Quality Control of Cannabis-Derived Prescription Drugs

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Outline

Cannabis as a source of mainstream (prescription) drugs

The origin issue: Natural vs synthetic phytocannabinoids

Coping with the residual phytochemical complexity of Cannabis extracts

Conclusions
<table>
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<tr>
<th>Pharmaceutical</th>
<th>Year of Approval</th>
<th>Formulation</th>
<th>Indications</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>Dronabinol</td>
<td>1986*</td>
<td>Suspension in sesame oil encapsulated in soft gel gelatin capsules (2.5-10 mg)</td>
<td>HIV/AIDS-induced anorexia, chemotherapy-induced nausea/vomiting</td>
<td>Schedule III</td>
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<tr>
<td>Nabiximols</td>
<td>2010**</td>
<td>Oral spray delivering 2.7 mg THC and 2.5 mg CBD per puff</td>
<td>Spasticity associated to MS (overactive bladder, neuropathic pain)</td>
<td>Schedule 4</td>
</tr>
<tr>
<td>Epidi(y)olex</td>
<td>2018***</td>
<td>Oral solution (100 mg/mL) dosed at 2-12.5 mg/Kg BID</td>
<td>Adjunctive therapy for seizures associated with LGS and DS and tuberous sclerosis complex</td>
<td>Schedule V</td>
</tr>
</tbody>
</table>

* FDA approval (Schedule III drug)  ** MHRA approval (Schedule 4 drug)  *** FDA approval (Schedule V drug)
Why the focus on the origin and the production method?
The qualification of the starting material

The qualified starting material depends on the nature of the product:

Cannabidiol (CBD) (from hemp) for the semi-synthesis $\Delta^9$-THC

Non-narcotic Cannabis strains for the isolation of CBD as an API (Epidiolex)

Specific Cannabis strains (*Cannabis sativa folium cum flore, Botanical Drug Substances*) for the preparation of the carbonic extracts of Nabiximols
**Isolation**

a) from *marijuana* (*Cannabis* > 0.3% THC)
b) from hemp (*Cannabis* <0.3% THC)

b) from non-*Cannabis* plant sources*
c) from transgenic organisms (plants, yeasts)

**Semi-synthesis**

* Claim from flax is unconfirmed and the one from hops have been shown to be fraudulent
CBDs of different origin have different regulatory status

USA:

*CBD from marijuana*: schedule I controlled substance

*CBD from hemp*: API, also a cosmetics ingredient but not a dietary ingredient (federal law, allowed by regional law in some States (CA, NY))

*Semi-synthetic CBD*: schedule I controlled substance

EU:

*CBD from isolation*: API and cosmetic ingredient

*CBD from semi-synthesis*: API and cosmetic ingredient
Natural vs synthetic phytocannabinoids: Chromatographic differentiation based on residual phytochemical complexity

Raw extract from hemp (THC < 0.2%)

Isolated CBD (THC < 0.01%)

nor-CBD  CBDV

CBDQ (HU-331)
The synthesis of phytocannabinoids

From fossil carbon

From biological carbon

p-Menthadien-1-ol

CBD

p-Menthadien-3-ol
Natural vs synthetic phytocannabinoids: Differentiation based on isotopical analysis and residual synthetic complexity

Isotopic analysis:
Olivetol is synthesized from $^{14}$C-depleted carbon sources (methylheptenylketone and dimethylmalonate)

Natural carbon is lighter than geological carbon due to a lower contents of the $^{13}$C isotope

The residual synthetic complexity is different from the residual phytochemical complexity
To qualify an extract as a Botanical Drug Substance:

- The starting plant material (herbal substance) need to be grown under GAP practices and its batches proved to comply with the proposed specs
- The preparation of the extract need to be adequately described, and appropriate in-process controls implemented
- COA (certificates of analysis) are needed for all starting material (herbal substance and solvents), along with specific identification tests
- Appropriate characterization of the extract need to have been undertaken and appropriate specs provided
- All potential toxic impurities present in the extract need to be identified and characterized
- Appropriate data of stability need to be provided to support a proper retest period
- Analytical methods need to be appropriately validated and be satisfactory for ensuring compliance with the extract specifications
Conclusions

- For Cannabis-based pharmaceutical products, origin and not only identity is important.
- The regulatory status of CBD needs harmonization between EU and USA in terms of origin (natural/semi-synthetic) and realms of use.
- Natural and synthetic phytocannabinoids can be distinguished based on residual chemical complexity (phytochemical vs synthetic) and isotopic contents.
- The qualification of an extract as a Botanical Drug Substance requires interfacing GAP and GMP rules.

COMPLYING WITH RULES IS BETTER THAN HAVING NO RULE