CANNABINOIDS: AN EXECUTIVE SUMMARY

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OBJECTIVES

- Update on State and Industry Regulation.
- What levels of cannabis and cannabis-derived compounds cause safety concerns?
- How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?
- How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?

OBJECTIVES

- Are there special human populations (e.g., children, adolescents, pregnant and lactating women) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?
- Recommendations/Summary

CURRENT KANSAS REGULATIONS

- Claire and Lola's Law—Possession of Certain Cannabidiol Treatment Preparations, Actions and Proceedings Prohibited, Affirmative Defense
- SB 28 creates and amends law related to possession of certain cannabidiol (with THC) treatment preparations. Signed by Governor Kelly- May 20th, 2019. Effective- July 1, 2019.
- Allows the use of CBD with THC of not more than 5% for "debilitating medical conditions" with subsequent protection under the law

CURRENT KANSAS REGULATIONS

- The bill creates “Claire and Lola’s Law,” which prohibits state agencies and political subdivisions from initiating child removal proceedings or child protection actions or proceedings based solely upon the parent’s or child’s possession or use of cannabidiol treatment preparation in accordance with the affirmative defense established by the second section of the bill. “Cannabidiol treatment preparation” is defined to mean an oil containing cannabidiol and tetrahydrocannibinol and having a tetrahydrocannibinol concentration of no more than 5 percent relative to the cannabidiol concentration in the preparation verified through testing by a third party, independent laboratory

CURRENT KANSAS REGULATIONS

- The bill prohibits construing its provisions to:
- ● Require the Kansas Medical Assistance Program or various other policies, plans, contracts, or organizations that provide coverage for accident and health services and that are delivered, issued for delivery, amended, or renewed on or after July 1, 2019, to provide payment or reimbursement for any cannabidiol treatment preparation; or
- ● Allow the possession, sale, production, redistribution, or use of any other form of **cannabis**

CURRENT KANSAS REGULATIONS

- The bill defines "debilitating medical condition" as a
  -- medically diagnosed chronic disease or medical condition
  --causing a serious impairment of strength or ability to function, including one that produces seizure.
  --for which the patient is under current and active treatment by a physician licensed to practice and surgery in Kansas

CURRENT KANSAS REGULATIONS

--must have possession of a letter that (a) shall be shown to a law enforcement officer on such officer's request, (b) is dated within the preceding 15 months and signed by the Kansas licensed physician who diagnosed the qualifying condition, (c) is on such physician's letterhead, and (d) identifies the person or minor child as such physician's patient and identifies the patient's qualifying condition.

CURRENT KANSAS REGULATIONS

- PERSONAL OPINION:
- An honest attempt at trying to do something positive
- But, an archaic law at best, putting an undue burden on patient and doctor.
- Why? Because the amount approved is basically less than medicinal doses of THC and should not require such stringent regulation as opposed to medicinal doses of THC.
- Has created confusion among Legislators, KBI, retailers and the public

INDUSTRY SELF REGULATION

U.S. Hemp Roundtable

INDUSTRY SELF REGULATION

- **THE U.S.HEMP ROUNDTABLE:**
- Launched in early 2017
- A coalition of over dozens of hemp companies
- Representing every link of the hemp product chain, from seed to sale
- Membership has grown to 75 companies in 2 years
- Established the Hemp Authority as a certification process to include GMP certification.

INDUSTRY SELF REGULATION

- **THE U.S.HEMP ROUNDTABLE:**
- Focused lobbying efforts in state capitols to fully legalize hemp and popular hemp-derived products like cannabidiol (CBD)
- Facilitating information exchange with law enforcement and federal agency officials
- Continued long-term legislative advocacy on other major policy issues, remaining vigilant against potential attempts of rival industries to halt hemp's progress
- Coordination with the US Hemp Authority, whose certification program promotes high standards, best practices and self-regulation, providing confidence to consumers that hemp products are safe and to law enforcement that they are legal

