Docket No. FDA-2019-N-1482

BEFORE

FOOD AND DRUG ADMINISTRATION

COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON THE

SCIENTIFIC DATA AND INFORMATION ABOUT PRODUCTS CONTAINING CANNABIS OR CANNABIS-DERIVED PRODUCTS

July 16, 2019

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Prefatory remarks

On April 3, 2019, the Food and Drug Administration ("FDA") published a request for information in the Federal Register ("the April 3 Notice")[1] in which the agency solicited information and comments concerning "Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds." The April 3 Notice also announced a public hearing that was held on May 31, 2019, on the same subject. In this notice FDA recognizes both the increasing public interest in cannabis and cannabis-derived products from consumers, researchers, and multiple industries as well as the multiple federal and state agencies that are charged with the complex regulatory and enforcement responsibility for such products. In particular, FDA cites its current position with respect to cannabis-derived products containing cannabidiol (CBD), which the agency has asserted is not a lawful ingredient in dietary supplements and foods based on FDA's determination that CBD-containing foods and dietary supplements were not marketed prior to the authorization or initiation of substantial clinical investigations of CBD-containing pharmaceutical products.[2]

Within the April 3 notice, FDA states the purpose of the public hearing and public comment period is to "obtain additional scientific data and other information related to cannabis and cannabis-derived compounds, both from botanical and synthetic sources, to inform our regulatory oversight of these products." FDA poses a number of questions focused on assessing the safety of these products, including information supporting the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds.

The American Herbal Products Association (AHPA) is the national trade association and voice of the herbal products industry. AHPA's members include domestic and foreign companies doing business as growers, collectors, processors, manufacturers, marketers, importers, exporters and distributors of herbs and herbal products. AHPA's members are engaged in the commerce of herbs and herbal products, including finished products such as teas and dietary supplements, plant extracts and other ingredients used in such products, and bulk botanical commodities. Relevant here, these herbs and herbal products include cultivars of *Cannabis sativa* L. and

[1] 84 Fed. Reg. 12,969 (Apr. 3, 2019).

[2] FDA Regulation of Cannabis and Cannabis-derived products https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers (accessed July 1, 2019)

products derived therefrom that qualify as hemp under federal law.[3] AHPA's members therefore have an interest in the subjects of the April 3 Notice that relate to these cultivars of the plant species and various products derived from it, which the 2018 Farm Bill[3] removed from the federal Controlled Substances Act.[4]

Submitted on behalf of AHPA's members, these comments reiterate AHPA's testimony[5] from the May 31, 2019, public hearing and provide additional information responsive to the April 3 Notice with a particular focus on hemp and hemp-derived products, including CBD and other ingredients that contain CBD. Unless noted otherwise, AHPA's comments are limited in scope to these hemp and hemp-derived products when consumed orally and do not generally extend to products that are inhaled or applied topically, or that contain "marihuana" as defined under the federal Controlled Substances Act.[6]

[3] The Agricultural Marketing Act of 1946, section 297A defines hemp as "the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9-tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis." 7 U.S.C. § 1639o(1).

[4] AHPA also notes that the laws of various states likewise permit the cultivation of hemp and the manufacture, distribution, possession, and use of various products derived from it.

[5] AHPA's full public statement can be accessed at http://www.ahpa.org/Portals/0/PDFs/Advocacy/19_0531_AHPA_Statement_FDA_CBD_meeting-FINAL.pdf.

[6] 21 U.S.C. § 802(16).

FDA should clarify the scope of the CBD-containing "articles" to which the agency believes the prior-drug exclusion provisions apply

FDA has stated its position, with which to date AHPA has neither agreed nor disagreed, that provisions of the Federal Food, Drug, and Cosmetic Act ("the FD&C Act") prohibit marketing as dietary supplements products containing hemp-derived CBD and adding hemp-derived CBD to conventional foods ("the prior-drug exclusion provisions").[7] AHPA notes that, even if FDA has correctly determined that these provisions can apply to certain uses of CBD or CBD-containing ingredients, they should not preclude use in dietary supplement and conventional food products of hemp and hemp-derived ingredients containing naturally occurring quantities of CBD (e.g., milled hemp flower, hemp flower extracts). AHPA urges FDA to publicly acknowledge this important distinction. FDA's revising its public statements to reflect the appropriate and precise scope of its interpretations of the prior-drug exclusion provisions as applied to CBD would provide much-needed clarity to consumers, industry, and state and local governments that have relied on FDA's insufficiently nuanced statements to date.

