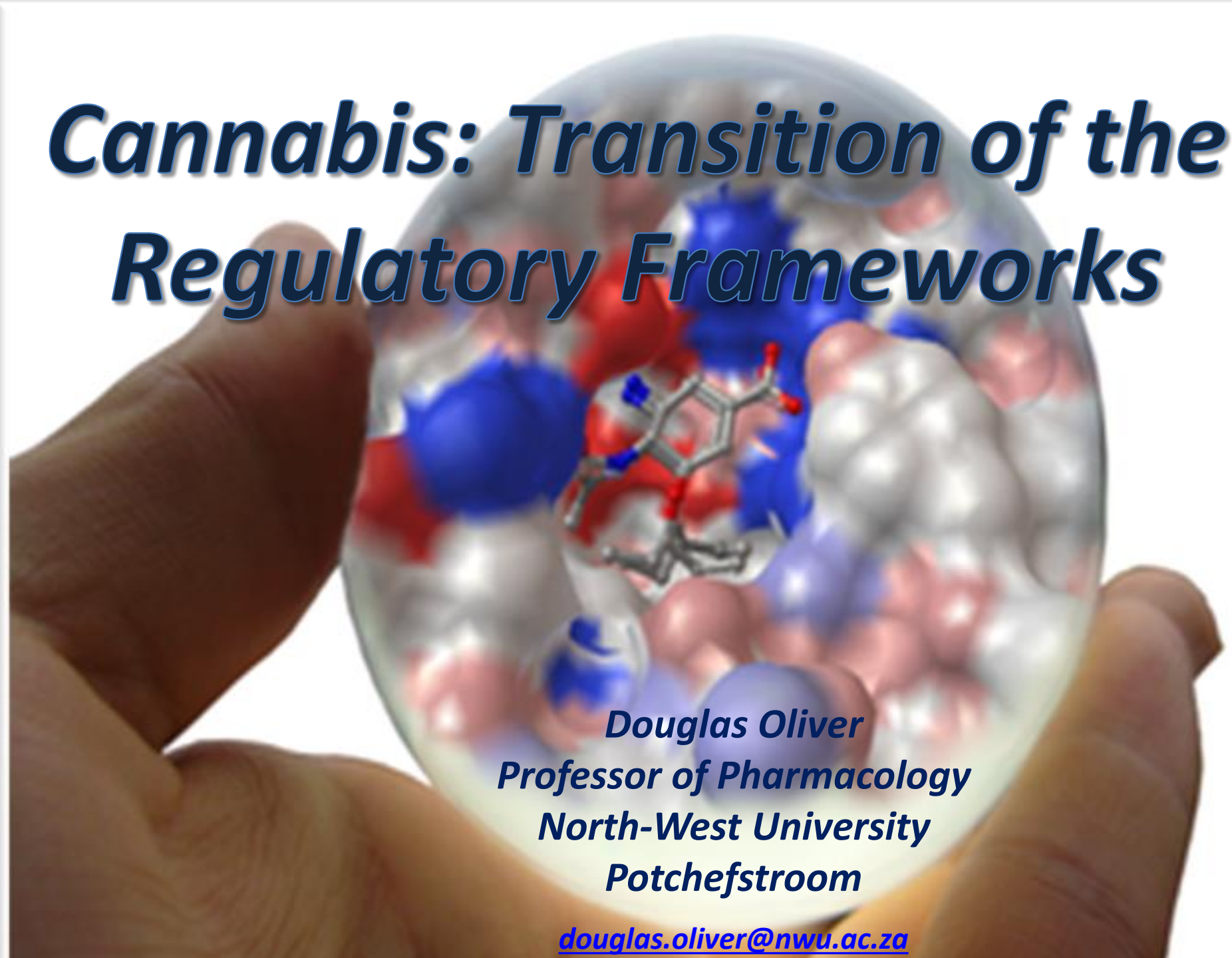
Cannabis: Transition of the Regulatory Frameworks



