

# Emerging Markets: Play it Safe or Roll the Dice?



Pritesh Kumar, Ph.D.

June 14<sup>th</sup>, 2016

# Overall Risks of the Emerging Markets: Cannabis

- Lack of developed standards / regulations / best practices
- Changing perceptions of commonly held views
- Policy shifts / resistance
- Talent acquisition / skill-set development / transferable skills
- Infrastructure / Government / Private Sector / Academia

# Question

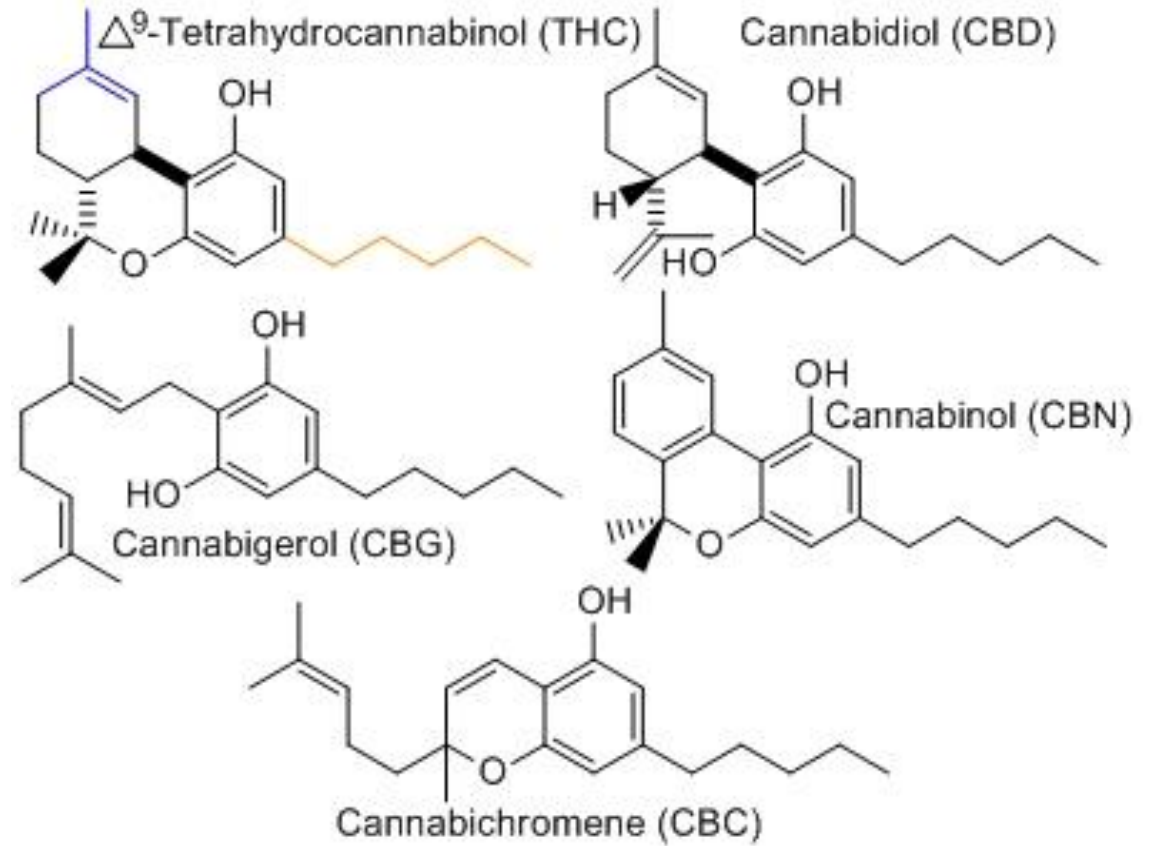


# Exile to Therapeutic – How did we get there?

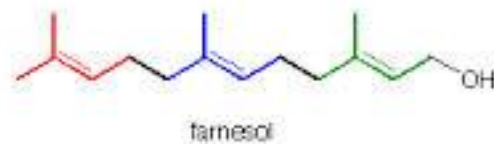
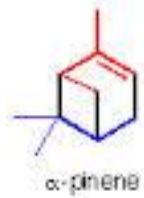
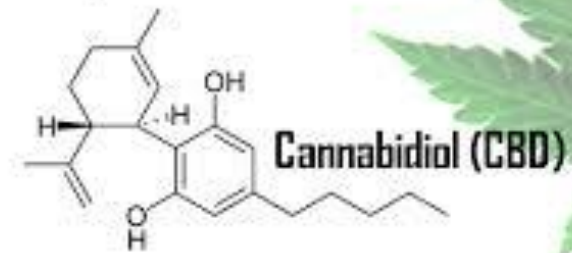
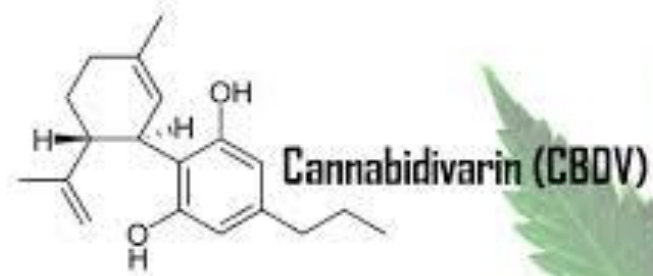