Based on the plain language of these provisions and applicable precedent, FDA's policy here should, at a minimum, recognize that an isolated, highly refined and purified cannabinoid that is the subject of drug development qualifies as a different "article" than a simple botanical ingredient that naturally contains the cannabinoid, such as an extract that contains the naturally-occurring amounts of hemp's botanical constituents, including CBD. Without recognizing this distinction, FDA would appear to interpret these prior-drug exclusion provisions as prohibiting any amount of CBD in a dietary supplement or food, whether naturally occurring or not. Such a conclusion would conflict with the plain language of the prior-drug exclusion provisions, which apply only to the same "articles" previously studied or approved as drugs, and applicable precedent, including FDA's approach to distinguishing traditional red yeast rice products from Cholestin for purposes of 21 U.S.C. § 321(ff)(3) in the Pharmanex proceedings.[8]

[7] FDA Regulation of Cannabis and Cannabis-derived Products: Questions and Answers, questions 9 and 11, at https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421168.htm#legal; *see* 21 U.S.C. §§ 321(ff)(3)(B), 331(ll).

[8] *See, e.g.*, Letter from William B. Schultz to Stuart M. Pape re Docket No. 97P-0441, at 22 (May 20, 1998).

AHPA believes that the prior-drug exclusion provisions at a minimum should not apply to products containing or consisting only of simple hemp-derived ingredient that contain naturally-occurring amounts of cannabinoids. Of some relevance here is FDA's evaluation of three generally recognized as safe ("GRAS") notices for hemp seed-derived food ingredients.[9] The Agency reported that it had no questions about the submitter's conclusion that the hemp ingredients are GRAS under their conditions of use described in the notices. The GRAS notices indicate that trace levels of cannabinoids such as THC and CBD may be present in these hemp seed ingredients. That FDA effectively authorized use of these ingredients in certain food products based on a review of testing data indicating that certain lots of these ingredients included quantifiable levels of CBD demonstrates FDA's recognition that the prior-drug exclusion provisions do not operate to prohibit the presence of any amount of CBD in any food or dietary supplement product.

Without agreeing or disagreeing with FDA's underlying interpretation of the applicability of the prior-drug exclusion provisions to at least certain uses of CBD or CBD-containing ingredients, AHPA therefore requests that FDA promptly revise its public statements on this point to reflect the appropriate scope of the CBD-containing articles to which these provisions may apply.

FDA should take prompt steps to permit use of CBD ingredients in dietary supplements and foods

Nevertheless, FDA might resolve all doubt regarding isolated, purified forms of CBD, as well as hemp and hemp-derived ingredients containing CBD as a naturally occurring constituent, by exercising its authority to issue regulatory exceptions here. To fully implement Congress's intent to allow access to products that contain hemp-derived CBD, and to further AHPA's and FDA's shared goal of ensuring safe and well-manufactured supplements and foods, AHPA requests that FDA promptly take one of the two following actions, as stated in its May 31, 2019, hearing testimony.

FDA should use its express authority under the FD&C Act's prior-drug exclusion provisions to issue a regulation – possibly as an interim final rule ("an IFR") with an accelerated effective date – permitting CBD as a lawful ingredient in dietary supplements and foods. AHPA notes that, under this approach, companies that

[9] The ingredients are identified as hulled hemp seed (GRN765), hemp seed protein powder (GRN771), and hemp seed oil (GRN778), and can be found in FDA's GRAS notifications inventory: https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm600302.htm.

market hemp and hemp-derived ingredients, including CBD, would still need to comply with all other applicable federal regulations for these product categories, such as those requiring food facility registration, compliance with current Good Manufacturing Practice ("cGMP") rules, reporting of serious adverse events, and labeling for nutritional content and the presence of major food allergens, and, most significantly, submission of any required New Dietary Ingredient Notifications (NDINs) or compliance with food additive/GRAS requirements. Such a regulation would allow FDA to vigorously enforce dietary supplement requirements against firms marketing any CBD-containing supplement, which based on FDA's current interpretation of the prior-drug exclusion provisions the Agency appears to believe it cannot do today.

AHPA acknowledges that, consistent with FDA's public-health mission and in recognition of the drug-development incentives underlying the prior-drug exclusion provisions, FDA may believe it necessary to include certain conditions in this regulation. These conditions include, for example, limits on the quantity of CBD included in a product or intended for consumption based on labeled serving sizes or recommendations for use. They might also include requirements to disclose material information regarding safe use in labeling. The availability of a clear federal regulatory pathway for all potential CBD-containing dietary supplements and foods, even with reasonable conditions that FDA might seek to impose, would provide certainty to the industry. It should also help address the growing state-by-state regulatory patchwork that has developed in apparent response to FDA's stated interpretations of the prior-drug exclusion provisions, which AHPA believes has created a misperception that FDA does not regulate hemp-derived products marketed as dietary supplements or conventional foods.