INDUSTRY SELF REGULATION

- **U.S. HEMP ROUNDTABLE EXECUTIVE COMMITTEE**
- American Shaman
- Barlean's
- Bluebird Botanicals
- Charlotte's Web, Inc.
- CV Sciences
- Elixinol
- GenCanna
- Zilis

INDUSTRY SELF REGULATION

INDUSTRY SELF REGULATION

- **The U.S. Hemp Authority™ Certification Program is our industry's initiative to provide high standards, best practices and self-regulation, giving confidence to consumers and law enforcement that hemp products are safe, and legal. In an effort funded by the US Hemp Roundtable, and joined by organizations such as the Hemp Industries Association, industry leading firms, top-tier testing laboratories, and quality assessors developed comprehensive guidance for growers and processors of hemp.**

INDUSTRY SELF REGULATION

- Atalo Holdings
- Balanced Health Botanicals, CBDistillery, Bota
- Barleans
- Bluebird Botanicals
- Charlotte's Web
- CV Sciences
- Daddy Burt Hemp
- Elixinol
- EVG Extracts
- Farmer's Daughter Hemp
- FSOil
- GenCanna Global
- Great Lake Cultivars
- HempDepot
- HempFusion

INDUSTRY SELF REGULATION

- Hemptown USA, KY
- HempWorx
- Kannaway, HempMeds, Dixie Botanicals
- Kentucky Crafted
- Medterra
- Nature's Hemp Oil
- Nutrition Formulators
- Pet Releaf
- Precision Seed Production
- Puffin Hemp
- Pure Vision Technology
- RAD Extracts
- Shaman Botanicals
- Shell Farms
- 28 Small Farms in Central KY
- Vitagenne
- Winged Nutrition
- Zilis

CANNABINOIDS: AN EXECUTIVE SUMMARY

- The Food and Drug Administration's Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds Part 15 Public Hearing May 31, 2019 7:00 AM – 6:00 PM U.S Food and Drug Administration White Oak Campus Building 31, Room 1503 - Great Room 10903 New Hampshire Avenue Silver Spring, MD 20993

What levels of cannabis and cannabis-derived compounds cause safety concerns?

--The overall safety of both CBD and CBDHO has been well established in normal, healthy humans and in humans with various diseases (Bergamaschi 2011, Iffland 2017).

--With increasing doses, the risk of minor side effects may increase.

--Doses above 20 mg/kg/day seem to produce more of these minor side effects than do lower doses.

What levels of cannabis and cannabis-derived compounds cause safety concerns?

- In many individuals, these minor side effects (nausea, dizziness, sleepiness, sensitivity) resolve with continued use; however, some individuals have to decrease or discontinue using CBD/CBDHO for these to resolve.
- Significant adverse side effects of drug-drug interactions (DDI) and abnormal liver function tests (LFT) results may occur in specific situations. (see upcoming slides)
- In addition, allergies to proteins that are common to all C. sativa plants (both marijuana and hemp) have been identified

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- Definitions:
- **AUC** – Area under the curve. The plot of plasma concentration of a drug versus time after dosage. This gives insight into the extent of exposure to a drug and its clearance rate from the body. Pharm Res. 2011 May; 28(5): 1081–1089

- **Cmax** is the maximum (or peak) serum concentration that a drug achieves in a specified compartment or test area of the body (i.e. plasma) after the drug has been administrated and before the administration of a second dose. Tracy TS (2004). "Pharmacokinetics". Modern pharmacology with clinical applications. Hagerstwon, MD: Lippincott Williams & Wilkins. p. 49.

- **Tmax** is the time after the administration of a drug when the maximum plasma concentration is reached; when the rate of absorption equals the rate of elimination.
  The Free Medical Dictionary. Com

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- **Low Dose Studies (< 30 mg of CBD): Oral Ingestion**

There is minimal difference in AUC and Cmax between oral and oromucosal administration routes for CBD doses less than 20mg (Millar 2018).

