NATURAL PRODUCTS ASSOCIATION

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Current Market Dynamics

1) What does the current market for CBD products look like? Please describe the types and forms of products available, manufacturing practices within the industry, market supply chain, how products are marketed and sold, the types of cannabinoids used in products, the marketed effects of CBD products, and the range of CBD doses currently found in the market.

In the past five years, over 3,000 CBD products have come to market without a consistent approach to regulation or any plan on how consumer access will be balanced with consumer safety by our public health officials at the Food and Drug Administration. NPA commissioned a poll that found seven in ten Americans believe the FDA is overdue to establish safety standards for CBD products in the marketplace. To make matters worse, 41% wrongly assumed the FDA had already developed these safety standards. There are three types of CBD, containing different compounds and concentrations:

Full spectrum: includes all parts of the cannabis plant. Full-spectrum products should contain less than 0.3% THC.
Broad spectrum: this contains most of the cannabis plant compounds. Unlike full-spectrum, broad-spectrum usually contains more than 0.3% THC.
Isolates: Should only contain CBD with no other cannabinoids or THC.

Since the FDA has not determined that CBD is generally recognized as safe (GRAS), we at NPA have long advocated for FDA to test CBD products for heavy metals, pesticides, and THC, all of which are proposed in this bill. Currently, through the United States Department of Agriculture, there are 37 hemp analytical testing laboratories. Any laboratory testing hemp for THC must be registered with the Drug Enforcement Agency through these facilities. Unfortunately, the combined volume of hemp produced, and the lack of facilities has led to industry-wide concerns. This is why we have proposed to establish a national testing center and corporate stewardship program for manufacturers of CBD products at the National Center for Natural Products Research at the University of Mississippi. This program would provide an independent verification program for product analysis. The program would randomly select 1,000 products per year that would purport to contain hemp/CBD. These products would be tested using known standards for their content of impurities, THC, CBD, and other cannabinoids. The data generated from this program would be provided to the FDA and published in a public-facing database for anyone to access.

When looking across the globe, other agencies have begun establishing their standards and regulations for CBD products. In 2020, the United Kingdom (UK) established a deadline to clean up the CBD market and bring manufacturers into compliance with novel food rules, which require some food ingredients to be tested and approved by food safety authorities before they reach consumers. CBD manufacturers had until March 31, 2021, to submit a novel food application to stay on the shelf.

With over 3,000 products on the market, we believe that not testing products for impurities, such as lead or other heavy metals, is unacceptable for a federal agency whose mission is to protect public health. Product testing should be conducted by federal authorities. Though the overall market situation for CBD-containing products is fraught with problems in terms of quality and consistency, responsible companies would welcome an avenue to be recognized for compliance. Some of these companies even strongly desired guidance during the FDA's May 31, 2019, hearing on CBD.

2) How has the market changed since the passage of the 2018 Farm Bill?

FDA has offered no regulatory guidance to date, despite the agency's public commitment to do so more than four years ago, using its existing food and dietary supplement pathways. According to Benzinga Cannabis, in 2019, the United States was growing eight times the amount of CBD hemp it can consume. At the time, the spot price for bulk CBD Isolate was roughly $3,500/kg, down from a high of $5,400/kg. Thanks to the

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FDA's unwillingness to utilize existing pathways for CBD products, one can purchase bulk CBD Isolate for as low as $250/kg today.

3) How is the lack of national standards for CBD products affecting the market?

Please see above.

Pathway

4) Please comment on the concerns FDA has raised with regard to regulating most CBD products through existing pathways (i.e., conventional foods, dietary supplements, and cosmetics), and FDA's view that there is a need for a new regulatory pathway for CBD products. If existing regulatory pathways are sufficient for regulating CBD products, please explain how these existing pathways can be used to address the concerns raised by FDA, as appropriate.

Specific to foods and dietary supplements, under current authorities, the FDA can set a daily consumption level (which would address the major public health concerns) in foods and dietary supplements. Establishing such a level would trigger other authorities dealing with labeling and product quality through good manufacturing practices (cGMP), which the agency can use to regulate the marketplace and analyze facilities and analyze products effectively. FDA can do this either through enforcement discretion (which has precedence for dietary supplements as recently as 2022 with N-Acetyl Cysteine) or through notice-and-comment rulemaking (an option that was written into statute in 1994 but has never been used by FDA). Once this pathway is established, it would be viable for the other cannabinoids.

The Dietary Supplement Health and Education Act of 1994 (DSHEA) created a new class of foods products, dietary supplements, containing one or more "dietary ingredients," which the law defined as a vitamin; a mineral; an herb or other botanical; a dietary substance for use by humanity to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any of these ingredients. 21 U.S.C. § 321 (ff)(1). CBD is a constituent of a botanical – in most cases, the cannabis plant – and so it meets the definition of a dietary ingredient.

