Summary of Cannabidiol Safety Studies

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Note: This talk will focus primarily on Human Supplements with our detailed written comments to also include a discussion of Animal Supplements.

Dixie Brands Inc.

- Dixie Brands Inc. (Dixie) based in Denver, CO has been a pioneer in hemp and CBD products since 2009, and is now a publicly listed company on the Canadian and US exchanges
- Dixie is a leader of the global industry in the development, packaging design, and product innovation for the commercial production and sale of hemp products
- Dixie includes two well-researched and scientifically formulated broad spectrum hemp wellness brands in the human and animal supplement categories
- The animal supplement brand just partnered with a major university veterinary school for a clinical study of CBD and canine joint health
- Both the Human and Animal Supplement brands use broad spectrum hemp with naturally-occurring cannabidiol and, of course, manufactured in certified GMP facilities
- Per our regulatory counsel, both our supplement brands are marketed and labeled as hemp (and not CBD) products
- Founding member of several national legislative policy and business-oriented industry organizations, including the Cannabis Trade Federation (CTF)

Summary of Select *in vivo* Safety Studies in Human
(1973-2010 in Ascending Dose Order)

Study	Route	Dose	Findings
Karniol, et al. (1974)	Oral	15-60 mg	No significant side effects on heart rate, psychological reaction and timed production tasks
Hollister (1973)	Oral	20-100 mg	No significant side effects
Zuardi, et al. (1982)	Oral	1 mg/kg bw	No significant effects on heart rate and bodily functions
Cunha, et al. (1980)	Oral	3 mg/kg bw; 200 mg and 300 mg per day	No effects on neurological and physical exams, blood and urine analysis, electrocardiogram, and electroencephalogram
Crippa, et al. (2010)	Oral	300-600 mg/ day	No significant side effects
Bergamaschi, et al. (2011)	Oral	600 mg	No significant effects on heart rate, blood pressure, skin conductance, bodily symptoms, and psychological measurements
Consroe, et al. (1991)	Oral	10mg/kg/day	No significant side effects
Zuardi, et al. (2006)	Oral	40-1280 mg/ day	No significant side effects

The Epidiolex Safety Trial and Extended Access Program

- 607 patients in the Safety arm of the Extended Access Program
- Extended study starting at a dosage of 2-10 mg/kg/day to a maximum dose of 25 – 50 mg/kg/day (Epidiolex recommended maintenance dosage is 20 mg/kg)
- The study findings correspond to a daily dose range of 20 mg to 500 mg per day for the study and a 200 mg per day maintenance dose of Epidiolex for a 10 kg child
- Primary findings: CBD is generally well tolerated in a vulnerable patient population: children with Dravet Syndrome and children with Lennox-Gastaut Syndrome
- A majority of the reported adverse events were associated with interactions with Clobazapam (somnolescence) and Valproate (elevated hepatic aminotransferase levels)
- The CBD-Clobazapam interaction was previously characterized by Geffrey, et al. (2015)
- Potential mechanism of drug interaction appears to be inhibition of hepatic cytochrome p450 enzymes

Devinsky, et al. 2017, Szaflarski, et al. 2018, Geffrey, et al. 2015

A Critique of Ewing, et al. 2019

- Mouse trial concluding hepatotoxicity from serum chemistry, histological, and gene expression analyses after extremely high doses of CBD-rich extracts
- The study has numerous flaws and weaknesses including but not limited to:
  - The test substance is not representative of Epidiolex, a purified CBD isolate
  - Specifically, the test substance was a ***hexane*** extract of federally compliant hemp plant matter containing 57.9% CBD, 2.03% Cannabichromene, ***1.69% Δ^9-THC***, 1.07% Cannabigerol
  - Residual solvents were measured at less than 0.5%; however, the Colorado limit for hexane in hemp and cannabis extracts is substantially lower (< 60 ppm or 0.006%)
  - Therefore, the test substance is not permissible in any hemp extract-containing supplements per Colorado State, Colorado Department of Health, Washington, Oregon, or California regulations for cannabis or hemp extracts
- The complex nature of the test substance in the study design, dosage calculations (simple BSA allometric scaling), and delivery method provide innumerable confounding variables which are not properly controlled and therefore significantly limit the translation of their findings to human populations

Ewing, et al. 2019

Conclusions on the Safety of Cannabidiol

- Studies of the safety of Cannabidiol in humans have shown safety across a wide range of dosages (15 mg to 1280 mg) in both healthy and vulnerable populations
- The Epidiolex safety trials showed safety in a vulnerable patient population at dosages of up to 50 mg/kg with an optimized dosage of 20-25 mg/kg
- Cannabidiol, like other safe and natural ingredients currently in commerce (Grapefruit, St. John's Wort, Garlic), can alter hepatic cytochrome p450 levels which can lead to potential herb-drug interactions
- Current consumer products range from 10 mg to 125 mg (< 1 – 2.8 mg/kg for a 60 kg adult) per serving size, well within the demonstrated safe dosage range for healthy adults from a review of the literature
- Based upon a review of the available scientific data, the maturation of hemp and cannabis safety standards in states like Colorado, the lack of any reports of serious adverse effects, and the rigorous safety standards enforced by the FDA for all approved pharmaceuticals, a well-supported, research-based conclusion that Cannabidiol is a safe molecule can be made

Note: The Dixie Brands written comments will also include a detailed discussion of safety in Animal Supplements.

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