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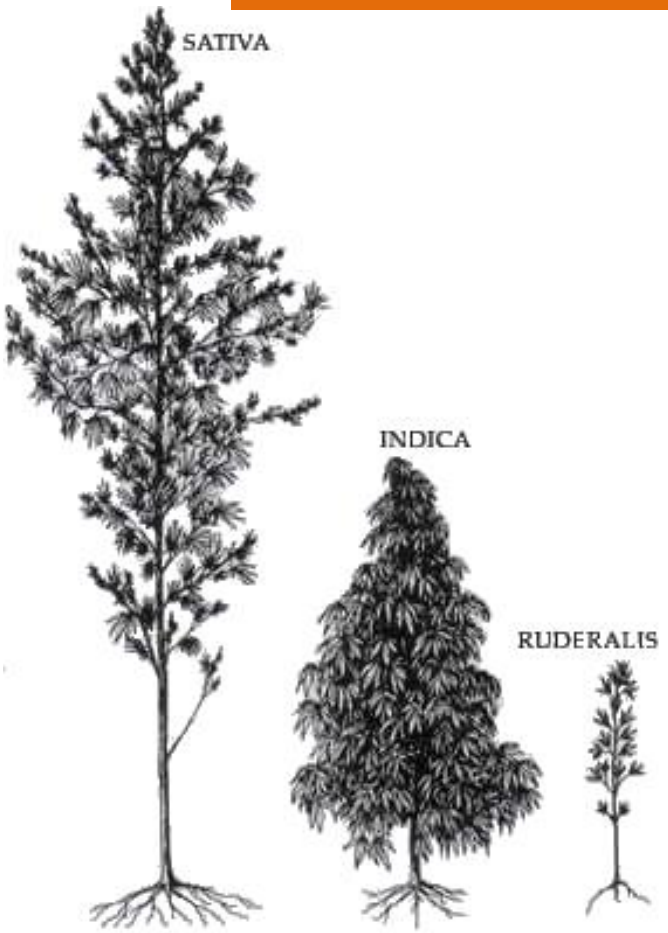
Overview

- Pharmacology
- Legal - Context
- Legal status of cannabis: Internationally INCB and Countries
- Legal status of cannabis: RSA
- Scheduling status of cannabis
- Guidelines on growing cannabis for medicinal use
- Access of cannabis products for medicinal use
- Conclusions and future

Pharmacology - 1

- *Cannabis indica* and *Cannabis sativa* are the best-known species.
- A product's chemical profile is more important than the strain of plant from which it originated.
- Percentages of cannabinoids determine potency and effects (> 20%)
- > 110 Cannabinoids (interactions???)

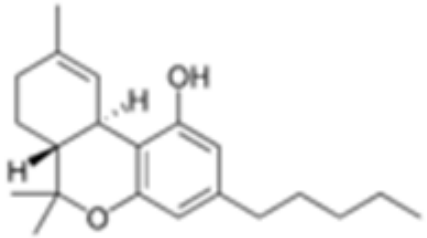
Cannabis and Cannabinoids: Differences/Similarities???



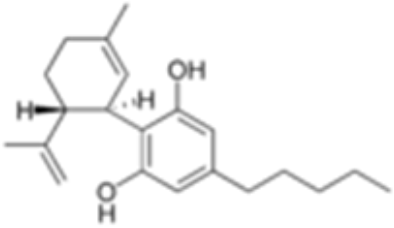
Molecular Pharmacology - 2

Cannabinoid receptors, CB_1 and CB_2

- G protein-coupled cannabinoid receptor located primarily in the central and peripheral nervous system.
- It is activated by the endocannabinoid neurotransmitters anandamide and 2-arachidonoylglycerol (2-AG)



Δ9-tetrahydrocannabinol (THC)



Cannabidiol

Cannabinoid receptors???

- GPR18, GPR55 and GPR19:
- Understanding Partial Agonism

CB_1 most widely expressed Gαi protein-coupled receptors in the brain

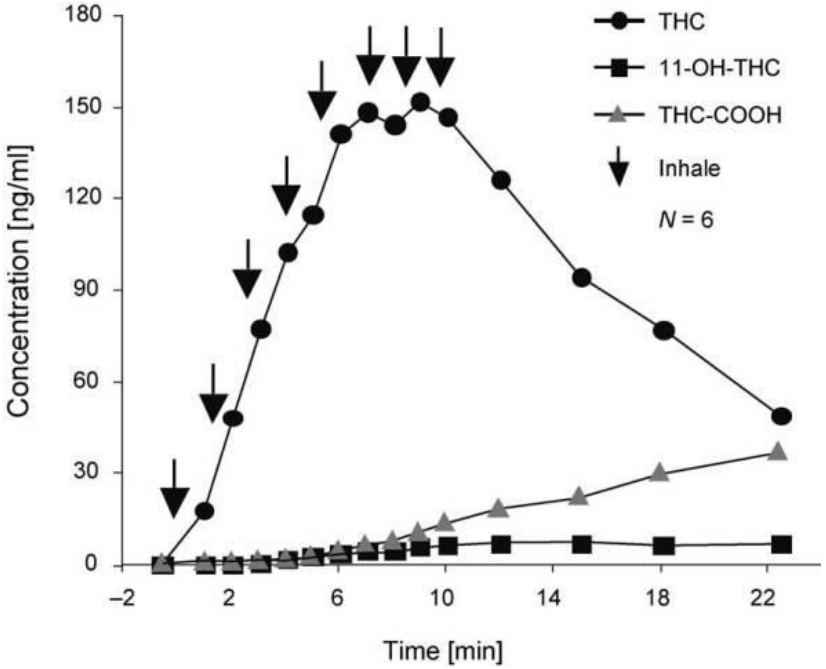
CB_2 expressed on T cells of the immune system, on macrophages and B cells, and in hematopoietic cells.

