Beyond Schedule I or II: On the Development of Cannabinoid-Based Drugs Appropriate for Less Restrictive Scheduling Under the Controlled Substances Act

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Abstract

As medicines derived from cannabis move from clinical development and towards regulatory review, the influence of the Controlled Substances Act (CSA) on ultimate scheduling decisions for these drugs will have a profound impact on patients' access to these therapies, as well as their commercial viability. In developing CSA scheduling recommendations, the Drug Enforcement Administration, Food and Drug Administration, and National Institute on Drug Abuse, must consider 8 factors listed in the CSA to develop their recommendations for new medicinal products. In general, CSA scheduling is based on the abuse potential of the substance (i.e., chemical or molecular entity) and all products with that active entity are placed in the same CSA schedule. Although unusual, product formulation differences can lead to products with the same active ingredient being scheduled differently. For example, oral dronabinol products (e.g., Marinol®), in which the active ingredient is mixed sesame oil in capsules, is placed in Schedule III, whereas a product with a synthetic version of the same substance and with the same pharmacological effects is placed in Schedule II.

CSA scheduling determinations are very important in patient care and public health because the more restrictive scheduling, by design, increases the barriers to prescribing and use. For the most dangerous substances, such as morphine, hydrocodone, and fentanyl, which cause widespread addiction and more than 35,000 overdose deaths per year, Schedule II placement is well supported by the data. However, for cannabinoids, which rarely result in overdose death and whose overall profile of abuse-related effects is much weaker (National Academies, 2017), many experts question whether Schedule II is the appropriate schedule in consideration of apparently relatively low rates of physiological and psychological dependence, withdrawal, overdose deaths, and treatment seeking as compared to Schedule II opioids. Inappropriately stringent scheduling might also produce the unintended consequence of reducing the likelihood that people in need will turn to cannabinoid-based medicines when natural cannabis products can be legally obtained in many states.

Lessons learned in the development and regulation of cannabinoids and more recently opioid medications have important implications for the development of cannabis-based pharmaceuticals. These lessons can not only increase their chances of approval for therapeutic use, but also to support recommendations for placement in schedules that are less restrictive than Schedule II. This poster will summarize the types of testing and outcomes that would likely be required to support placement in schedules less restrictive than Schedule II.

Considerations for Developing Cannabinoid Medicines

- Oral vs Inhaled? Does the route of administration make sense for the targeted indication?
- Proper dosing for adequate therapeutic effect but with minimal subjective effects related to abuse potential
- Consideration of antagonists or aversives that may deter dependence and abuse
- Tamper-resistant packaging and/or formulations
- Will improper scheduling decisions prevent patients with the targeted indications from gaining adequate access?

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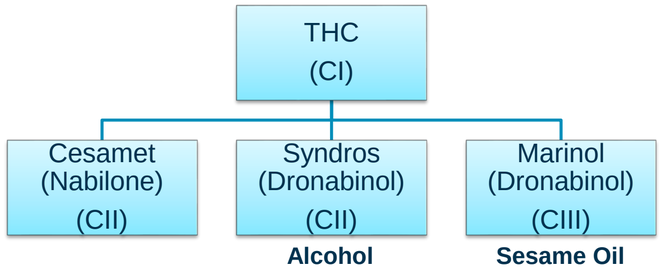
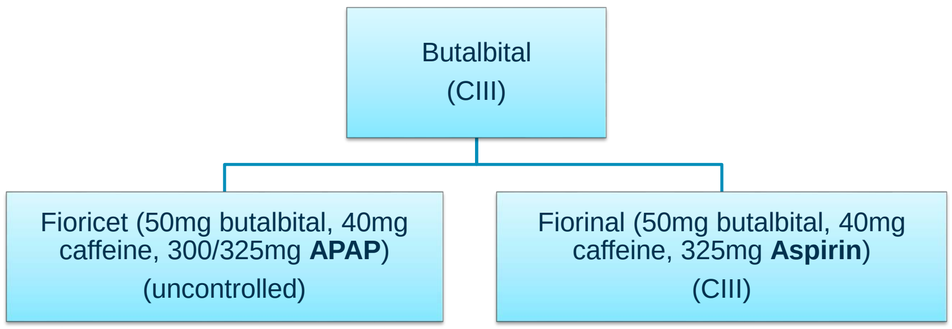
Formulation Matters