# Phytocannabinoids (Plant)

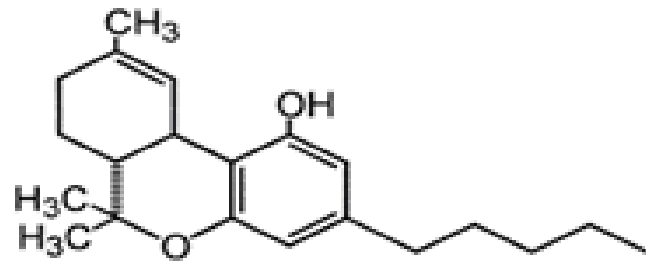


# Phytocannabinoid continued...

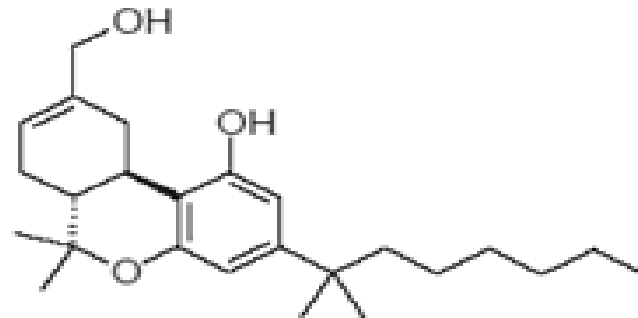


# Synthetic Cannabinoids

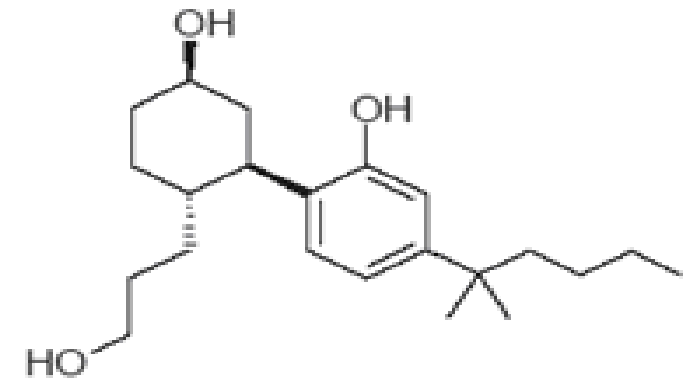
## Cannabinoid Receptor Agonists



$\Delta^9$ -THC

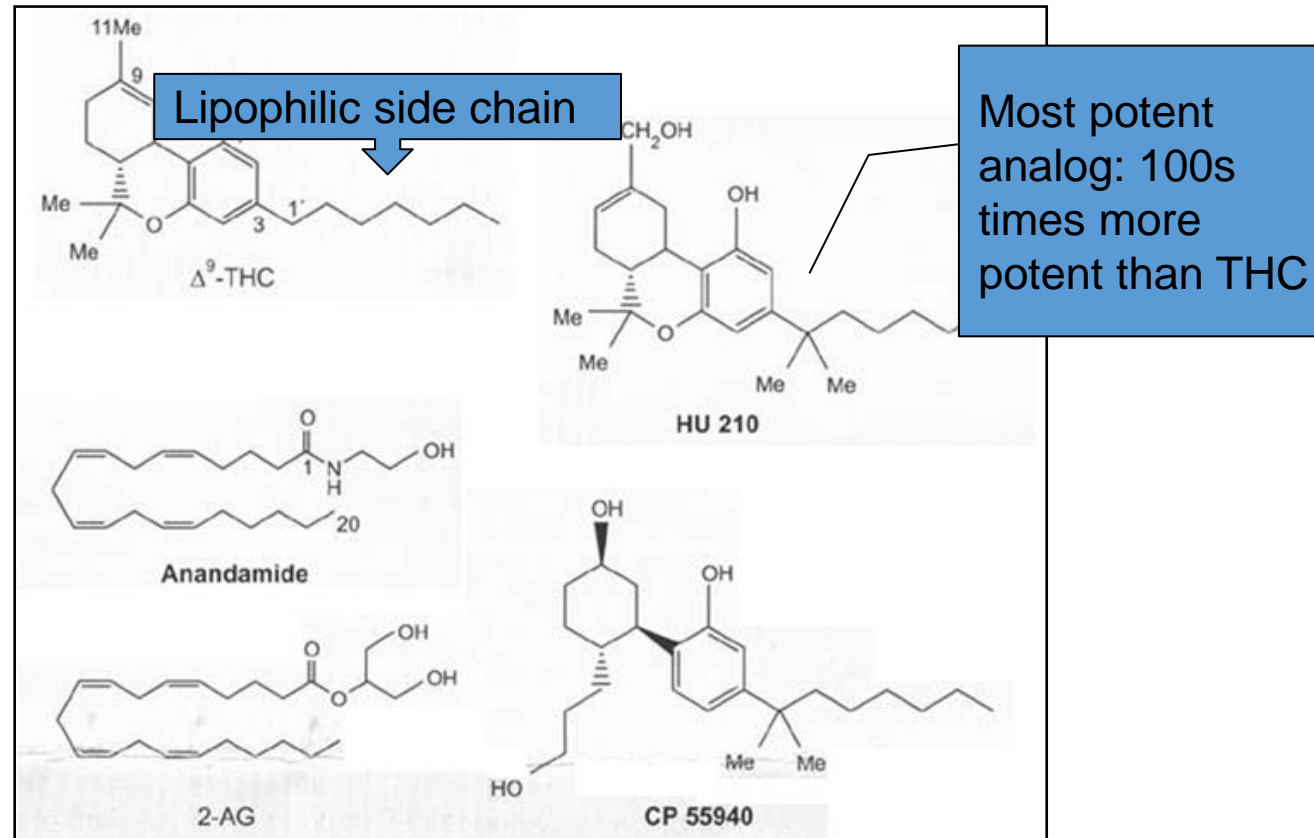


HU-210



CP-55940

# Structures continued...





# Endogenous Cannabinoids



anandamide



2-AG-ether (noladin ether)