THC non-selective for the cannabinoid CB_1 and CB_2 receptors

Cannabidiol has low affinity for the CB_1 and CB_2 receptors (antagonist)

Pharmacology - 3

Inhalation by smoking or vaporization	Oral	Oro-mucosal or sublingual	Topical or Rectal
(herbal cannabis, resin, concentrates)	(prescription cannabinoids, edibles, tinctures)	(lollipops, lozenges, nabiximols)	(herbal cannabis, resin, concentrates)



Mean (N=6) plasma concentrations during smoking

Pharmacokinetics:

Oral THC: two compartment model

- High first pass effect (bioavailability for system circulation (10-20%): hepatic impairment
- large volume of distribution (long excretion time)
- initial (alpha) half-life ~4 hours
- terminal (beta) half-life of 25 to 36 hours
- principal active metabolite, 11-OH-delta-9-THC
- Inactive metabolite, THC-COOH

Pharmacology -4 Clinical Status

Prescription cannabinoid preparations include

Dronabinol (Marinol)

THC capsule approved for treatment of anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond

((-)-transdelta-9-tetrahydrocannabinol)

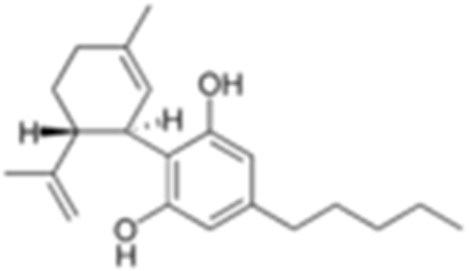
Nabilone (Cesamet)

THC capsule approved for treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional entiemetic treatments.

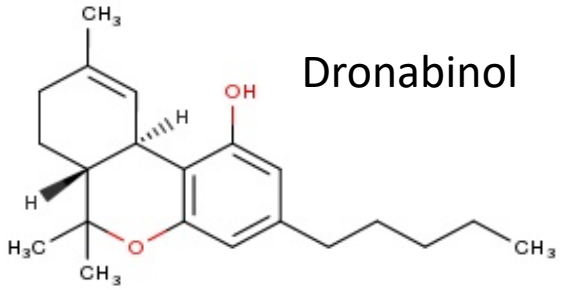
Nabiximols (Sativex)

(Not yet approved in the U.S.)

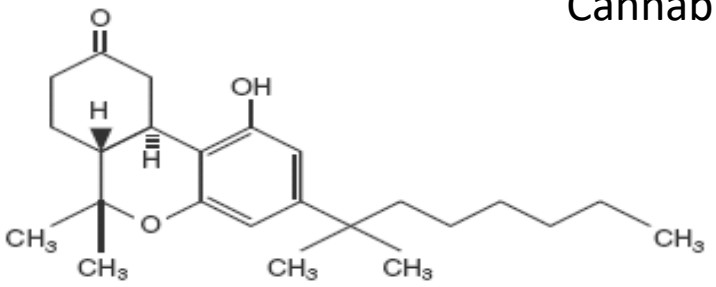
Whole plant extract containing both THC and CBD, administered sublingually



Cannabidiol



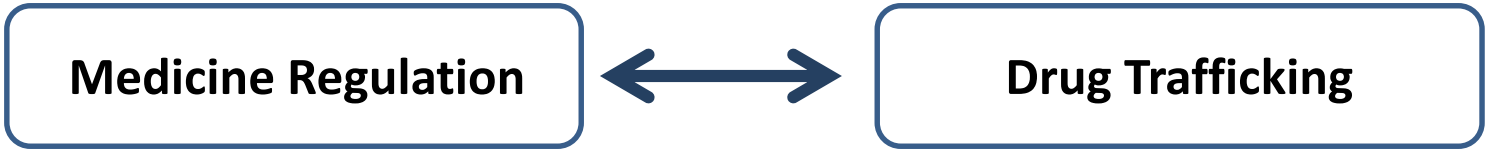
Dronabinol



Nabilone

Legal Context - 1

Multiple legislations for substances and medicines



South Africa:

- The Medicines and Related Substances Act, 1965 (Act 101 of 1965)
- The Dugs and Drug Trafficking Act, 1992 (Act 40 of 1992)
- The Criminal Procedure Act, 1977 (Act 51 of 1977)

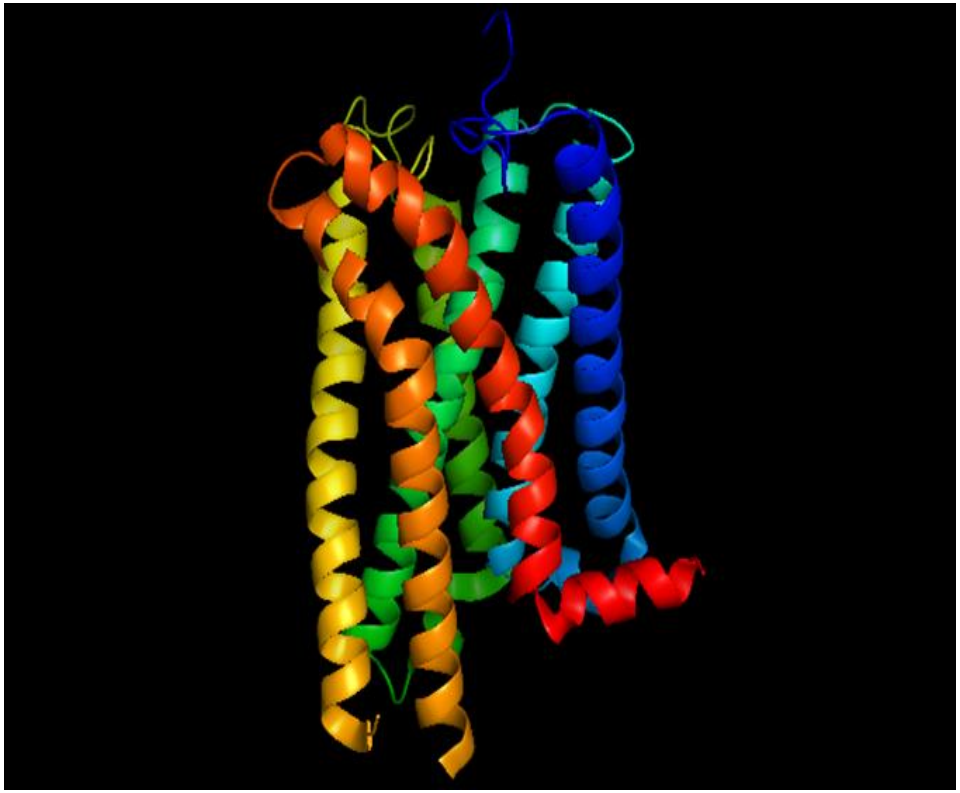
Classifications complex and different globally:

- Classes: A, B, C
- Schedule: I, II ….
- Schedule: 1, 2….
- POMs, P, ….

Legal Context – 2: Regulatory pillars of Medicines

- Quality: ??
- Safety: ??
- Efficacy: ??

- **R&D: Chemistry, Formulation Design, Stability**
- **Preclinical: PK/PD, Tox,**
- **Clinical: Trials, PK/PD**
- **Post Registration safety**



Product lifecycle control

INCB: UN Single Conventions 1961

Cannabis and cannabis resin
Schedule I (*liable to abuse and to produce ill effects*) and
Schedule IV (*is not offset by substantial therapeutic advantages) (WHO recommendation to INCB)*

Obligations:

1. Governments have established programmes for the use of cannabis for medical purposes to ensure that the
2. prescription of cannabis for medical use is
    1. performed with competent medical knowledge and
    2. supervision and that
    3. prescription practice is based on
    4. available scientific evidence and consideration of
    5. potential side effects.

RSA is a signatory

INCB Board 2016 Annual Report

- Reminding governments 'that, in recognition of the
- public health risks associated with its
    - abuse, cannabis has been subjected to the highest levels of control under the international drug control treaties through its inclusion in Schedules I and IV of the 1961 Convention'.

"To reiterate: cannabis is subject to the highest levels of control"

Amended 1972

INCB: UN Single Conventions 1961

INCB alerts: 2017 for Governments

1) produce estimates of anticipated consumption
2) submitted to the INCB along with further details
3) numbers of people using the drug for medical purposes.
4) If cultivation is planned, details of the area and geographical location must be included.
5) cultivation must be accompanied by the formation of a national cannabis agency to oversee proceedings, according to articles 23 and 28 of the 1961 Single Convention.

