



July 16, 2019

Dr. Norman E. Sharpless
Acting Commissioner, Food and Drugs
c/o Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-N-1482 for Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing; Request for Comments

Dear Dr. Sharpless:

On behalf of the American Veterinary Medical Association (AVMA) and our member veterinarians, we thank you for the opportunity to provide comments as the Food and Drug Administration (FDA, the Administration) works to clarify its regulatory strategy around cannabis, cannabis-derived, and cannabis-related products. The AVMA appreciates the FDA's efforts to gather stakeholder input regarding these products, including their efficacy, quality, safety, labeling, marketing, and sales, and potential pathways for a predictable and efficient regulatory framework.

Veterinarians have a strong interest in and enthusiastically support exploring the therapeutic potential of cannabis-derived and cannabis-related products, but we want to be sure we can have continued confidence in the efficacy, quality, and safety of products used to treat our patients. We are aware of several research institutions with both completed and ongoing investigations into the therapeutic benefits of cannabinoids for companion animals, with results that appear promising in some areas (e.g., osteoarthritis, epilepsy, pain management, oncology). At the same time, we continue to receive reports from our members indicating that animal owners are actively purchasing these products and administering them to their pets and horses to treat medical conditions, often in the absence of veterinary consultation, and without the assurance that comes with FDA review and approval of therapeutic claims being made by their manufacturers and distributors. To facilitate the FDA's efforts to collate information, we have structured our comments as responses to specific items addressed by the referenced Federal Register notice.

Health and Safety Risks

Based on what is known about the safety of products containing cannabis and cannabis-derived compounds, are there particular safety concerns that FDA should consider regarding its regulatory oversight and monitoring of these products?

- At present, our concerns regarding safety and efficacy of cannabinoid products stem largely from a lack of FDA evaluation and approval of such products. FDA approval is the accepted gold standard by which safety and efficacy are demonstrated. As the FDA explores establishing a regulatory system, it must consider the available evidence indicating clinical efficacy, or lack thereof, of individual ingredients within a product, as well as any potentially harmful effects of those same ingredients. Anecdotal

reports from veterinarians also suggest that many of the products utilized by pet owners appear to be marketed to provide what has been postulated to be a synergistic effect of several cannabis compounds (e.g., cannabinoids, terpenes, flavonoids) that is commonly referred to as the “entourage effect”. Accordingly, in addition to evaluating the individual components of these products, the efficacy and safety of all components within the product also need to be evaluated with respect to their combination with all other substances within the product.

- As multiple states have legalized marijuana for medical or recreational use by humans, cannabis products of all types have become more accessible and veterinarians are witnessing a corresponding increase in toxicoses due to exposure (intentional and not). Although most cases of cannabis toxicosis in veterinary patients occur due to exposure to marijuana products used recreationally or medicinally by their owners, the ASPCA Animal Poison Control Center¹ has indicated that dogs that have consumed greater than recommended doses of cannabidiol (CBD)-containing products have shown signs consistent with pets exposed to products high in tetrahydrocannabinol (THC). The Pet Poison Helpline Division of SafetyCall International also shared during the FDA’s public hearing on May 31, 2019 (Products Containing Cannabis or Cannabis-Derived Compounds, Public Hearing; hereafter referred to as “hearing”) that up to 45% of CBD exposures reported to that organization required veterinary intervention.² Their decision to recommend veterinary intervention was based on factors such as clinical signs, dose, current and prior medical history, co-ingestants, and concomitant medications. Of the animals that were ataxic, 16% had been exposed to CBD products and, of those that were lethargic, 23% had been exposed to CBD products. Of those animals that were laterally recumbent, 5% had been exposed to CBD and of those with urinary incontinence, 6% had been exposed to CBD. These results are concerning as such clinical signs are anticipated by toxicologists in cases of THC or synthetic cannabinoid exposure, but not with exposure to CBD. We highly recommend that FDA consult directly with ASPCA’s Animal Poison Control Center and the Pet Poison Helpline Division of SafetyCall for additional information regarding these cases. Although some adverse effects of CBD on specific organ systems have been reported in the human medical literature, the presence or absence of such effects have not been well delineated for veterinary patients. Therefore, in many of the cases reported to these poison control centers, it is unknown whether the reported toxicosis may be due to CBD, other compounds inherent to cannabis and its derivatives, or to contaminants introduced during growth and manufacturing (e.g., pesticides, heavy metals, nitrates/nitrites, solvent residues). For these reasons, not only must the safety and efficacy of CBD and other compounds within cannabis-derived products be established, but manufacturers of products that may be marketed and labeled for use in animals must adhere to strict purity standards, tolerance levels, and verification protocols, and be subject to robust testing and controls, as is currently expected of manufacturers of labeled and approved products.
- Also of concern to veterinary practitioners is potential interaction between CBD products and FDA-approved therapeutic products used in practice. Evidence from the human literature, reiterated by several researchers during FDA’s hearing, demonstrates the potential inhibition or potentiation of