As noted above, FDA might promulgate this regulation as an IFR under the Administrative Procedure Act ("the APA").[10] As a prerequisite for issuing an IFR, an agency must for "good cause" find that pre-publication notice and comment are "impracticable, unnecessary, or contrary to the public interest."[11] The legislative history of the APA provides useful instruction on the interpretation of these terms:

- "'Impracticable' means a situation in which the due and required execution of the agency functions would be unavoidably prevented by its undertaking public rule-making proceedings."

[10] 5 U.S.C. § 553.

[11] 5 U.S.C. § 553(b)(3)(B).

- "'Unnecessary' means unnecessary so far as the public is concerned, as would be the case if a minor or merely technical amendment in which the public is not particularly interested were involved."

- "'Public interest' supplements the terms 'impracticable' or 'unnecessary'; it requires that public rule-making procedures shall not prevent an agency from operating and that, on the other hand, lack of public interest in rulemaking warrants an agency to dispense with public procedure."[12]

In making a "good cause" finding to use an IFR in this case, FDA may consider the following rationales to establish this prerequisite:

Good Cause on "Impracticability" Grounds

- FDA could determine that the exploding market for ingested CBD-containing products necessitates prompt creation of a legal framework for regulating such products under the existing provisions for foods and dietary supplements. This step would allow the Agency a basis to accept and review NDINs and GRAS notifications for CBD-containing ingredients, which would permit the Agency to perform its ingredient-by-ingredient safety evaluation functions.
- FDA could also determine that use of a full notice-and-comment rulemaking process, which former FDA Commissioner Scott Gottlieb has signaled could take multiple years, would impracticably delay implementation of Congress's intent to create a legal pathway for hemp-derived CBD-containing foods and dietary supplements as reflected in the 2018 Farm Bill.

Good Cause on "Unnecessary" Grounds

- FDA could determine that these regulatory exceptions would resolve FDA's technical bases for asserting that firms may not market at least certain CBD-containing foods or dietary supplements. Indeed, FDA could determine that this regulation is necessary to promptly remove the remaining technical impediment to implementation of Congress's intent to

[12] *See* Administrative Procedure Act: Legislative History, S. Doc. No. 248 79-258 at 200 (1946).

create a legal pathway for all hemp-derived CBD-containing foods and dietary supplements as reflected in the 2018 Farm Bill.

Good Cause on "Contrary to the Public Interest" Grounds

- FDA could determine that creating these exceptions through interim final rulemaking would address a pressing public health issue by allowing the Agency to regulate the exploding market of ingested CBD-containing products under its existing frameworks for foods and dietary supplements. For example, as a practical legal matter, FDA cannot technically enforce dietary supplement requirements against firms marketing CBD-containing products labeled as dietary supplements consistent with the Agency's determination that the statute excludes them from the definition of "dietary supplement" today. FDA's primary recourse here involves bringing actions against these products on the basis that they qualify as unapproved new drugs or foods prohibited from entering interstate commerce, which may prove challenging and resource-intensive depending on the circumstances.

- Rather than enforce from a reactive position, promptly creating these exceptions would signal that marketers must comply with the existing regulatory frameworks for these product categories, may spur compliance with these requirements by firms already in this market, and would allow responsible legacy firms that have stayed on the sidelines due to FDA's stated position to enter the market. In turn, this should improve public confidence in the existing marketplace, allow for more targeted enforcement of labeling, manufacturing, and other violations of dietary supplement and food requirements, and perhaps further deter firms who will not or cannot comply with these requirements from entering or remaining in the market.

- These exceptions would also allow FDA a basis to accept and review NDINs and GRAS notifications for all CBD-containing ingredients and thereby facilitate use of the Agency's safety evaluation functions for products already in or subsequently entering the market. Recognizing that FDA does not have the resources or wherewithal to "boil the ocean" (to use Dr. Gottlieb's phrase from recent Congressional testimony), issuing regulatory exceptions via an interim final rule would provide a prompt, alternative method for FDA to regulate the marketplace under the existing

regulatory frameworks for dietary supplements and foods, including the important ingredient safety requirements for each.