Art 23&28

(a) Designate the areas in which, and the plots of land on which, cultivation of the cannabis plant for the purpose of producing cannabis shall be permitted;

(b) License cultivators authorized to cultivate cannabis;

(c) Specify through such licensing the extent of the land on which the cultivation is permitted;

(d) Purchase and take physical possession of all cannabis crops from all cultivators as soon as possible, but not later than four months after the end of the harvest; and

(e) Have the exclusive right of importing, exporting, wholesale trading and maintaining stocks of cannabis.

Regulatory Frameworks – USA

Cannabis Schedule 1

As specified in 21 U.S.C. 812(b)(1), in order for a substance to be placed in schedule I, the Acting Administrator must find that:

A. The drug or other substance has a high potential for abuse.
B. The drug or other substance has no currently accepted medical use in treatment in the United States.
C. There is a lack of accepted safety for use of the drug or other substance under medical supervision.

Regulatory Frameworks – USA

In the absence of NDA or ANDA approval, DEA has established a five-element test for determining whether the drug has a currently accepted medical use in treatment in the United States. Under this test, a drug will be considered to have a currently accepted medical use only if the following five elements are satisfied:

1. The drug's chemistry is known and reproducible;
2. There are adequate safety studies;
3. There are adequate and well-controlled studies proving efficacy;
4. The drug is accepted by qualified experts; and
5. The scientific evidence is widely available.

Schedule I drugs have
*"**no currently accepted medical use in treatment in the United States**" and "a lack of accepted safety for use of the drug under medical supervision," while*
Schedule II drugs do have
"a currently accepted medical use in treatment in the United States."

Regulatory Frameworks – USA

"It is best not to think of drug scheduling as an escalating 'danger' scale - rather, specific statutory criteria (based on medical and scientific evidence) determine into which schedule a substance is placed"

Chuck Rosenberg
Acting Administrator DEA
2016

New Frameworks in >20 States in USA, adopted for Cannabis:

The term **"industrial hemp"** includes the plant Cannabis sativa L. and any part or derivative of such plant, including seeds of such plant, **whether growing or not, that is used exclusively for industrial purposes** (fiber and seed) with **a tetrahydrocannabinols concentration of not more than 0.3 percent on a dry weight basis**. The term "tetrahydrocannabinols" includes all isomers, acids, salts, and salts of isomers of tetrahydrocannabinols.

Regulatory Frameworks – Australia

Acts:

- Narcotic drugs act 1967
- Therapeutic goods act 1989

Schedule 1	Not currently in use
Schedule 2	Pharmacy Medicine
Schedule 3	Pharmacist Only Medicine
Schedule 4	Prescription Only Medicine OR Prescription Animal Remedy
Schedule 5	Caution
Schedule 6	Poison
Schedule 7	Dangerous Poison
Schedule 8	Controlled Drug
Schedule 9	Prohibited Substance
Schedule 10	Substances of such danger to health as to warrant prohibition of sale, supply and use

Regulatory Frameworks – Australia

Schedule 8 Dronabinol

Delta-9-tetrahydrocannabinol when prepared and packed for therapeutic use

Schedule 8 Nabiximols

Botanical extract of cannabis sativa which includes the following cannabinoids: tetrahydrocannabinols, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acids, tetrahydrocannabivarol, and cannabidivarol, where **tetrahydrocannabinols and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content)** in a buccal spray for human therapeutic use

Schedule 8 Tetrahydrocannabinol

1. in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with either of the following warning statements:
    1. not for internal use; or
    2. not to be taken; or
2. in products for purposes other than for internal human use containing 50 mg/kg or less of tetrahydrocannabinols; or
3. separately specified in the nabiximols entry in this schedule

Schedule 4 Cannabidiol

Schedule 8 Cannabis

•including seeds, extracts, resins and the plant, and any part of the plant) when prepared or packed for **human therapeutic use**, when:……

Regulatory Frameworks – Australia

The following table provides an overview of how the legislative requirements work together.