sn-2 arachidonyl - glycerol



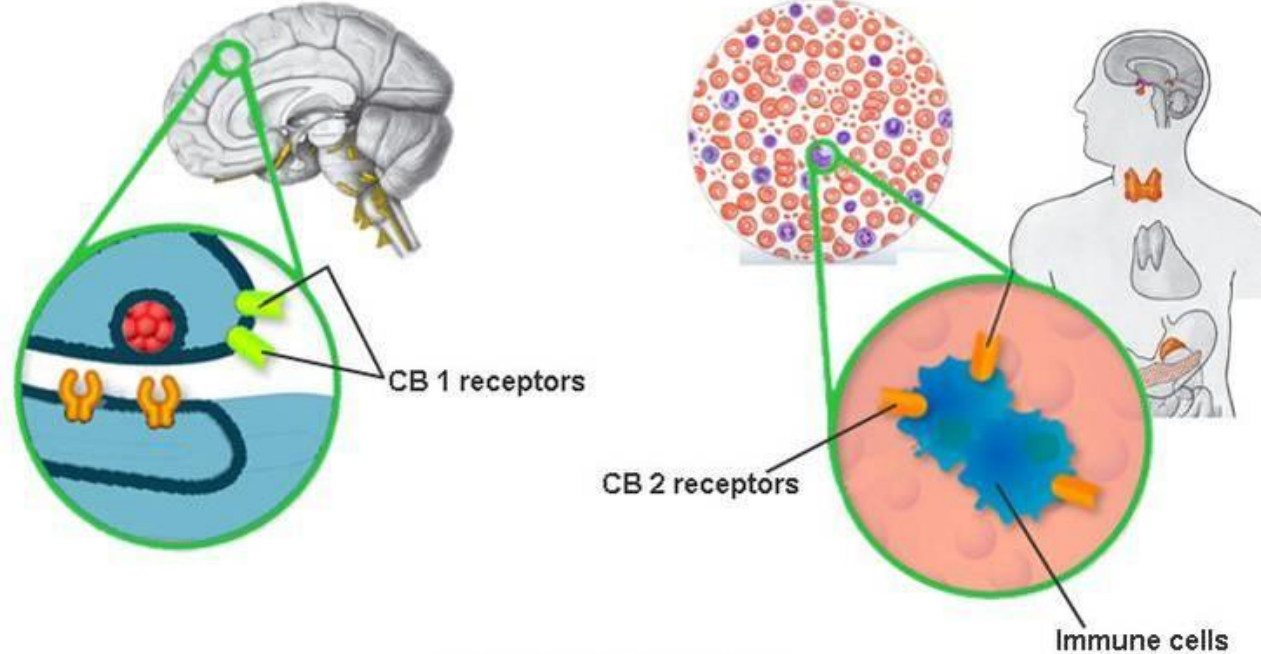
O-arachidonylethanolamine  
(virodhamine )

# 2 GPCRs: 2 Distinct Functions

## Mode of action

**CB1 receptors**  
mainly localized in the brain  
(hippocampus, cerebellum and cerebrum)

**CB2 receptors**  
mainly situated in the periphery  
(spleen, tonsillar and immune cells)



Sobotta: Atlas der Anatomie des Menschen  
©Elsevier GmbH, Urban & Fischer Verlag München

Elsevier and Technische Universität München  
Neuro Endocrinol Lett. 2004 Feb-Apr;25(1-2):14-23.

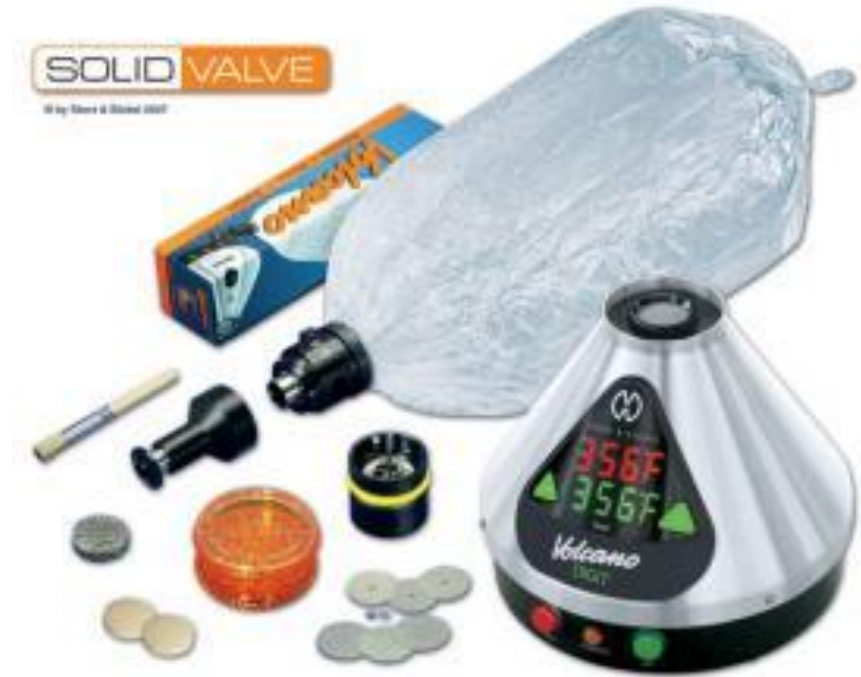
# Clinical Relevance



**Potential Therapeutic Uses of Medical Marijuana**

# Vaporization of medical cannabis

- Cannabinoids vaporize at a temp lower than combustion
- Increasingly popular
- Lower % of noxious chemicals