¹ American Society for the Prevention of Cruelty to Animals. (2019) *CBD, Hemp Pet Treat Dangers and Overdose Treatments*. Available at <https://www.aspcapro.org/resource/cbd-hemp-pet-treat-dangers-overdose-treatments>. Accessed on July 16, 2019.

² United States Food and Drug Administration. Hearing on Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; May 31, 2019. Testimony of Dr. Rick Kingston of Pet Poison Helpline Division of SafetyCall International, PLLC.

metabolizing enzymes by CBD and THC and subsequent changes in blood concentration of various approved drugs. Reported drug interactions associated with human products that are also used in an extralabel manner by veterinarians include warfarin, tacrolimus, theophylline, ketoconazole, and zonisamide. It is unknown whether similar or additional drug interactions exist in companion animal species. With respect to the identification of safe concentrations and modes of delivery of CBD, although preliminary pharmacokinetic studies³ of canine populations of relatively small sample size have indicated a general tolerance over a 6-week period for oral, transdermal, and transmucosal routes of administration, elevations in liver enzymes were also detected. Related short- and long-term effects for veterinary patients are not known. Research continues to progress, but information obtained to-date is early-stage and preliminary.

- Along with the risk of adverse effects and drug interactions, we have additional concerns regarding therapeutic claims purported for veterinary patients. Although we are encouraged by some of the information obtained from therapeutic investigations into the use of cannabis for treatment of epilepsy and osteoarthritis, few well-controlled studies have been published and results thus far are inconsistent. While more information is available from the human medical literature, much of what we know regarding the use of these products in veterinary patients is anecdotal. It is not our intent to suggest that benefits may not exist. To the contrary, there appears to be real potential for cannabis-derived products in the veterinary medical space. However, the path to market must support pursuit of the research necessary to produce safe and efficacious products with valid label claims.

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

- Although the use of cannabis-derived products (i.e., CBD) within the United States has been limited to companion animal species to date, there is discussion within the livestock feed manufacturing community regarding the potential for use of hemp-derived products in livestock feed. As was expressed during the recent hearing, due to the profile of omega-3 fatty acids and proteins within hemp, its use in forage and silage is under consideration. Hemp seeds are high in fiber and some have suggested this may help support a healthy digestive tract. Hemp has also been said to be a good source of minerals, such as copper, iron, boron, zinc, manganese, and nitrogen. However, as is the case with all substances that may be fed to food-producing animals, the potential for residues in meat, poultry, eggs, milk, and other animal products intended for human food must be considered. At present it is unlawful to utilize a product within feed intended for a food-producing animal for which the scientific evidence of appropriate withdrawal times (time between when a substance can be fed to a food-producing animal and when the animal is milked or slaughtered) has not been established. Therefore, research needs to be conducted and withdrawal times must be determined before cannabis and cannabis-derived compounds (including CBD) can be incorporated into a feed intended for livestock. To our understanding, the American Association of Feed Control Officials has not yet received data that would allow hemp or hemp-derived products to be incorporated into animal food/feed intended for either companion animals or food-producing animals. Such data would be necessary to determine whether specific hemp or hemp-derived products meet requirements to be Generally Recognized as Safe (GRAS)

³ Bartner LR, McGrath S, Rao S, et al. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Canadian J Vet Res* 2018;82:178-183.

or to support a food additive petition and subsequently be added to the list of substances that can legally be included in pet food or other animal feed.

How does the existing commercial availability of food products containing cannabis-derived compounds such as CBD (which may in some cases be lawful at the State level but not the Federal level) affect the incentives for, and the feasibility of, drug-development programs involving such compounds?