Process step		Therapeutic Goods Act (TGA)	Narcotic Drugs Act (ODC)	States and territories involved?
Patient need Medical authorisation		✔ Special access scheme OR ✔ Authorised prescriber	✖ No	✔ Yes
Import (if obtaining from overseas)		✔ Responsibility of the sponsor	✔ Licence and permit to import controlled substances	✔ Yes
Distribution	**PATIENT** with medical authorsation	✖ No	✔ Responsibility of the licensee	✔ Yes
Manufacture of medicine in its dosage form		✔ Licensable	✔ Licences and permits	✔ Yes
Manufacture of active ingredient		✔ Licensable	✔ Licences and permits	✔ Yes
Harvest (termed 'production' in the Narcotic Drugs Act)		✖ No	✔ Licences and permits	✖ No
Cultivation		✖ No	✔ Licences and permits	✖ No

Regulatory Framework -Uruguay

- **UN Conventions: before 2013**
- **New Framework since 2013**
- **Non medical (recreational) - 3 mechanisms** (register for one)
  - Self cultivation (6 plants per house)
  - Membership clubs (Authorized 15-49 member) 99 plants, 64 clubs
  - Community pharmacy selling September 2017 – 11 x Pharmacies
    - Fingerprint registered 10 g per week 40 g/ month
    - 2 companies (State)
      - Types of Cannabis products: Alpha 1 (*indica*), THC 2 %; Beta 1 (*sativa*) THC 2%
  - Challenges: Number of Pharmacies, Bank funding, Shortages
  - View of Pharmacy:
    - Pharmacies generally against
    - Recreational use is not medicinal product
    - Not to sell psychoactive substance
- **Legal cultivation and legal membership since 2014**
- Adults 18 years
  - Citizens and residents
  - 2017 September: 13489 persons registered

Regulatory Framework Health Canada

Schedule I – IX

SCHEDULE II

Cannabis, its preparations and derivatives, including

- Cannabis resin
- Cannabis (marihuana)
- Cannabidiol
- Cannabinol
- Tetrahydrocannabinol

Cannabis Act: July 2018

- control the production, distribution, sale and possession of cannabis
- Act create 2 new criminal offences, with 14 years in jail - providing to youth

First Session, Forty-second Parliament,
64-65-66 Elizabeth II, 2015-2016-2017

HOUSE OF COMMONS OF CANADA

BILL C-45

An Act respecting cannabis and to amend the Controlled Drugs and Substances Act, the Criminal Code and other Acts

FIRST READING, APRIL 13, 2017

Première session, quarante-deuxième législature,
64-65-66 Elizabeth II, 2015-2016-2017

CHAMBRE DES COMMUNES DU CANADA

PROJET DE LOI C-45

Loi concernant le cannabis et modifiant la Loi réglementant certaines drogues et autres substances, le Code criminel et d'autres lois

PREMIÈRE LECTURE LE 13 AVRIL 2017

Regulatory Framework MHRA

Medicine Classifications UK

- Prescription-Only Medicine (POM)
- Pharmacy (P)
- General Sales List (GSL)

- **THC/Cannabidiol** is the first cannabis-based medicine (oral spray) recognised in the UK to have medicinal properties (recognised medicinal or legitimate use): Schedule 4, Class B drug (Misuse of Drugs Act 1971)

- **Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 2001**
- The Misuse of Drugs Act 1971 controls drugs that are “dangerous or otherwise harmful” under a 3-tier system of classification (A, B and C)
- Schedule 2 to the Misuse of Drugs Act 1971 and in Schedules 1 to 5 to the Misuse of Drugs Regulations 2001

- B1 = Cannabis (resin, oil), THC, Cannabidiol
- Dronabinol B2
- Cocaine A2
- Diazepam C4

Regulatory Framework EU

Medicine Classifications EU

- Prescription-Only Medicine (POM)
- Pharmacy (P) OTC
- General Sales List (GSL)

- **THC/Cannabidiol** is the first cannabis-based medicine (oral spray) recognised in the UK to have medicinal properties (recognised medicinal or legitimate use): Schedule 4, Class B drug (Misuse of Drugs Act 1971)

Dronabinol and Cannabidiol

- 9 October 2015, orphan designation (EU/3/15/1564) was granted for the treatment of glioma

Regulatory Frameworks –South Africa

Schedule 0:	Available through general sales outlets
Schedule 1:	Pharmacy OTC products
Schedule 2:	Pharmacist-prescription products
Schedules 3-6:	Prescription-only medicines; authorised prescribers
Schedule 7:	**Prohibited substances**
Schedule 8:	Limited use; special permits issued by DG

- **Section 22A(9)(a)(i)** of the Medicines Act provides mechanism for the acquisition, usage, possession, manufacturing or supplying of cannabis as a whole plant or part thereof.
  - **Director-General may issue permit authorising** a medical practitioner, analyst, researcher or veterinarian to use cannabis:

    For treatment or prevention of a medical condition in a particular patient, or

    For purpose of education, analysis or research

Regulatory Frameworks –South Africa

- Scheduling 0-8
- Access
  - Dronabinol
  - Cannabidiol

- **S6:** Dronabinol ((-)-transdelta-9-tetrahydrocannabinol), when intended for therapeutic purposes. (S7)
- **S4:** Cannabidiol when intended for therapeutic purposes. (S7)

Regulatory Frameworks – South Africa

Approval of application for **drug product made from Cannabis**: Scheduling review criteria :

- **S7: Cannabis (dagga), the whole plant or any portion or product thereof**, except:

a. when separately specified in the Schedules; (S6) or

b. **processed hemp fibre containing 0,1 percent or less of tetrahydrocannabinol and products manufactured from such fibre**, provided that the product does not contain **whole cannabis seeds** and **is in a form not suitable for ingestion, smoking or inhaling purposes**; or

c. processed product made from **cannabis seeds containing not more than 10 milligram per kilogram (0,001 percent) of tetrahydrocannabinol** and **does not contain whole cannabis seeds.**

["Processed" means treated by mechanical, chemical or other artificial means but does not include - (a) harvesting; or (b) the natural process of decay"].bis sativa.]

Regulatory Frameworks –South Africa

- Scheduling 0-8
- Access or Prohibition
  - THC
  - Synthetic cannabinoids
  - Cannabidiol

- **S7: Tetrahydrocannabinol and their alkyl homologues,** except:

a. when separately specified in the Schedules;

b. **dronabinol ((-)-transdelta-9-tetrahydrocannabinol), when intended for therapeutic purposes; (S6)**

c. **in hemp seed oil**, containing **10 milligram per kilogram or less of tetrahydrocannabinols,** when labelled "Not to be taken" or “Not for internal human use”; or

d. in products for purposes **other than internal human use** containing **10 milligram per kilogram or less of tetrahydrocannabinols.**

["Hemp seed oil" means the oil obtained by cold expression from the ripened fruits (seeds) of Cannabis sativa.]

Regulatory Frameworks –South Africa

Cannabis for Medicinal use

Application Process Cultivation

- Personnel
- Security
- Building & Facilities
- Production
- Documentation
- Enforcement & Compliance
- Access to unregistered cannabis for medicinal use

Section 21 application for unregistered medicines

Inhalation Cannabis for medicinal use vs. Cannabinoids products

- Smoking cannabis is a crude THC delivery system that transports several harmful substances into the body including the brain:
  - Compare metered dose-inhalers
- Smoking cannabis is not recommended for any long term medical use.
- Adverse effects of cannabis smoke on the respiratory system would almost offset any possible benefit.
- Pesticides, hormones, metals
  - Compare medicine control

Advantages of cannabinoids

- Pharmaceutical preparations have excellent quality control.
- Pharmaceutical preparations enable precise dosing.

Additional Comments

Pharmacological active substances: Yes
Potential medicinal value: Yes

Under reporting: Yes (i.e. safety)

Harmless: No
Toxicology: Yes
Safety Concerns: Yes
Interactions: Studies needed
- Diseases and other medications