Specifically, for oral doses from 5 to 20 mg, the AUC is consistently less than 20 (h x ng/ml) and the Cmax less than 5 ng/ml, with the half-life ranging from 3-10 hours for all types of preparations (sprays, tinctures, and pro-nanoliposphere formulations) (Millar 2018, Altsmon 2018).

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- However, recent research using nano-lipospheres to deliver CBD has shown that oral absorption (i.e. gastric) can be increased up to 3-4 times that of CBD oromucosal absorption.(Cherniakov 2017)

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- **Low Dose Studies (< 30 mg of CBD): Inhalation**

- Inhalation or smoking of CBD/CBDHO results in a much higher AUC and Cmax, and generally a lower Tmax, even at much smaller dosage levels (Millar 2018).

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- **Low Dose Studies (< 30 mg of CBD): Inhalation**

- AUC and Cmax from inhalation or smoking can vary tremendously from individual to individual, and this variation is ten times that seen with oral or oromucosal administration (Millar 2018, Ohlsson 1986).

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- **Low Dose Studies (<30 mg of CBD): Transcutaneous**

- Transcutaneous absorption of CBD and other cannabinoids does occur and can have systemic effects.(Giacoppo 2015, Huestis 2007)

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- **Low Dose Studies (<30 mg of CBD): Transcutaneous**

- Although, the pharmacokinetics are not well established, the amount of absorption of CBD via various transcutaneous applications (creams, ointments, etc.) appears to be in the same range or less as that of oral or oromucosal ingestion when low dose CBD (<30mg/ml) is applied.

How does the mode of delivery (e.g., ingestion, absorption, inhalation) affect the safety and exposure to cannabis and cannabis-derived compounds?

- **High dose studies (>50 mg of CBD):** Reported high dosage studies (>50 mg) have primarily used the oral route of administration.
- The findings include:

(1) Increasing oral doses led to less than dose-related elevations of AUC and Cmax with increasing variability of both from subject to subject ***(more is not better)***

(2) Steady-state CBD plasma levels occur after approximately two days of dosing; and

(3) CBD elimination is multiphasic, with the terminal elimination half-life being approximately 60 hours and the effective half-life ranging from 10 to 17 h, thereby supporting twice a day dosing

(Millar 2018,Taylor 2018).

How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?

- **OVERVIEW**:
- CBD is metabolized in the liver via the CYP450 system
- Drug-drug interactions (DDI) can occur with drugs metabolized by that enzyme system (Zendulka 2016, Arellano 2017, Arnold 2018, Yamaori 2010, Yamaori 2011a, Yamaori 2011b).
- Other drugs can affect blood CBD and CBD metabolite levels, and CBD can affect the blood levels of other drugs and their metabolites (Morrison 2019).

How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?

- **Epileptic medications:**

- Most studies of DDI in humans have involved epilepsy drugs (Gaston 2017, Devinsky 2018a, Devinsky 2018b).
- In healthy volunteers, some epilepsy drugs can increase some metabolites of CBD, although not CBD itself, while CBD can increase the blood levels of some epilepsy drugs.
- **Epidiolex** (a form of CBDHO) can affect the blood levels of some epileptic drugs, the greatest being the inhibition of metabolism of desmethylclobazam (Gaston 2017, Devinsky 2018a). These effects tend to occur at the oral dose of 10 mg/kg/day.

  So, for example, a 131-pound adult woman (~25th percentile average weight in USA) would require dosing of 600 mg/day of CBD/CBDHO to cause this DDI.

How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?

- **Warfarin:**
- One case of Epidiolex (CBDHO) causing an elevation in INR has been reported in a patient with epilepsy and a history of a CVA who was on warfarin (Grayson 2017).
- Again, the increase was seen at an oral dose of 10 mg/kg/day.
- Decreasing or titrating the individual's warfarin dosing was necessary while the dose of CBD was being increased.

How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?