Raw Cannabis



Structural Modification



Preloaded Cartridges



Metered-Dose Delivery





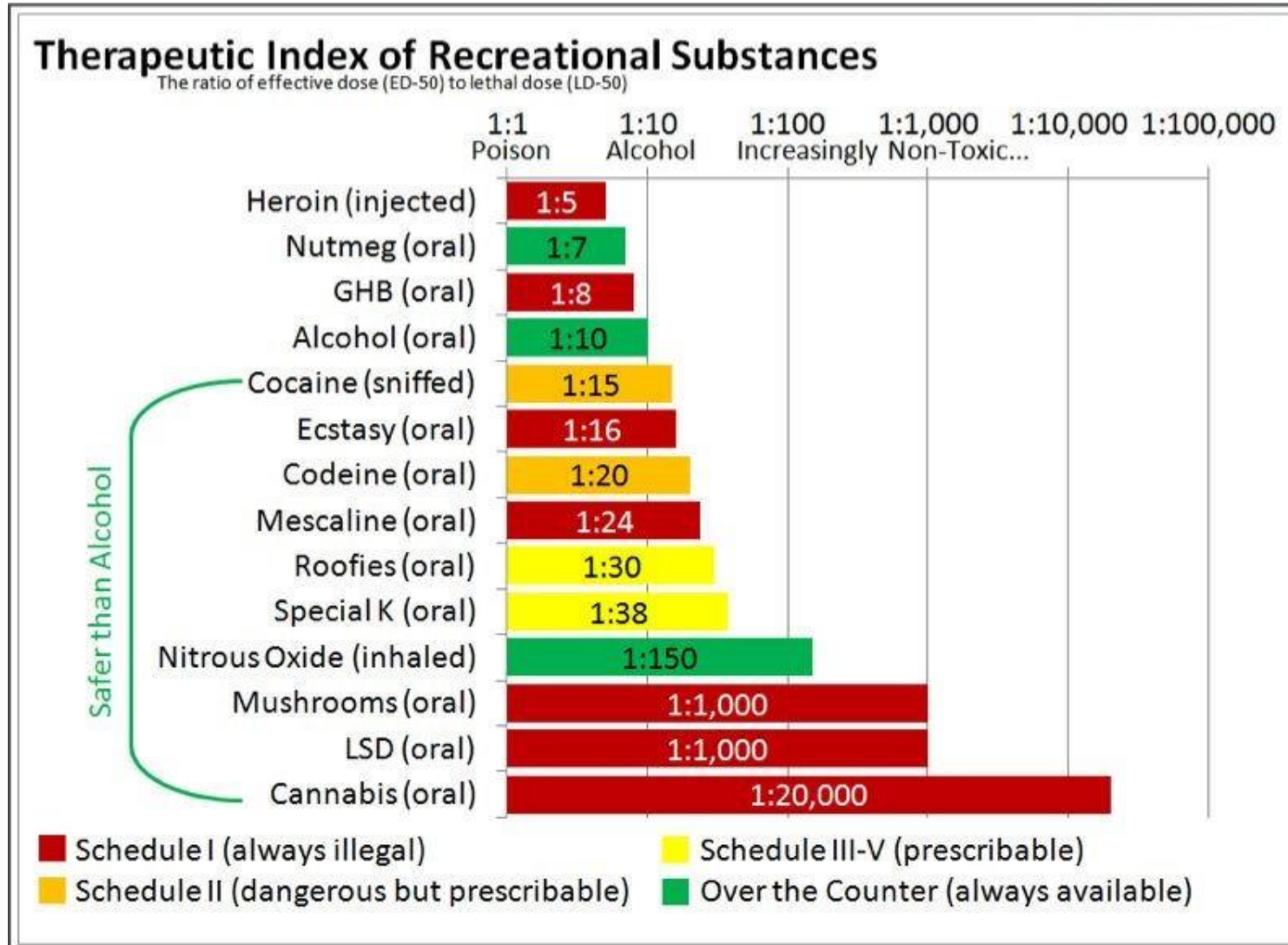
# Side Effects – More than a simple case of the munchies..



# Potential Adverse Effects of Cannabis Use

Adverse Effects	Description
<i>Acute effects</i>	
Euphoria	Decreased anxiety, alertness, tension, depression
Sedation	CNS depression, drowsiness
Perception	Temporal and spatial distortion
Motor function	Ataxia, incoordination, reduced reaction time
Psychomotor function	Impaired hand-eye coordination
Cognition	Deficit in short-term memory, mental confusion
Psychosis	Anxiety, confusion, disorientation, may aggravate schizophrenia
Tolerance	Reduced acute effects of cannabis use
Immunosuppression	No evidence for long-term immunosuppression
<i>Chronic effects</i>	
Respiratory system	Bronchitis, emphysema as with normal cigarette smoking
Cardiovascular system	Tachycardia, postural hypotension, ↓ body temperature, may aggravate existing heart disease
Reproductive system	Decreased sperm counts

# What is the LD<sub>50</sub> of THC?



# Challenges of Developing Cannabinoid Therapeutics: Quality and Manufacturing Demands





# Under the microscope...



The glandular trichomes on the edge of a flower case.  
Width of the image is 0.5 mm wide.