However, there is an exclusion clause in the definition of "dietary supplement" that provides that any article that is an approved new drug or was authorized for research purposes as an investigated new drug (IND) before it was marketed as a food or dietary supplement cannot be marketed as a dietary supplement if the drug is approved or if substantial clinical investigations of the article have already begun and the existence of those investigations has been made public. 21 U.S.C. § 321(ff)(3)(B)(i), (ii). This is the clause that FDA alleges applies to CBD supplement products and is part of their loosely formed basis on why the agency needs a new regulatory system for hemp/CBD.

An additional piece of the story is the debate over CBD being a new dietary ingredient (NDI). It is important to note that the NDI section of DSHEA provides that a dietary supplement is adulterated unless it 1) contains only dietary ingredients that have been present in the food supply as an article used for food in a form in which the food has not been chemically altered or (2) the manufacturer or distributor notifies FDA that it intends to introduce a new dietary ingredient into the US market and provides evidence of safety. 21 U.S.C. §§ 350b, 342(f). The law defines a new dietary ingredient as an ingredient that was not marketed in the U.S. before October 15, 1994. While CBD has always been present in hemp, the question pivots on whether it qualifies as an article used for food versus FDA's interpretation that it was a constituent of a food. FDA finding that CBD wasn't precluded as a dietary supplement, or a conventional food would mean that a CBD product would have to go through the NDIN process for a dietary supplement or GRAS process for foods prior to going to market.

CBD was first marketed as an active pharmaceutical ingredient (API), which creates some legal hurdles in marketing it as a dietary supplement or conventional food. The industry needs to be provided with guidelines they need and consumers the assurance that what they are consuming is safe and is manufactured to quality standards.

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While CBD was technically a federally "scheduled" substance before the passage of the 2018 Farm Bill in December, sales of CBD products continued to rise. At the present moment, there are well over 3,000 CBD products on the market. Since the passage of the 2018 Farm Act, which eliminated hemp from the definition of marijuana under the Controlled Substances Act- we've seen a significant increase in the production and sales of CBD products. FDA clearly states that "FDA has concluded that THC and CBD products are excluded from the dietary supplement definition under sections 201(ff)(3)(B)(i) and (ii) of the Federal Food, Drug, and Cosmetic Act."[1]

Despite this, the warning letters FDA has issued to companies marketing CBD as a dietary supplement largely focus on claims. The Food and Drug Administration has enforcement authority over labeling requirements. Two well-recognized types of claims are health claims and structure-function claims. Health claims describe the relationship between foods and dietary supplements and reduced risk of a disease or health-related condition. These claims are subject to premarket review and authorization by the FDA. Structure-Function claims describe the role of a nutrient or dietary ingredient intended to affect the normal structure or function of the human body for example, "calcium builds strong bones." Also, they may characterize how a nutrient or dietary ingredient acts to maintain the structure or function. The FDA requires manufacturers to have substantiations that such claims are truthful and not misleading. The FDA released a statement following the most recent string of warning letters. FDA not only cited how recipients of warning letters have violated the Federal Food, Drug, and Cosmetic Act, but they also cited the lack of scientific information supporting the safety of CBD in food and indicated that they cannot conclude that CBD is generally recognized as safe (GRAS) among qualified experts for its use in humans or animal food. As outlined in some of the warning letters issued by the FDA, violations included marketing CBD products as a dietary supplement since these products do not meet the definition of a dietary supplement. FDA Principal Deputy Commissioner Amy Abernethy, M.D., Ph.D. even went as far as to say, "We remain concerned that some people wrongly think that the myriad of CBD products on the market, many of which are illegal, have been evaluated by the FDA and determined to be safe.

Scope

5) How should CBD and/or cannabinoid-containing hemp products be defined? What compounds should be included and excluded from a regulatory framework? Should Congress or FDA limit the amount of intoxicating or potentially intoxicating substances produced by *Cannabis sativa L.* in food and dietary supplements? Which substances, if any, warrant greater concern? How should these substances of concern be addressed? What products, if any, should not be allowed on the market? How should Congress or FDA identify appropriate limits for THC and other cannabinoids in finished products? Relatedly, how should a framework account for "total THC," including tetrahydrocannabinol acid (THCA), in FDA's regulation of intermediate and finished products? Should FDA regulate the manufacture and sale of "semisynthetic derivatives," or "biosynthetic cannabinoids," which are still scheduled under the CSA?