Alternately, and especially if FDA cannot issue this requested regulation promptly, FDA should issue guidance to state the Agency's intent to exercise enforcement discretion with respect to the provisions of the FD&C Act on which FDA bases its position that CBD-containing supplements and foods are unlawful. The Agency has stated that it does not currently operate under a policy of enforcement discretion for these products. However, the Agency's limited enforcement actions taken against CBD-containing products on the market (e.g., issuance of warning letters alleging that claims or other statements made by their marketers render these products unapproved new drugs) indicate that FDA has not prioritized enforcement against such products in the absence of (as Dr. Gottlieb described in recent Congressional testimony) "over-the-line" disease claims.

Issuing such a statement during FDA's consideration of a potential rulemaking on this subject would align the Agency's interim policies with Congress's intent to permit the sale of products containing hemp-derived CBD as expressed in the 2018 Farm Bill. AHPA would support FDA's conditioning (and would expect FDA to condition) this exercise of enforcement discretion on full compliance with all other regulations applicable to these product categories and perhaps additional conditions (e.g., cautionary labeling, dosage limits). Thus, given the existing marketplace for these products, taking this interim step would confer many of the above-described benefits that prompt issuance of regulatory exceptions would.

AHPA responses to FDA questions

Health and safety risks

In the April 3 notice, FDA poses several questions in an effort to "inform FDA's regulatory oversight of these products, especially as we consider whether it is appropriate to exercise our authority to allow the use of CBD in dietary supplements and other foods." FDA requests submission of information, including data and studies, related to the safety of cannabis products in the following areas.

As previously stated, AHPA's comments regarding health and safety risks focus on hemp and hemp-derived compounds intended for oral ingestion, unless noted otherwise.

Safety concerns

With respect to AHPA's focus on hemp and hemp-derived compounds consumed orally, numerous authoritative bodies and international research scientists have undertaken comprehensive reviews of the safety of CBD via oral delivery. For example, in 2018, the World Health Organization's ("WHO's") Expert Committee on Drug Dependence published a review on CBD.[13] WHO's review notes that CBD is "generally well tolerated with a good safety profile." A 2016 review by Food Standards Australia[14] states that orally administered CBD "has been shown to be well tolerated at doses greater than 1000 mg per day" and that "[n]o reports of adverse effects attributable to oral CBD were located in the published literature." A review by Devinsky et al. (2014)[15] concluded that "multiple small studies of CBD safety in humans in both placebo-controlled and open trials have demonstrated that it is well tolerated across a wide dosage range." Iffland and Grotenhermen[16] (2017) expressed similar conclusions in their review of available CBD clinical data.

[13] WHO, Cannabidiol (CBD) Critical Review Report. Expert Committee on Drug Dependence. 40th Meeting, Geneva, 4-7 June 2018.

[14] Food Standards Australia New Zealand: Supporting Document 2, Cannabidiol hazard profile – Proposal P1042 (2016).

[15] Devinsky, O., Cilio, M. R., Cross, H., Fernandez-Ruiz, J., French, J., Hill, C. and Martinez-Orgado, J. (2014): Cannabidiol – pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*, 55(6), 791-802.

[16] Iffland, K. and F. Grotenhermen. 2017. An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. *Cannabis Cannabinoid Res*. 2.1, 139-154.

AHPA does acknowledge, however, that reviews of CBD's safety profile identify and recommend areas in which additional research is warranted.

AHPA recommends that, in FDA's reviewing scientific data regarding hemp and hemp-derived compounds, FDA consider the following:

- Any safety concerns identified for these compounds should be specific to the route of consumption of the substance under study, and the data used to support any eventual regulatory policy decision must be specific to that route of consumption or extrapolated from data on other routes of consumption based on appropriate scientific principles. For example, FDA should not accord scientific studies that consider or draw conclusions on the effects of smoking hemp flower undue weight in the Agency's evaluation of the effects of oral consumption of hemp ingredients.
- Publications that consider or draw conclusions on the effects of isolated compounds, such as CBD, should not be extrapolated to make any conclusion on any other isolated hemp compound, or any other hemp-derived ingredients, absent an appropriate scientific basis to do so.
- The scientific basis for any regulatory policy decision involving hemp-derived ingredients should appropriately account for the potential differences between the chemical profiles of specific parts of the *Cannabis* plant. As such, FDA must exercise caution in relying on studies on the effects of oral consumption of hemp leaf or flower when evaluating regulatory policy applicable to ingredients derived from the seed or other parts of the plant, such as stalk fiber or seed oil.