# Terminology / Quality Standards

**Stage 1**

**Botanical Raw Material  
(BRM)**

Plants grown, harvested, dried and  
leaves and flowers removed



**GAP**

(Good Agricultural  
Practice)

**Stage 2**

**Botanical Drug Substance  
(BDS)**

BRM milled and treated to  
produce concentrated extract



**GMP**

(Good Manufacturing  
Practice)

**Stage 3**

**Botanical Drug Product  
(BDP)**

BDS used with ethanol and propylene  
glycol to produce oro-mucosal spray

*Note: Above terms are all taken from FDA botanical guidelines* <sup>33</sup>



# Indoor Control





# Botanical Raw Material: Control of Starting Materials



Purple DanX



Purple Erkle



Super Silver Haze



Trainwreck



Bubba Kush



OG Kush



Purple Kush



Sour Diesel

- Uniform Genetics
- Precise Propagation Timings
- Tightly Controlled Temperature
- Near Uniform Light Intensity
- Automated Irrigation
- Automated Irrigation
- Bespoke Growth Medium
- Tightly Controlled Plant Nutrition
- 'Organic' Pest/Disease Prevention
- Attention to detail by trained staff



**Controlled genetics  
and standardized  
environment to  
produce consistent  
starting material**

# Overview of the Manufacturing Process

- focus on cGMP / Isolation





**Uniform plants grown in controlled conditions**



**Highly controlled drying conditions**



**Highly controlled Extraction process**



**Fully automated GMP manufacturing**



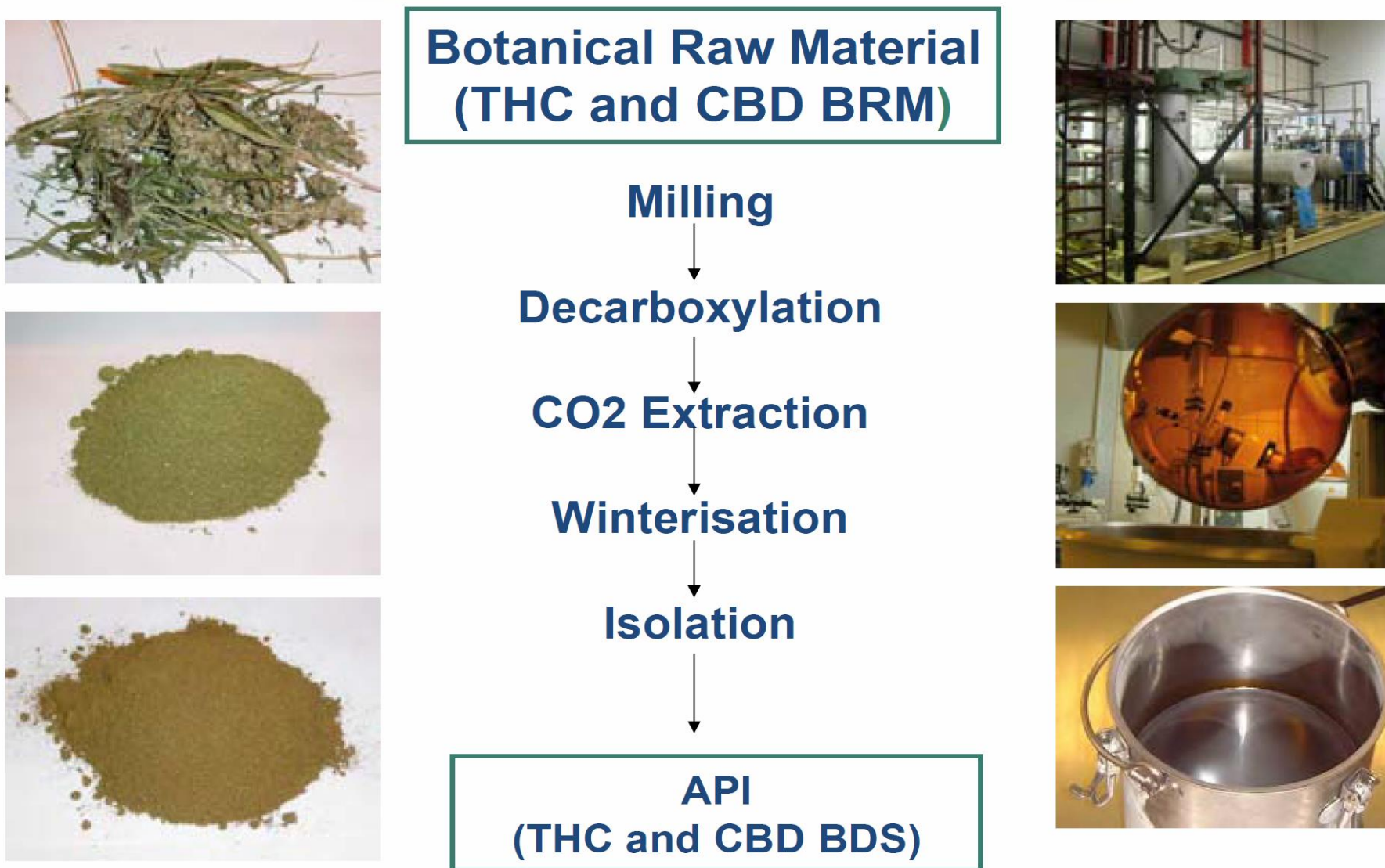
**Fully automated GMP labelling & packing**