- There is concern surrounding potential disincentives that may exist because of the current commercial availability of food (and other) products containing CBD. Some pharmaceutical companies that may otherwise initiate clinical investigations on a sufficiently large scale to deliver robust results regarding the safety and efficacy of cannabinoids may be disincentivized by the substantial number of consumers purchasing unapproved products for therapeutic purposes. Therefore, without clear delineation of the indications for products marketed as pharmaceuticals and those marketed and available as food products, there is the distinct possibility for a lack of incentive, and an active disincentive, for companies that would otherwise research and develop products intended for therapeutic use to do so.

How would the incentives for, and the feasibility of, drug development be affected if food products containing cannabis-derived compounds, such as CBD, were to become widely commercially available? How would this change if FDA established thresholds on acceptable levels of cannabinoids, including CBD, in the non-drug products it regulates? What else could FDA do to support drug development from cannabinoids?

- The FDA should establish a clear and efficient process for approval of cannabis-derived and -related therapeutic products and then conduct consistent enforcement against manufacturers and distributors who are noncompliant. The FDA should ensure delivery of prominent public messaging so that manufacturers, consumers, and healthcare providers are aware of the terms of the approval process and the risks associated with utilizing products that have not been approved. The FDA should also prominently communicate the Administration's desire to discuss with manufacturers their product development at every stage of the process and to provide guidance for manufacturers. The ultimate result of such engagement with the public, manufacturers, and healthcare providers should be real potential for safe products that are effective for their intended uses to be brought to consumers through an efficient process. Clear, consistent, and timely communication from, and enforcement by, the FDA is imperative to achieve this result.
- Without a regulated and legitimate pathway for the approval of products, the result may be increased reliance on compounding, as veterinary medicine has seen happen with a number of other therapeutics where an incentive to develop labeled products does not exist and disincentive does. While compounding remains essential to veterinary practice in several instances, it is no substitute for the confidence that comes from the use of an approved and appropriately labeled product. Such a future hardly seems a reasonable path forward for what could be a promising therapeutic opportunity that contributes to the advancement of veterinary medical care. Research toward therapeutic applications, verification of potential uses, the establishment of safety measures, and other considerations as expressed in these comments shall never come to fruition unless FDA determines there will be a valid path forward and provides guidance to industry accordingly. Instead, the industry may become an example of unrealized potential and our patients may suffer due to use of products that are neither efficacious nor safe.

Manufacturing and Product Quality

Please provide data and information on how products containing cannabis or cannabis-derived compounds (other than those marketed as drugs in compliance with the FD&C Act) are currently manufactured, including information about methods for ensuring product quality and consistency. More specifically, we are interested in obtaining information on, among other things:

Are there particular standards needed to address any safety issues related to the manufacturing, processing, and holding of products containing cannabis and cannabis-derived compounds (e.g., genotoxic impurities, degradation of active compounds)? Please identify or describe those standards.

- Veterinarians have significant concerns regarding a lack of quality assurance associated with many CBD products readily available to pet owners. A report⁴ in the Journal of the American Medical Association (JAMA) described results of an evaluation of the concentrations of cannabidiol extracts sold online and challenged the labeling accuracy of those extracts. In that analysis, 58 of 84 (69%) extracts evaluated either exceeded or fell short of stated label concentrations by more than 10 percent. A review⁵ from ConsumerLab of 19 products also indicated a lack of quality control in multiple areas. A more recent study⁶ investigating the label accuracy of 13 hemp oil products marketed for veterinary patients indicated there was significant inaccuracy regarding the actual concentration of THC and CBD in these products as compared with information on the label. Of the 13 products analyzed, 4 did not list CBD concentrations on the label, but instead listed units of hemp extract/ml. Of the 9 remaining products, 7 had plus or minus 20% of the CBD concentration indicated on the label. We also worry when we hear that of the 13 products investigated, 12 had THC concentrations higher than the Canadian acceptance level of 10 ppm. Similar results from other chemical analyses were shared during the hearing.