AHPA strongly recommends that any FDA regulatory policy decisions for specific hemp-derived ingredients or articles appropriately reflect potential differences in exposure effects based on the route of administration as well as the particular plant part.

Special human populations

Based on evidence profiled in AHPA's Botanical Safety Handbook 2nd Ed.[17] and other authoritative references addressing botanical safety issues, the labels of dietary supplements containing various botanical ingredients appropriately include

[17] AHPA. Botanical Safety Handbook, 2nd Ed. (2013).

cautionary statements regarding use by pregnant women, lactating women, and children. Like other botanical dietary supplement products, those containing hemp and hemp-derived ingredients may require similar cautionary labeling statements based on a review of the available data.

Collection of safety information

Dietary supplement products must comply with the Dietary Supplement and Nonprescription Drug Consumer Protection Act.[18] FDA's implementation of AHPA's above request to use the Agency's authority under the prior-drug exclusion provisions would provide FDA a means of collecting additional safety information about CBD-containing products to which FDA has asserted these requirements do not apply today. Marketers of dietary supplements must provide a domestic address or telephone number on product labels for use by consumers in reporting adverse experience information to the designated "responsible person" for the product in question. The serious adverse event reporting requirements for dietary supplements are the same as those for over-the-counter medicines. Marketers must maintain records of adverse event reports and submit detailed reports of all serious adverse events to FDA within 15 days of receiving such a report. Under this adverse event reporting system, manufacturers and marketers are also required to retain all adverse event reports, including those that are not serious, for six years.

In its examination of the FDA CFSAN Adverse Event Reporting System ("CAERS") database entries from the last five years (2014 to 2019), AHPA identified reports for relevant products identified using "CBD" (51 reports) and "hemp" (20 reports) as search terms. For the CBD products, 34 were identified as dietary supplements, one as a beverage, and one as a cosmetic; 15 were not identified specifically. For the hemp products, 17 were identified as dietary supplements, one as a food, and two as cosmetics. The presence of these reports indicates that stakeholders have already used the CAERS system to report potential safety issues involving hemp and CBD products to FDA.

Media reports[19] have estimated the number of hemp and hemp-derived products containing CBD currently being marketed in the United States as dietary supplements

[18] Pub. L. 109-462,120 Stat. 3469 (Dec. 22, 2006).

[19] Runestad T. March 21. 2019. Outgoing FDA chief says new laws are preferred to regulations. Accessed July 16, 2019 at https://www.supermarketnews.com/laws-regulations/outgoing-fda-chief-says-new-cbd-laws-are-preferred-regulations.

and foods to be well over 1000 products. Should FDA issue a regulation clarifying the lawful status of all hemp-derived CBD products marketed as dietary supplements, the adverse event reporting requirements would immediately apply to all firms marketing such products. Accordingly, taking this action should improve FDA's ability to assess any post-market safety signals related to such products while also subjecting all such products to the default safety requirements of the FD&C Act that apply to all dietary supplements.

Maximum daily intake and safe use levels

As previously mentioned, AHPA's review of the currently available scientific literature identified studies documenting the general safety of orally ingested CBD. FDA could appropriately use the existing data from the scientific literature in assessing safe levels of use for food and supplement products. A determination of such levels could inform regulatory policy decisions, including any potential conditions that FDA might include in a regulation creating exceptions to the prior-drug exclusion provisions or in an interim enforcement discretion policy (as necessitated by FDA's current interpretations of these provisions). Should FDA determine it necessary to do so, AHPA would recommend that FDA consider utilizing a model such as that proposed by the European Industrial Hemp Association ("EIHA").[20]

AHPA notes that it is rare for FDA to determine specific safe or maximum use levels for botanical dietary supplement products as a condition of their lawful marketing. As a class of goods, dietary supplements have an excellent safety record as compared to other product categories regulated by FDA. Notwithstanding the unique circumstances presented by FDA's current interpretation of the prior-drug exclusion provisions, AHPA recommends that FDA generally treat hemp and hemp-derived ingredients used in dietary supplements as the Agency would any other botanical dietary supplement ingredient. Manufacturers preparing NDINs or GRAS notifications/determinations should have responsibility for identifying the maximum use levels or safe use levels, as appropriate, in the process of developing these documents and the underlying safety assessments.

AHPA is not aware of any animals used as a source of food that are currently consuming cannabis or cannabis-derived compounds, including hemp.