- **Other drugs:**

- No other DDI has been reported in the literature.
- In animals, the amounts of CBD that cause DDI are very high – greater than 30 mg/kg/day (Iffand 2017), and similar levels may be needed to cause significant clinical DDI reactions in humans.
- However, other than in epilepsy, there are no DDI reports or studies in humans using >30 mg/kg/day.
- The absence of reports of CBD/CBDHO causing DDI with other drugs indicates that total daily exposure of >30mg/kg/day is necessary for DDI in most clinical situations (Kosel2002, Bergamaschi 2011).

How do cannabis and cannabis-derived compounds interact with other substances (e.g., drug ingredients)?

- **Other drugs:**
- Observationally, it is know that CBD/CBDHO can cause vasodilatation, so utilization with antihypertensives at **high doses (>30 mg/kg)** may increase potential for adverse reactions, such as syncopal episodes. Lower doses have not been shown to increase adverse events
- **Formulation of the CBD/CBDHO product** can be a factor as well, as water-soluble nano-molecular products can be given in lower doses with better absorption for affect and thereby decrease the potential for DDI, as opposed to an oil based product which typically requires higher doses for affect due to poorer absorption

Are there special human populations (e.g., children, adolescents, pregnant and lactating women) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?

- **Children/Adolescents:**
- It has been well-established that CBD and CBDHO have significant effects on many different brain functions (Schonhofen 2018, Pannekoek 2013, Crippa 2004, Fusar-Poli 2009, Stern 2015, Jurkus 2016, Lee 2017, Hudson 2018, Renard 2016, Stern 2012, Murillo-Rodriquez 2017).

- It has been shown that THC adversely affects the normal development of brain function and structure in adolescents and that these effects can persist throughout life (Ashtari 2011, Yucel 2016, Solowij 2008, Broyd 2016, Rubin 2014, Burggren 2018).

Are there special human populations (e.g., children, adolescents, pregnant and lactating women) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?

- **Children/Adolescents:**

- At the same time, anecdotal human reports and animal studies have shown that not only is CBD/CBDHO effective in treating therapy-resistant epilepsy, it may improve other conditions commonly found in children.

- These conditions range widely and include emotional/cognitive disorders (e.g., anxiety and ADD/ADHD.) and allergy/immunological disorders (e.g., atopic dermatitis, asthma, urticaria, and rheumatoid arthritis), as well as other conditions.

- Therefore, the potential risks of CBD/CBDHO in adolescents and children must be seriously weighed against the potential benefits.

Are there special human populations (e.g., children, adolescents, pregnant and lactating women) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?

- **Pregnant/Lactating Women:**
- It is unknown if CBD crosses the placenta in humans; however,

- THC does cross the placenta and, because the two compounds tend to have similar absorption and metabolic characteristics, it is assumed that CBD crosses also (Wang 2017).

- The endocannabinoid system plays a crucial role in the ontogeny of the central nervous system and its activation during brain development, can induce subtle and long-lasting neurofunctional alterations.(Compologo 2009)

Are there special human populations (e.g., children, adolescents, pregnant and lactating women) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?

- **Pregnant/Lactating Women:**

- In mice, high doses of CBD/CBDHO given to pregnant mice throughout pregnancy did not have any adverse effect on gross fetal development (McCuistion 2018).

- In human placenta cultures, CBD changes the placenta's morphological and physiologic characteristics, and may reduce its protective function.(Feinshtein 2013).

Are there special human populations (e.g., children, adolescents, pregnant and lactating women) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?

- **Pregnant/Lactating Women:**
- Yet, spontaneous premature labor may result from anxiety or depression, and CBD has been shown to decrease both of these (Staneva 2015, Campos 2016)
- Animal studies have shown that CBD may reduce perinatal hypoxic brain damage, especially if given prior to the insult (Lafuente 2011, Garberg 2017, Pazos 2012, Pazos 2013, Castillo (2010).
- CBD is found in breast milk and breast-feeding infants can ingest it.(Huestis 2007, Wie 2016)

Are there special human populations (e.g., children, adolescents, pregnant and lactating women) that should be considered when assessing the safety of products containing cannabis and cannabis-derived compounds?