**GMP packaging, includes product information, tamper evidence and anti-counterfeit features**



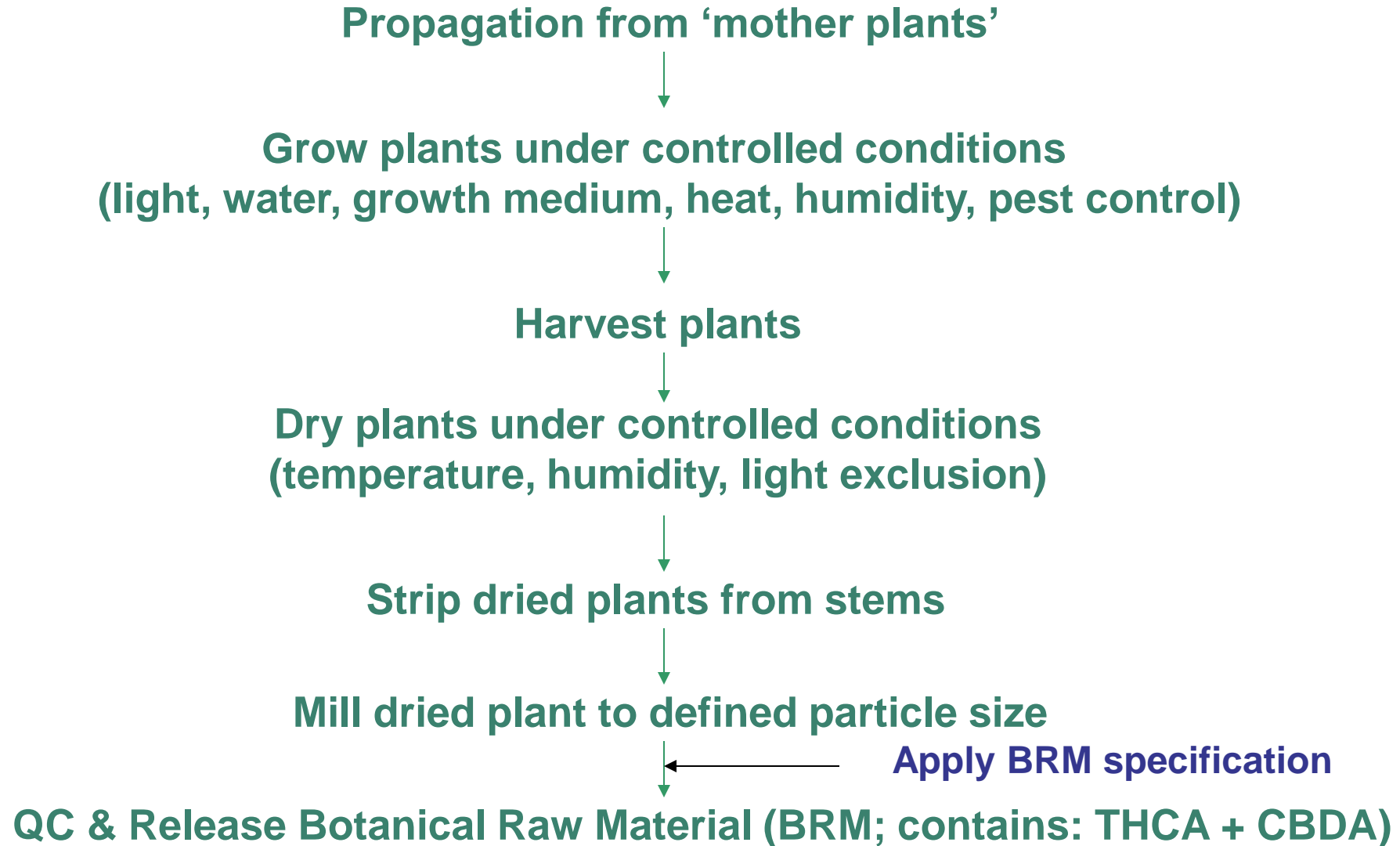
# How do we get the compounds out of the plant?