[20] EIHA position paper (2017). Reasonable regulation of cannabidiol (CBD) in food, cosmetics, as herbal natural medicine, and as a medicinal product. Accessible at http://eiha.org/media/2014/08/17-01-EIHA-CBD-position-paper.pdf

Impact on drug development programs

In preparing these comments, AHPA conducted a search of the www.clinicaltrials.gov database to determine how many clinical trials involving the cannabinoid CBD have been registered to date. As of July 5, 2019, 77 total clinical trials have been registered in the database. The earliest of these registered studies had a start date of May 2007 and involved the combination THC/CBD drug Sativex®. Of this total, 23 studies (almost 30% of the total) had listed start dates of July 1, 2018, and later, and thus commenced in the past 12 months or so. AHPA notes that this same approximately one-year timeframe overlaps with a period during which perhaps the largest growth in the market for CBD-containing products marketed as foods or dietary supplements to date occurred. Accordingly, while the availability of these dietary supplement and food products has risen sharply in the recent past, the increased availability does not seem to have resulted in a decrease in the number of new clinical studies evaluating potential drug uses of CBD.

The definition of a "dietary supplement" under the FD&C Act includes articles that were first marketed as dietary supplements and that subsequently are studied or approved as drugs (perhaps in a different form, dose, or route of administration). In contrast, articles that are first drugs are prohibited from subsequently being marketed as dietary supplements, unless permitted by the Secretary of Health and Human Services through a regulation. However, nothing in the FD&C Act prohibits the development of drug products containing ingredients previously marketed in dietary supplement products. Further, dietary supplements are prohibited from bearing claims to diagnose, treat, cure, or prevent any disease, so any entity wanting to be able to make such claims about cannabis or cannabis-derived compounds must pursue a drug development program. Thus, AHPA does not believe that FDA's taking the actions requested herein would materially reduce incentives for development of CBD-containing drug products.

A greater disincentive for drug-development programs for cannabis and cannabis-derived compounds likely arises from the continued classification of "marijuana" as a Schedule I substance under the federal Controlled Substances Act. Relatedly, the lack of high-quality, research-grade cannabis material available for use in clinical trials may similarly provide a disincentive. While the Drug Enforcement Administration ("DEA") has substantially increased the amount of cannabis that can be grown for research purposes by the current approved supplier (University of Mississippi), it has yet to take action in authorizing cultivation by additional domestic suppliers despite

pledging to do so in 2016. Members of Congress have expressed interest in alleviating these roadblocks to further clinical research on cannabis through the introduction of legislation.[21]

Manufacturing and product quality

In the April 3 notice, FDA states it seeks "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."

AHPA's responses to these questions again are limited to consideration of hemp and hemp-derived ingredients used in dietary supplement and food products.

Safety standards

AHPA strongly believes the existing cGMP regulations for both dietary supplements (21 C.F.R. part 111)[22] and foods (21 C.F.R. part 117)[23] are sufficiently robust to address such issues for hemp-derived ingredients used in these product categories. For example, the dietary supplement cGMP regulations require the supplement manufacturer to "establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement to ensure the quality of the dietary supplement."[24] Furthermore, the manufacturer must establish "in-process specifications for any point, step, or stage in the master manufacturing record where control is necessary to help ensure that specifications are met for the identity, purity, strength, and composition of the dietary supplements

[21] S. 2032 — 116th Congress: Cannabidiol and Marihuana Research Expansion Act." www.GovTrack.us. 2019. https://www.govtrack.us/congress/bills/116/s2032

[22] Current good manufacturing practice in manufacturing, packaging, labeling, or holding operations for dietary supplements https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=111 (Accessed July 2, 2019)

[23] Current good manufacturing practice, hazard analysis, and risk-based preventive controls for human food https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=117 (Accessed July 2, 2019)

[24] 21 C.F.R. § 111.70(b)(3).

and, as necessary, for limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement."[25]

AHPA has encouraged its members that undertake manufacturing, processing, and holding activities for dietary supplements containing hemp or hemp-derived ingredients to provide FDA with the details of any additional standards or specific processes they utilize for these operations.

Manufacturing standards

As mentioned previously, AHPA strongly believes the existing cGMP regulations for both dietary supplements and foods are sufficiently robust to ensure manufacturing quality and consistency of products marketed in these categories that contain hemp-derived ingredients.

AHPA has adopted a guidance policy[26] that encourages all entities that market products containing hemp-derived ingredients such as CBD to comply with all applicable federal regulations for that product category, such as the cGMP requirements, even if uncertainty remains about whether the prior-drug exclusion provisions, as interpreted by FDA, apply to their products.