Tamper/Extraction Resistant Formulation



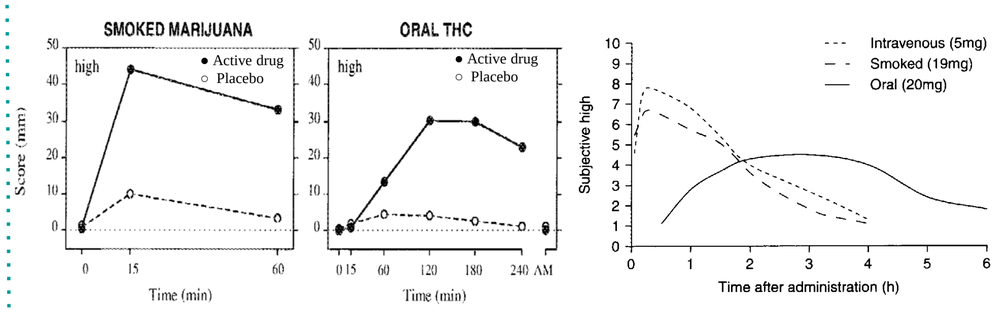
- In 1999, Marinol was switched from CII to CIII because the DEA found "the difficulty of separating dronabinol from the sesame oil formulation and the delayed onset of behavioral effects due to oral route administration supported a lower abuse potential of Marinol"
- Syndros was kept in CII because the DEA concluded "this liquid formulation can be manipulated to produce concentrated extracts of dronabinol for abuse by inhalation"
- As cannabinoid medicine development is still an area of evolving science and regulation, the proposed approach to tamper testing would need to be discussed with FDA

Aversives



- The Controlled Substances Act 811(g)(3)(A) provides a pathway for exemption if the drug in question includes an active non-narcotic controlled substance and a non-scheduled compound that decreases abuse potential
- Exemption requirement for APAP is 70mg to 15mg of butalbital (Fioricet is 97:15)
- Exemption requirement for Aspirin is 188mg to 15mg of butalbital (Fiorinal is 97:15)
- Are there aversives or protectorants that could be used with cannabinoid derived products to deter abuse?

Route of Administration



- Orally administered THC may have lower abuse potential than smoked cannabis due to delayed onset and intensity of subjective measures
- Subjective measurements of "high" are lower for orally administered THC

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Impact of FDA Abuse Deterrent Guidance

Although not intended to guide abuse potential assessment and scheduling the 2015 Abuse Deterrent Opioids guidance provides valuable insights for drug assessment, e.g., in planning studies to address 2017 Abuse Potential Assessment guidance directive under Module 3 (Chemistry):

"The composition and physiochemical properties of the drug product should be discussed in the abuse potential assessment section in the context of their possible impact on abuse potential of the drug substance, and relative to the drug schedule of already-marketed formulations containing the same drug substance if it is a controlled substance."

FDA's Seven Categories of Abuse Deterrent Products

1. Physical/Chemical Barriers
2. Agonist/Antagonist Combinations
3. Aversion
4. Delivery System
5. New Molecular Entities and Prodrugs
6. Combination
7. Novel Approaches

Study Type	Desired Outcome
In Vitro	Tamper/Extraction Resistance
In Vivo	Delayed or Diminished PK/Likability/Subjective Effects
Post-Marketing	Abuse Reduction/Adverse Events

References

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Disclosures

PinneyAssociates consults with pharmaceutical companies that market a wide variety of prescription and over-the-counter medications including prescription opioids and stimulants. However, no financial support was provided for the preparation or presentation of this poster.