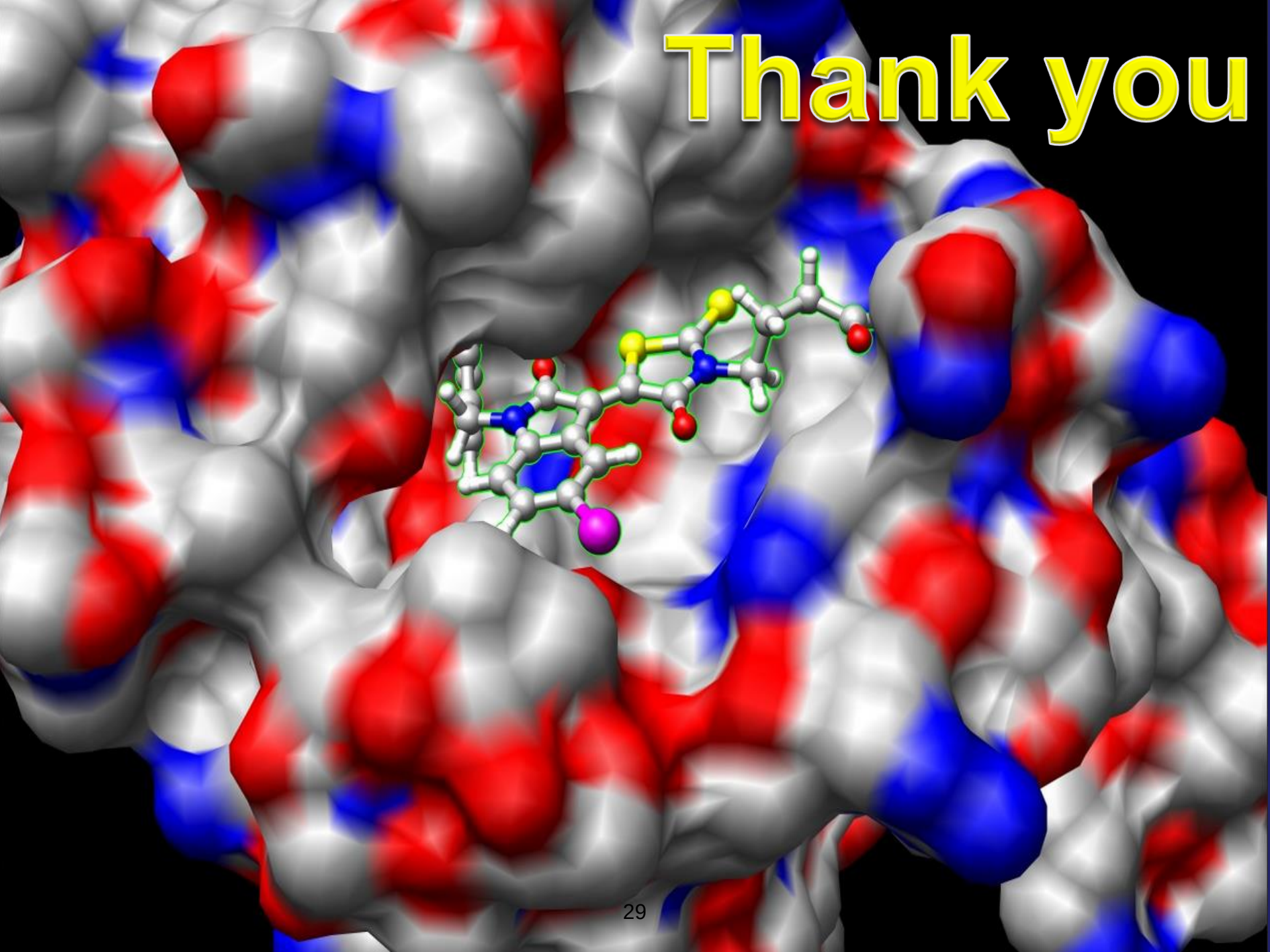
Do we know everything: No
Research needed: Yes
Level of access: Control needed

Quality of Cannabis Products, batch to batch (product life cycle)
- Single cannabinoid containing products
- Mixtures/extracts with multi-cannabinoid containing products
- Cannabis growing, harvesting and manufacturing process
- Stability and Shelf life
- Regulatory Frameworks

Key discussion points for access:
- Medicinal claim – indications
- Medical supervision in decision making
- Outcomes monitoring
- Pharmacoviligance and adverse reporting

Summary Conclusions

- Frameworks are evolving national and internationally
- Cannabinoids:
  - Increasing evidence of medicine potential of actives present in Cannabis and recognized with the current regulatory framework based on QSE (small molecule approach): Products registered
  - Scheduling accordingly conducted
- Cannabis Products
  - First line products (extracts with QSE approaches) emerging and reviewed on QSE
- Access frameworks:
  - Cannabinoids – established
  - Cannabis Products (cultivation etc.) – in transition
- Cannabis for Medicinal use: Challenges:
  - Quality (approval of products by the Nederlands),
  - Safe,
  - Efficacy


Thank you

Conclusion

Acute and Chronic use and effects:

Do we know everything: No
Research Pre-clinical needed: Yes
Research Clinical needed: Yes
Long term studies needed : Yes
Population studies needed: Yes
Pharmacovigilance needed: Yes
Pharmacogenomics needed: Yes
Interactions Studies needed: Yes
Level of access: Scientifically base

Critical and wide-ranging role of the endocannabinoid system in the brain during development and maintenance:
Requires research which aspects of cannabis

- exposure
- age at initiation,
- quantity used,
- frequency of use,
- duration of use, and
- potency of cannabis used

poses greatest risk for the development of **cannabis use disorder** **or for other adverse consequences (i.e., cognitive deficits, lack of motivation, or psychosis).**

Vulnerable populations
children, adolescents, the elderly, women, unborn, or individuals with other disorders may experience novel toxic effects (as well as the potential benefits).