Analytical testing

Validated analytical testing needed to support manufacturing of safe and consistent products starts with the analytical methods for primary cannabinoids of interest such as THC and CBD.

Testing for THC is required to confirm compliance with the federal limit of not more than 0.3% THC as required by the 2018 Farm Bill's definition of hemp and any specifications set by the manufacturer for THC content. The results of such testing may also to provide a means of confirming any other quantitative limits that may be placed on the amount of THC in products (e.g., under state law).

[25] 21 C.F.R. § 111.70(c)(1).

[26] AHPA Guidance policy for dietary supplements and food containing hemp and hemp-derived cannabidiol (CBD) http://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Policies/AHPA_Supplements___Food_Hemp_CBD.pdf (Accessed July 2, 2019)

Likewise, validated analytical testing for CBD is needed to confirm any quantitative limits and validate product label claims regarding CBD content as individual marketers may make.

Multiple reputable standards development organizations such as AOAC International,[27] ASTM International,[28] and USP[29] are developing analytical methods and monographs to address the needs of the cannabis industry, including for products containing hemp-derived CBD. The American Herbal Pharmacopoeia ("AHP")[30] has developed a monograph addressing quality parameters for *Cannabis* spp. inflorescence. The National Institute for Standards and Testing ("NIST") has initiated a project to develop a hemp quality assurance program and hemp reference materials, which will also support for the hemp-derived CBD supplements industry in conducting required analytical testing.

AHPA recognizes that firms marketing foods and dietary supplements containing hemp-derived ingredients will likely need to conduct additional analytical testing on, for example, incoming components and finished products during the compliant manufacture of hemp and hemp-derived supplements (e.g., testing for heavy metals, microorganisms, pesticides), but existing established testing methods for these analytes are generally available.

Standardized terminology

AHPA is aware of several publications that contain useful definitions for the cannabis industry in general, including AHPA's Recommendations for regulators documents for cannabis cultivation, manufacturing, laboratory, and dispensing operations.[31] AHPA

[27] AOAC International Cannabis Analytical Standards Program (CASP) https://www.aoac.org/AOAC_Prod_Imis/AOAC/SD/CASP/CASPAbout/AOAC_Member/SDCF/CASP/CASP_Main.aspx?CASPCCO=About&hkey=a86e6520-635f-431c-98aa-84bd61eaecf8 (Accessed July 2, 2019)

[28] ASTM International Committee D37 Cannabis https://www.astm.org/COMMITTEE/D37.htm (Accessed July 2, 2019)

[29] US Pharmacopeial Convention https://www.usp.org/

[30] AHP Cannabis inflorescence quality control monograph https://herbal-ahp.org/online-ordering-cannabis-inflorescence-qc-monograph/ (Accessed July 2, 2019)

[31] These AHPA documents are available at the following url: http://www.ahpa.org/AboutUs/Committees/CannabisCommittee.aspx.

is also in the process of developing a hemp industry glossary and will provide this document for the Agency's review upon completion.

In addition, ASTM International is developing a consensus terminology standard for the cannabis industry. NSF International is developing cannabis-related definitions to support requirements for hemp products in its standard NSF/ANSI 173 – Dietary supplements.

Marketing/labeling/sales

For this subject area, FDA requests "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."

AHPA has observed that, in general, marketing and sales practices for hemp and hemp-derived CBD products are similar to those for other products in the dietary supplement category; for example, specialty retailers, mass retailers, and e-commerce outlets all sell such products. Foods and beverages containing hemp-derived CBD are also being offered in retail food establishments such as coffee shops and restaurants.

Product warnings

With respect to hemp and hemp-derived ingredients in dietary supplements and foods, AHPA supports the use of existing federal labeling regulations[32] for these product categories as they are sufficient to address consumer needs. In addition, dietary supplement products must be labeled with required contact information for consumer reporting of adverse events to the responsible party for the marketed product. Current law also requires labeling disclosing the presence of major food allergens.

AHPA notes that, under the FD&C Act, FDA requires dietary supplement and food labels to contain information that is considered material to the consumer's understanding of how to use the product or of a label claim about the product. For example, FDA has indicated the importance of this concept both in the context of

[32] 21 C.F.R. part 101, Food labeling.

NDINs[33] for dietary supplements and in the context of making specific nutrient content claims.[34] AHPA expects that, under certain circumstances, FDA may determine that the use of certain hemp or hemp-derived ingredients in dietary supplements or foods may trigger existing requirements to disclose all facts material to the consumer's use of the product on the label.