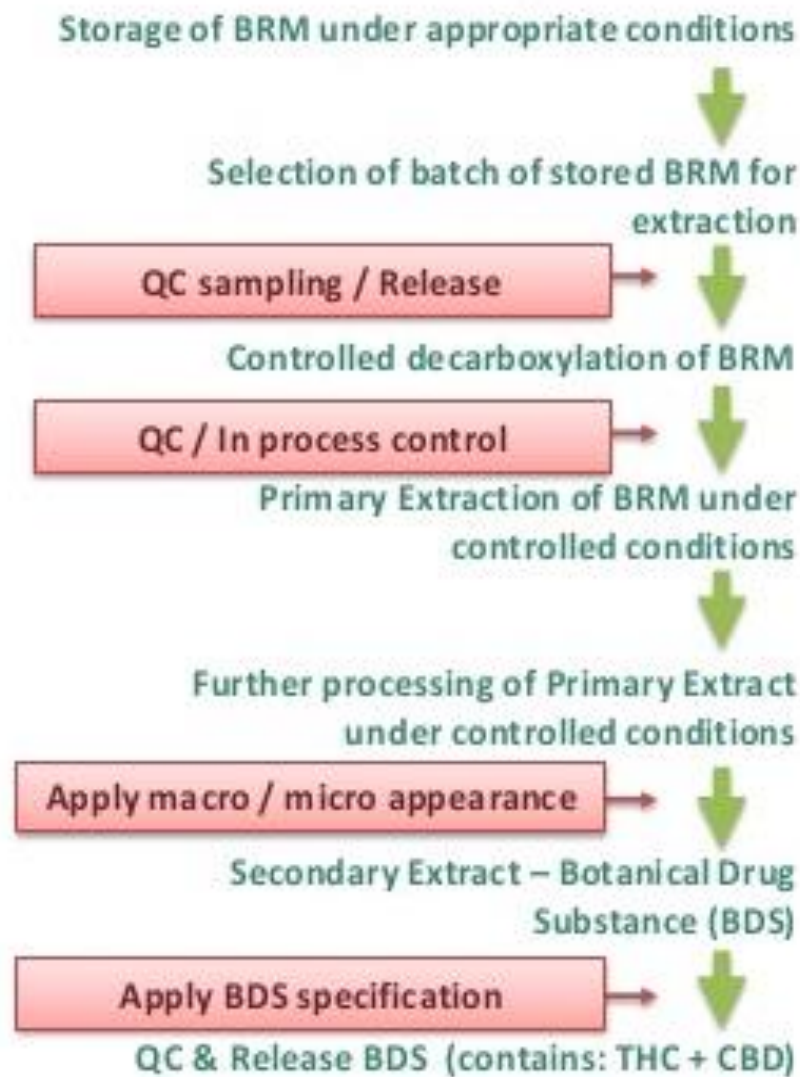
# Supercritical CO<sub>2</sub> – lesson from the Coffee Industry



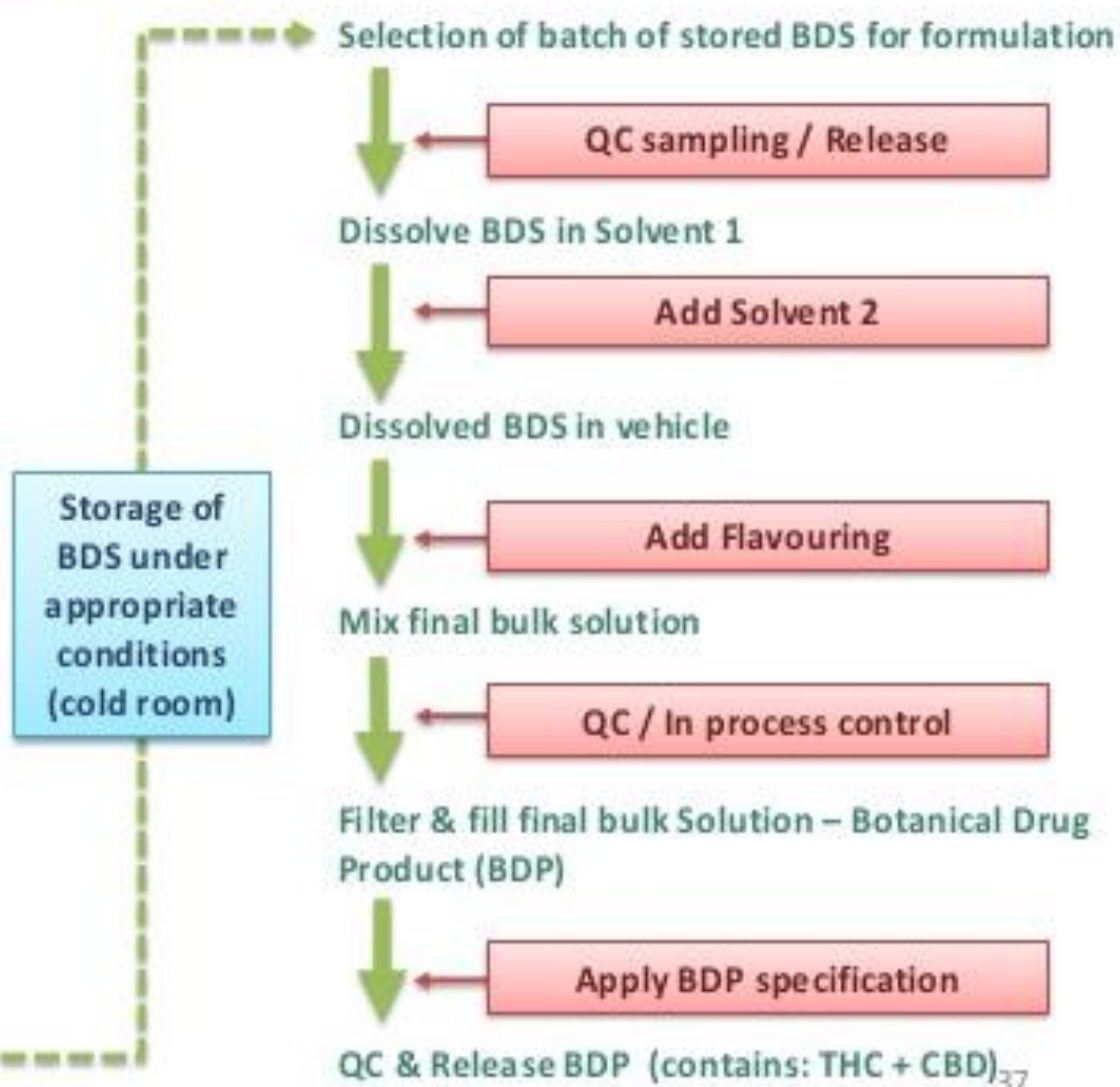
# Control of Starting Materials: GAP Cultivation



