Summary of the application: Isopropyl Alcohol (IPA) extract from *Cannabis sativa* L.

Applicant: Charlotte's Web, Inc. Address: 1600 Pearl Street, Suite 300, CO 80302 Boulder, the United States of America.

Charlotte's Web (CW) hemp-derived isopropranol (IPA) extract is the novel food under application which contains cannabidiol (CBD) at approximately 43%. The rest of the extract contains other cannabinoids, terpenes, non-cannabinoid lipids and carbohydrates. CW's hemp-derived IPA extract is intended to be used in food supplements for use by the general population above 3 years of age, excluding pregnant and lactating women. CW's hemp-derived IPA extract is obtained by solvent-based extraction (isopropanol) of the hemp plant material followed by desolvation and decarboxylation of the resulting hemp extract.

The manufacturing process of CW's hemp-derived IPA extract can be described as follows: 1. Hemp from fields located in the US are harvested, sampled and sent for extract processing. 2. In-house processes at the Charlotte's Web, Inc. LOFT produce Charlotte's Web hemp-derived IPA extract using isopropyl alcohol (IPA) as the solvent. 3. Raw hemp is delivered to the alcohol extraction process suites for extraction. Extract is produced by isopropanol extraction and is sampled, labelled, placed under the designation of Quality Control Hold, then transferred to a secure Work-In-Process (WIP) storage location until testing is returned and the extract can be released for use in finished products.

Charlotte's Web has performed genotoxicity testing and sub-chronic toxicity testing. The genotoxicity of Charlotte's Web hemp-derived IPA extract was assessed with a Good Laboratory Practices (GLP)-compliant bacterial reverse mutation test, conducted in accordance with Organisation for Economic Co-operation and Development (OECD) guideline 471. The results showed that Charlotte's Web hemp-derived IPA did not show evidence of bacterial mutagenicity, and is therefore considered to be non-mutagenic. The literature further supports that hemp-derived extracts obtained via supercritical CO2 extraction are non-genotoxic and non-mutagenic (Marx et al. 2018).

A review of the literature showed that a standard battery of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use *(*ICH*)*/GLP-compliant genotoxicity tests have been conducted (Ames assay, in vivo micronucleus assay in rat and in vivo alkaline COMET assay) for the approval of CBD in the treatment of Dravet and Lennox-Gastaut syndrome in the US and the EU. Both the European Medicines Agency (EMA) and the United States Food & Drug Administration (US FDA) concluded that CBD was negative for mutagenicity and clastogenicity in adequately conducted assays (EMA 2019; FDA 2018; GW-Pharma-Ltd 2019).

The subchronic toxicity of Charlotte's Web hemp-derived IPA extract was investigated in two GLP-compliant 14-day and 90-day toxicity studies. Studies were run following OECD Guideline 407 (2008) and OECD Guideline 408 (1997), respectively. In the 90-day oral toxicity study conducted by the applicant, the NOAEL for Charlotte's Web hemp-derived IPA extract (9%) in olive oil (91%) was 800 mg/kg bw/day for female and 400 mg/kg bw/day for male rats. By applying an uncertainty factor of 100, a safe dose (also known as ADI or acceptable daily intake) of 4 mg/kg bw/day of the diluted extract was calculated for Charlotte's Web hemp-derived IPA extract. This would equivalate to a safe exposure of 0.36 mg of the IPA hemp extract per kg bw/day (or 25.2 mg/day) and 0.24 mg CBD/ kg bw/day (16.8 mg per daily serving) per proposed daily serving for adults. In addition, an exhaustive subchronic ICH/GLP-compliant package was submitted for the approval of CBD – the main

cannabinoid in CW's hemp-derived IPA extract - for the treatment of Dravet and Lennox-Gastaut syndromes in the US and the EU. The NOAEL in the 26-week rat study was 150 mg CBD/kg bw/day. The corresponding safe dose applying a 100-times margin of safety is 1.5 mg CBD/kg bw/day.

Nevertheless, CBD, the main cannabinoid in Charlotte's Web hemp-derived extract, has been widely studied and shown to be administered up to single doses of 6,000 mg in healthy subjects in children and adults. Based on the studies with healthy subjects, a safe dose is considered between 400-700 mg CBD per day (EMA 2019; Jadoon et al. 2017; Ltd 2019; Manini et al. 2015; Martin-Santos et al. 2012; Schoedel et al. 2018; Taylor et al. 2018; Winton-Brown et al. 2011). Charlotte's Web hemp-derived IPA extract will be marketed to the general population aged 3 years and older, excluding pregnant and lactating women as a precautionary measure. No literature was identified to raise concerns for the use of hemp extracts in these groups, nonetheless the restriction of use is wished to be taken by CW as a precautionary act.

CW's hemp-derived IPA extract does not pose a safety risk to human health, on the basis of the safety tests performed. CW's hemp-derived IPA extract has a maximum recommended dose of 0.36 mg/kg bw/day, which is x100 times less than the NOAEL established in the 90-day rat study conducted by the applicant. Overall, the information reviewed and provided in this application supports safety of Charlotte's Web hemp-derived IPA extract as novel food under the proposed conditions of use and dose level.

References

EMA (2019), 'Epidyolex European Public Assessment Report'.

FDA (2018), 'Cannabidiol non-clinical Review'.

GW-Pharma-Ltd (2019), 'Epidyolex SmPC'. Jadoon, K. A., Tan, G. D., and O'Sullivan, S. E. (2017), 'A single dose of cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study', JCI Insight, 2 (12).

Ltd, G. W. Pharma (2019), 'Epidyolex SmPC'.

Manini, A. F., et al. (2015), 'Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans', J Addict Med, 9 (3), 204-10.

Martin-Santos, R., et al. (2012), 'Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers', 18 (32), 4966-79.

Marx, T. K., et al. (2018), 'An Assessment of the Genotoxicity and Subchronic Toxicity of a Supercritical Fluid Extract of the Aerial Parts of Hemp', J Toxicol, 2018, 8143582.

Schoedel, Kerri, et al. (2018), 'A randomized, double-blind, placebo-controlled, crossover study to evaluate the abuse potential of purified cannabidiol (CBD) in subjects with a history of recreational polydrug use (P1.266)', Neurology, 90 (15 Supplement), P1.266.

Taylor, L., et al. (2018), 'A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects', CNS Drugs, 32 (11), 1053-67.

Winton-Brown, T. T., et al. (2011), 'Modulation of auditory and visual processing by delta-9-tetrahydrocannabinol and cannabidiol: an FMRI study', Neuropsychopharmacology, 36 (7), 1340-8.