- **Pregnant/Lactating Women:**
- Given the role of the endocannabinoid system in pregnancy implantation, placentation, and fetal neurologic development, it is entirely plausible that CBD/CBDHO could have both adverse and favorable effects on pregnancy and the fetus (Metz 2018).
- These findings raise the possibility that there may be some benefit in administering CBD/CBDHO to women during pregnancy.

CANNABINOIDS: AN EXECUTIVE SUMMARY

- **Recommendations:**
- **1) Given this research, we recommend that a safe level can be established.**
- We recommend that a **total CBD exposure level of <60mg/day be established for OTC** use of CBD/CBDHO products.
- This would provide a safety index (minimal dose causing a reaction/maximum recommended dose) of 10 or higher for adults weighing over 131 pounds (~82% of the adult population) who are taking other drugs that might cause a DDI or an elevated LFT.

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- **Recommendations:**
- This safety index of 10 is based upon untreated (no nano-liposphere technology) CBD/CBDHO.

- If the CBD/CBDHO is treated with absorption enhancing nano-liposphere technology, the Safety Index decreases to 2.5 due to better absorption. Thus taking higher doses is not necessary and could be determental.

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- **Recommendations:**

- Conditions or individuals requiring >60mg/day of CBD should be directed and followed by a physician.

- It is assumed that more products (pills, oromuocal sprays, oral liquids, nasal sprays, etc.) will be produced in the near future using nano technology that will enhance the absorption of CBD/CBDHO, that is why we have recommend this daily level (60mg/day)

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- **Recommendations:**

- **2) To achieve this dosing, we recommend that products for oral, oromucosal, and transcutaneous delivery contain <30mg/ml or 5-10mg/capsule of CBD to be taken for a total daily dose of 60 mg.**

- The typical modes of oral and oro-mucosal delivery (droppers, sprays, etc.) can be easily calibrated and used to measure appropriate increments for accurate dosing.

- Transcutaneous application can be easily adjusted for incremental dosing, as well.

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- **Recommendations:**
- **3) Given the paucity of good PK/bioavailability of CBD/CBDHO on administration via modes of delivery other than oral, oromucosal, and transcutaneous administration, no scientific conclusions can be drawn on safe dosing through any other mode.**
- The smoking/inhaling route is obviously unsuitable for medicinal drug delivery (Devinksy 2014).

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- **Recommendations:**
- Further, the high variability noted in the little data that is available on smoking/inhaling of CBD/CBDHO suggests the use of much lower doses than those recommended for oral and oromucosal administration.
- Therefore, we recommend currently restricting modes of delivery to only oral, oromucosal, and transcutaneous administration.

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- **Recommendations:**
- **4) CBD/CBDHO to children/adolescents should be available only via adult supervision and/or under the care of a health care professional.**

- Since CBDHO contains small amounts of THC, we recommend that CBD be used as a trial first for children/adolescents, followed by CBDHO only when adequate response to CBD is not obtained (Schonhofen 2018).

- In addition, since synthetic cannabinoids tend to have more adverse health effects (Van Amsterdam 2015), we recommend that hemp oil-derived CBD/CBDHO should be used.

- **5) Due to the current lack of knowledge among health care professional regarding CBD/CBDHO and the endocannabinoid system, we further recommend a directed education of health care professionals, so that they can help guide patients and their guardians.**

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- **Recommendations:**
- **6) As in children/adolescents, the benefits of use of CBD/CBDHO in pregnancy must be weighed against the possible adverse effects and should only be taken under the supervision of medical professionals.**

- To this end, we recommend substantial efforts at educating health care professional regarding CBD/CBDHO and the endocannabinoid system, so that they can help guide patients intelligently.

- **7) In light of the possibility of beneficial aspects for administering CBD/CBDHO in pregnancy, we recommend a registry to gather data to be able to answer the question of the safety of CBD/CBDHO in pregnancy.**

- **THANK YOU FOR YOUR ATTENTION**