## BRM → BDS



## BDS → BDP



Storage of  
BDS under  
appropriate  
conditions  
(cold room)



# New Paradigm in Cannabinoid Pharmaceutical Drug Development

# Cannabinoid Botanical Medicines

- **Breeding and cultivation of cannabis plant varieties**
  - Varieties bred for content of selected cannabinoid molecules
  - **Strict control of growing environment**
    - Controlled breeding of cloned plants
    - Computer-controlled glasshouses
    - Strict quality control procedures
- **Standardised whole plant extracts (GMP extraction)**
- **Formulation into non-smoked drug delivery systems**
- **Full commercial pharmaceutical development programme including pre-clinical and clinical research**
- **Submission and approval from regulatory authorities**

**Data must provide robust evidence for  
Quality, Safety, Efficacy**

# Control of Starting Materials: Chemovar Consistency

- Extracts produced from specially bred plants (“chemovars”)
- Result of a 15 Year Breeding Programme
- Each plant selectively bred for:
  - High rate of cannabinoid production
  - High yield of cannabinoid per unit area
  - High level of purity of the desired cannabinoid (purity as used here defines the consistency of cannabinoid content as a ratio)
  - High inflorescence to leaf ratio (the ‘harvest index’)
  - Natural resistance to pests and diseases
  - Sturdy growth capable of bulk plant handling
  - Ease of harvesting
  - Plant height
  - Optimal time to flowering (critical day length)

# Automation





# What Happens when you Roll the Dice?



# Rolling the Dice continued...

- Leads to ground-breaking research
- Leads to new visions
- Changes the perception / conversation
- Changes thought processes
- Triggers policy discussion / debate
- Continued learning



# Reality



In industry, there is less writing vs academia...



# Iceberg Theory...





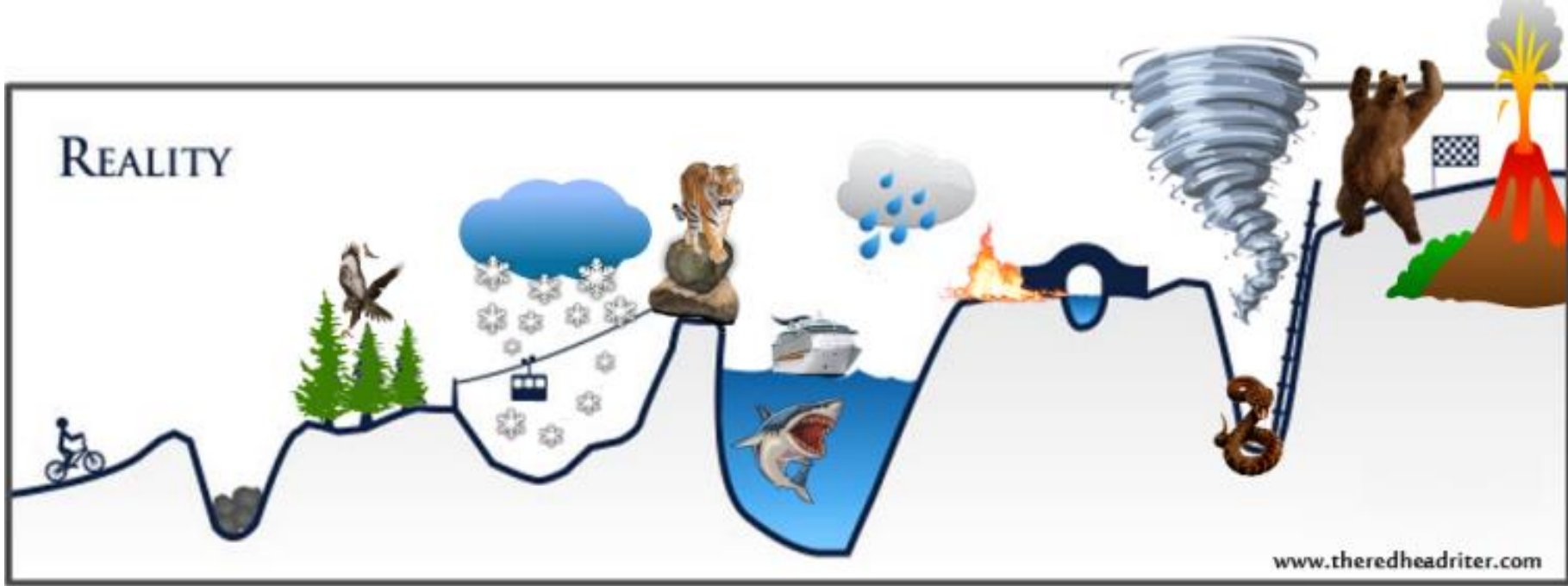
YOUR PLAN



Success



what people think  
it looks like



Success



what it really  
looks like

# Acknowledgements

- Office of Graduate and Postdoctoral Studies, University of Louisville
- CRAFT Seminar Series
- Dr. Russell Salter

# Questions?

