Emerging Markets: Play it Safe or Roll the Dice?

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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

Δ^9-THC
HU-210
CP-55940
Structures continued…

Lipophilic side chain

Most potent analog: 100s times more potent than THC
Endogenous Cannabinoids

- Anandamide
- 2-AG-ether (noladin ether)
- sn-2 arachidonyl - glycerol
- O-arachidonoyl ethanolamine (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)

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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
Side Effects – More than a simple case of the munchies.
## Potential Adverse Effects of Cannabis Use

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Acute effects</strong></td>
<td></td>
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<tr>
<td>Euphoria</td>
<td>Decreased anxiety, alertness, tension, depression</td>
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<tr>
<td>Sedation</td>
<td>CNS depression, drowsiness</td>
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<tr>
<td>Perception</td>
<td>Temporal and spatial distortion</td>
</tr>
<tr>
<td>Motor function</td>
<td>Ataxia, incoordination, reduced reaction time</td>
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<tr>
<td>Psychomotor function</td>
<td>Impaired hand-eye coordination</td>
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<tr>
<td>Cognition</td>
<td>Deficit in short-term memory, mental confusion</td>
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<tr>
<td>Psychosis</td>
<td>Anxiety, confusion, disorientation, may aggravate schizophrenia</td>
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<tr>
<td>Tolerance</td>
<td>Reduced acute effects of cannabis use</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>No evidence for long-term immunosuppression</td>
</tr>
<tr>
<td><strong>Chronic effects</strong></td>
<td></td>
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<tr>
<td>Respiratory system</td>
<td>Bronchitis, emphysema as with normal cigarette smoking</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>Tachycardia, postural hypotension, ↓ body temperature, may aggravate existing heart disease</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Decreased sperm counts</td>
</tr>
</tbody>
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Croxford, JL. CNS Drugs 2003; 17(3)
What is the LD$_{50}$ 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

Stage 2
Botanical Drug Substance (BDS)
BRM milled and treated to produce concentrated extract

Stage 3
Botanical Drug Product (BDP)
BDS used with ethanol and propylene glycol to produce oro-mucosal spray

GAP
(Good Agricultural Practice)

GMP
(Good Manufacturing Practice)

Note: Above terms are all taken from FDA botanical guidelines
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  

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• 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 CO2 – lesson from the Coffee Industry
Control of Starting Materials: GAP Cultivation

1. Propagation from ‘mother plants’
2. Grow plants under controlled conditions (light, water, growth medium, heat, humidity, pest control)
3. Harvest plants
4. Dry plants under controlled conditions (temperature, humidity, light exclusion)
5. Strip dried plants from stems
6. Mill dried plant to defined particle size
7. Apply BRM specification
8. QC & Release Botanical Raw Material (BRM; contains: THCA + CBDA)
BRM → BDS

1. Storage of BRM under appropriate conditions
2. Selection of batch of stored BRM for extraction
3. QC sampling / Release
4. Controlled decarboxylation of BRM
5. QC / In process control
6. Primary Extraction of BRM under controlled conditions
7. Further processing of Primary Extract under controlled conditions
8. Apply macro / micro appearance
9. Secondary Extract – Botanical Drug Substance (BDS)
10. Apply BDS specification
11. QC & Release BDS (contains: THC + CBD)

BDS → BDP

1. Selection of batch of stored BDS for formulation
2. QC sampling / Release
3. Dissolve BDS in Solvent 1
4. Add Solvent 2
5. Dissolved BDS in vehicle
6. Mix final bulk solution
7. QC / In process control
8. Filter & fill final bulk Solution – Botanical Drug Product (BDP)
9. Apply BDP specification
10. QC & Release BDP (contains: THC + CBD)
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

API (THC and CBD BDS) -> Bulk Solution -> Filling -> Packaging
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
Reality

Success

what it really looks like
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Questions?