In addition to obvious problems with label accuracy regarding what cannabinoids and how much of them are contained within these products, veterinarians recognize that some products have been shown to be contaminated with mycotoxins, pesticides, bacteria, synthetic cannabinoids, metallic particles, or residues from solvents such as ethanol, petroleum ether, or butane that are used during extraction. Also alarming are employee experiences shared during the hearing about questionable manufacturing practices in certain facilities. Without appropriate testing and verification, we cannot be assured of the safety of these products for our patients.

- Because increasing hemp production in the United States is expected to lead to additional availability of products derived from cannabinoids and their subsequent use in animal populations, it is important that there be a uniform standard for sampling, testing, and processing that guarantees the concentration of substances within hemp plants, seeds, their derivatives, and resultant products,

⁴ Vandrey R, Raber JC, Raber ME, et al. Cannabinoid dose and label accuracy in edible medical Cannabis products. *J Am Med Assoc* 2015;313(24):2491–2493.

⁵ Consumer lab (2019) CBD and Hemp Extracts Supplements Review. Available at <https://www.consumerlab.com/reviews/cbd-oil-hemp-review/cbd-oil/12>. Accessed on July 16, 2019.

⁶ Cannabis Science and Technology (2019) Analysis of Veterinary Hemp Based Oils for Product Integrity by LC/MS. Available at <http://www.cannabissciencetech.com/cannabinoids/analysis-veterinary-hemp-based-oils-product-integrity-lcms>. Accessed on July 16, 2019.

particularly in the case of THC. As we have conveyed to USDA as it prepares to regulate hemp production, it is imperative that guidance from USDA be carefully developed and clearly communicated. The ability of the federal government to effectively regulate these products as pharmaceuticals, food additives, or in other forms will depend on these standards and parameters. We urge collaboration between USDA and FDA with respect to hemp and its products to help protect the health and wellbeing of our patients.

Marketing/Labeling/Sales

FDA is interested in information about how products containing cannabis or cannabis-derived compounds, other than drug products approved by FDA for human or animal use, are marketed, labeled, and sold. More specifically, we seek information on, among other things:

How should consumers be informed about the risks associated with such products (e.g., directions for use, warnings)? What specific risks should consumers be informed about? Are there any subpopulations for which additional warnings or restrictions are appropriate? Please explain your reasoning.

- With respect to the labeling of cannabis and cannabis-derived products, FDA should consider the multiple components found in the most commonly used products. As is the case for all pharmaceutical products, the labels and accompanying package insert should clearly indicate all ingredients, their respective quantities, appropriate warnings, appropriate dosing instructions, potential side effects, and product interactions. If such information is not known for a product, that should also be clearly indicated on its label. The format for relaying risk should mimic the familiar format utilized by FDA-approved products so that consumers are familiar with and can easily digest what is known (and not known) regarding drug interactions, contraindications, and use in pregnant, nursing, pediatric, and geriatric populations.

FDA should also clearly indicate the marketing status of “animal supplements” containing CBD or other cannabis-derived products. Such products are being actively promoted to veterinarians, with company representatives telling veterinarians that their use of such “animal supplements” to treat companion animals (e.g., inflammatory bowel disease) is appropriate and outside FDA authority. To the contrary, our understanding of the New Animal Drug provisions in the Food, Drug, and Cosmetic Act (FDCA) indicates that any particular use or intended use for the purpose of treating disease in animals with an “animal supplement” that has not been approved by FDA under the New Animal Drug provisions would render such supplement an unapproved New Animal Drug and unsafe under the Act. Should FDA determine to exercise enforcement discretion for such products, the boundaries should be clearly articulated, the products should be labeled as not approved by FDA, and any known adverse events or contraindications should be required on the product labeling. FDA should also set boundaries for companies promoting such products. As indicated, some use surrogates in the marketplace today to tell veterinarians that such products are beyond the reach of FDA, even when used for the purpose of treating disease.

What conditions, restrictions, or other limitations on the manufacturing and distribution of these products have been put in place under State or local law, particularly with respect to food products containing cannabis-derived compounds such as CBD (which may, in some cases, be lawful at the State level but not the Federal level)? What other conditions, restrictions, or other limitations might be appropriate to ensure adequate consumer information and to protect the public health?