As previously mentioned, based on evidence profiled in AHPA's Botanical Safety Handbook 2nd Ed.[35] and other authoritative references addressing botanical safety issues, the labels of dietary supplements containing various botanical ingredients appropriately include cautionary statements regarding use by pregnant women, lactating women, and children. Like other botanical dietary supplement products, those containing hemp and hemp-derived ingredients may require similar cautionary labeling statements based on a review of the available data.

Conditions, restrictions, or use limitations

AHPA observes that numerous states and local jurisdictions are enacting legislation related to the manufacturing and marketing of dietary supplements and foods containing hemp-derived CBD.[36] Some of these laws appear intended to facilitate the manufacture, marketing, and consumer use of such products, while others appear intended to restrict or prevent further sales. Regardless of intent, such legislation has created a confusing patchwork of conflicting or inconsistent regulations across states and localities. States and local jurisdictions appear to have considered or adopted their own controls for hemp- or CBD-containing products due in part to either a perceived absence of federal regulations that pertain to these products or unfamiliarity with the existing federal regulatory frameworks and how they are or can be applied to these products.

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[33] 21 C.F.R. § 190.6.

[34] *See, e.g.*, Food Labeling; Nutrient Content Claims: Definition for ''High Potency'' and Definition of ''Antioxidant'' for Use in Nutrient Content Claims for Dietary Supplements and Conventional Foods, 62 Fed. Reg. 49,868 (Sept. 23, 1997) (Final Rule).

[35] AHPA. Botanical Safety Handbook, 2nd Ed. (2013).

[36] Recent state examples include Louisiana (https://www.theadvocate.com/baton_rouge/news/politics/legislature/article_8a8ea0e8-8646-11e9-a7e8-2343d72c48f5.html), California (https://hempindustrydaily.com/california-may-soon-join-other-states-in-legalizing-cbd-foods-bypassing-fda/), and New York City (https://www.crainsnewyork.com/op-ed/city-set-enforce-cbd-ban-where-are-regulations)

As previously stated at the May 31, 2019, public hearing, AHPA urges FDA to take prompt action at the federal level that will provide state and local governments with confidence that FDA appropriately regulates these products. In turn, this should help deter further growth of an unnecessary but otherwise growing patchwork of inconsistent state and local regulations for dietary supplement and food products containing hemp-derived CBD.

Statutory or regulatory restrictions

As an example of state regulatory activity relevant to this question, the California legislature is considering a bill[37] for supplements and foods containing hemp-derived CBD that would require such products to include the following warning:

> "CANNABIDIOL USE WHILE PREGNANT OR BREASTFEEDING MAY BE HARMFUL. KEEP OUT OF REACH OF CHILDREN."

As with other dietary supplement products, individual marketers may add cautions appropriate for their products to bring consumer attention to the presence of specific constituents (e.g., "contains X mg of caffeine") or known interactions with medications or other supplements.

Other labeling considerations

With respect to hemp and hemp-derived ingredients in dietary supplement products, AHPA suggests that any of these products that contains a measurable amount of THC (while also in compliance with the federal limit on THC as established in the definition of "hemp") should declare this on the product label.

[37] California AB228 available at https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201920200AB228

Concluding statement

AHPA urges FDA to quickly take specific actions that would serve to clarify the regulatory status of hemp and hemp-derived ingredients used in dietary supplements and foods that contain CBD. In addition, FDA should acknowledge that simple hemp-derived products that contain naturally-occurring levels of hemp's botanical constituents do not trigger the prior-drug exclusion provisions.

As stated in AHPA's May 31, 2019, hearing testimony, FDA should use its statutory authority to issue a regulation permitting hemp-derived CBD as a lawful ingredient in dietary supplements and foods, preferably using an interim final rule process. If unable to issue such a regulation promptly, FDA should promptly issue guidance to state the Agency's intent to exercise formal enforcement discretion with respect to the provisions of the FD&C Act on which FDA bases its position that CBD-containing supplements and foods are unlawful.

In answering FDA's questions as outlined in the April 3 notice, AHPA recommends that, wherever possible, FDA recognize the existing robust regulatory frameworks as appropriate for the regulation of dietary supplements and foods containing hemp and hemp-derived ingredients. Such action is consistent with AHPA's and FDA's shared goal of ensuring safe and well-manufactured supplements and foods and preserves FDA's ability to efficiently and effectively protect consumers from unsafe and unlawful products.

AHPA greatly appreciates the opportunity to present comments during this information gathering process. We welcome any questions that may arise from AHPA's comments and look forward to further prompt action from FDA.

Respectfully submitted,

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