- Although many states have legalized medical marijuana for use in humans, such laws do not apply to animals, and veterinarians are not currently allowed to dispense, prescribe, or recommend medical marijuana for animal patients under state law. There is significant variation in current state-level activities regarding the regulation of veterinary use of cannabis. Certain states such as California and New York have passed or proposed state laws that allow veterinarians to discuss cannabis products with pet owners. In other states, hemp-derived products are treated as unadulterated food, despite that a food with a drug added to it is, by federal law, adulterated. When pet owners purchase such products with the intent of using them to treat illnesses in their pets, veterinarians are placed in the position of being unable to practically provide relevant guidance. This issue is heightened by the relative lack of knowledge about these compounds' efficacy and safety for the treatment of medical conditions in animals. These situations are also challenging for veterinarians as they are aware that recommending such products may increase their legal risk should therapeutic failure or another adverse event occur.

What statutory or regulatory restrictions are in place under State or local law to warn about the use of these products by certain vulnerable human populations (e.g., children, adolescents, pregnant and lactating women) or animal populations (e.g. species, breed, or class)? Are there other steps that should be taken to warn about use by vulnerable populations? Please identify such steps and how they would apply to a particular subpopulation.

- Certain states have developed legislative language intended to prevent adverse consequences for animal populations associated with the use of cannabis-derived and cannabis-related compounds.

California, for instance, has statute that affords veterinarians the opportunity to discuss cannabis with their clients, although they may not prescribe or recommend its use. In addition, legislation has been proposed that would allow veterinarians to prescribe cannabis-derived products for their patients as long as they have completed cannabis-specific continuing veterinary medical education. Unfortunately, in creating the “qualified veterinarian” described in this legislation, restrictions are placed on who may offer qualifying education that are not consistent with California’s existing continuing education language within their veterinary medical practice act. In addition, language in that bill encourages sharing of information “about patients with colleagues and health care professionals”, which appears to violate another section of that state’s veterinary medical practice act that provides for limits on disclosure of information about patients and clients. Texas has proposed legislation that would require the formation of a Medical Cannabis Council made up of healthcare professionals from diverse professional backgrounds and would mandate that the Texas Veterinary Medical Board appoint a member to the Council who would be responsible for expertise and advocacy related to the best interest of animals as it relates to medical cannabis. Bills have also been proposed in New York that would create a “certified animal patient.”

While the foregoing are examples of efforts to place some parameters around the use of cannabis-derived and cannabis-related products in veterinary medicine, most states do not have and have not attempted to adopt measures to ensure that veterinarians are actively engaged in such conversations at the legislative and regulatory levels, as well as in the examination room. Further, states are acting without a robust body of scientific research on the use of these products in veterinary patients or assurances of safety and efficacy that come from FDA evaluation and approval.

The AVMA is a scientific organization that relies on evidenced-based medicine. We support additional research on cannabis-derived and cannabis-related products, so that veterinary practitioners may be better informed about their potential therapeutic uses and potential contraindications. Should this research result in FDA approval of such products, this would provide the assurance we need that products made available for use in veterinary patients are efficacious and safe. Further, in regard to U.S. Department of Agriculture (USDA) regulation and guidance on the commercial production of hemp, we hope the FDA will engage collaboratively with USDA in a way that will result in improved health and wellbeing for veterinary patients. We have engaged with USDA on their efforts as well.

Thank you again for the opportunity to provide feedback on the proposed revisions. We appreciate your consideration and look forward to continued collaboration with the USDA and the FDA. If you have further questions or would like more information, please contact Dr. Gail Golab, Chief Veterinary Officer, at 847-285-6618 or via e-mail to ggolab@avma.org; Dr. Dharati Szymanski, Assistant Director, Division of Animal and Public Health, at (847) 285-6742 or via e-mail to dszymanski@avma.org; or Dr. Lauren Stump, Assistant Director, Government Relations, at (202) 289-3211 or via email to lstump@avma.org.

Sincerely,

A handwritten signature in black ink that reads "Janet D. Donlin DVM, CAE". The signature is written in a cursive, flowing style.

Janet D. Donlin, DVM, CAE
Executive Vice President and Chief Executive Officer

The AVMA is the nation's leading representative of the veterinary profession and speaks for more than 93,000 member-veterinarians across the United States who care passionately about protecting animal health, animal welfare, and human health. Informed by our members' unique scientific knowledge, training, and practical experience, we advocate for policies that support our patients and their owners, advance the practice of veterinary medicine, and promote the critical work of veterinarians nationwide.