CBD or cannabinoid containing hemp (0.3% THC) products are botanical products. Botanicals, if they aren't claiming they treat, cure or mitigate disease are regulated as conventional foods or dietary supplements based on intended use. Any ingredients from hemp or hemp derived products which are intended to be used for recreational purposes to effect psychological states (e.g., to get high, to promote euphoria, or to induce hallucinations) and have potential for abuse, FDA considers these street drug alternatives to be unapproved new drugs and misbranded drugs under sections 505 and 502 of the Act.[2] FDA does not believe that street drug alternatives are intended to be used to augment the diet to promote health or

[1] Red Yeast Rice, National Center for Complementary and Integrative Health https://www.nccih.nih.gov/health/red-yeast-rice FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD) https://www.fda.gov/news-events/public-health- focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd

[2] https://www.fda.gov/media/71027/download#:~:text=FDA%20considers%20any%20product%20that,action%2C%20including%20seizure%20and%20injunction.

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reduce the risk of disease. Moreover, the FDA considers the diet to be composed of usual food and drink that may be designed to meet specific nutritional requirements. Illicit street drugs are not food or drink, and neither they, nor alternative street drugs, can be said to supplement the diet. While CBD possesses central nervous system (CNS) activity, it doesn't affect psychological states as described above, similar to other botanical ingredients like caffeine. Furthermore, "intoxicants" by intended use don't fit into the food or dietary supplement space. The issue of intoxication is not new in terms of FDA. If we go to the Structure/Function Final Rule on page 16, question 38, the agency gives their piece on the matter:

"*….A few comments argued that alcohol intoxication is a ''self-induced condition'' and not a disease. FDA continues to believe that alcohol intoxication, like all poisonings (mushroom, digitalis, or any drug overdose), meets the definition of disease, albeit a transient disease. The definition in § 101.14(a)(5), which FDA is incorporating in this rule, states, in part, that a disease is ''damage to an organ, part or structure, or system of the body such that it does not function properly * * *'' All poisonings, like alcohol intoxication, cause dose-related dysfunctioning and damage, ranging from mild impairments to death. Alcohol intoxication causes temporary damage to brain function, causing impairments of judgment, attention, reflexes, and coordination. The fact that it is ''self-induced'' does not remove it from the definition of disease. Deliberate barbiturate overdoses are also self-induced, but clearly meet the definition of disease.*"

While the discussion in the structure/function final rule is not specific to hemp/cannabinoids and I'm not attributing or debating "damage or dysfunction" caused by "intoxicating" cannabinoids, the construct for foods and dietary supplements doesn't allow for the inclusion of intoxication in those marketplaces. "Intoxicants" do appear in trace amounts in other conventional foods and dietary supplements, for example 0.5% ethanol in fermented Kombucha. Limits on intoxicants/contaminants are established per Good Manufacturing Practices (cGMPs). For example, the dietary supplement cGMPs state "You must establish limits on those types of contamination that may adulterate or may lead to adulteration of the finished batch of the dietary supplement" similar provisions are in the conventional food cGMPs and for food additives, limits on contaminants are established within the GRAS notice or food additive petition.[3]

Consistent with the Act, the presence of any intoxicants that weren't naturally occurring in a cGMP environment would adulterate the product. The CSA limits would also be governed by cGMP environment for conventional foods and dietary supplements. If a product was extracted, and effectively had the cannabinoids concentrated, this would include concentration of THC, extra steps would be required by the manufacturer to reduce the level of THC in such a concentrate that it doesn't render the product a controlled substance per the CSA, and additionally, if there is new science that shows that a daily exposure to THC had to be limited to 0.5 mg a day theoretically, or it would render the product an intoxicant, then that too would and could be controlled by the cGMPs. This is no different than current controls for things like microbial contamination in foods, where limits are established for pathogenic bacteria.

Disclosure of THC, if considered a material fact, and likely it would, FDA has authority to initiate to notice and comment rulemaking to mandate disclosure of total THC.[4] Additionally, and what may be a faster step, than notice and comment rulemaking, like caffeinated beverages, most firms voluntarily disclose the amount of caffeine per serving and per container.

Also specific to conventional foods, in Technical Assistance provided to the House Energy and Commerce Committee on October 30th, 2020, FDA expressed concern with CBD in conventional food products. FDA has no data to determine whether the Reference Amounts Customarily Consumed (RACC) is inappropriate or would be misused for foods and beverages with CBD. The agency's mandate isn't abuse of foods. Considering the obesity epidemic, the agency has never suggested it regulate the abuse of other food additives or GRAS substances such as the potential abuse of high fructose corn syrup in snack foods. This is because the RACC is consistent with the intended use of the product.

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[3] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=111&showFR=1 ; https://www.fda.gov/food/guidance-regulation-food-and-dietary-supplements/current-good-manufacturing-practices-cgmps-food-and-dietary-supplements

[4] https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part-101

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6) Other non-cannabinoid products are available on the market that have raised safety concerns among some individuals, which FDA has regulated without a substance-specific regulatory framework (e.g., kratom, caffeine, etc.). How has FDA dealt with products containing those substances? How might these products be implicated by a CBD-specific product framework?

FDA has previously provided a path to market as dietary supplements/foods for natural products that contain an API by establishing a daily exposure level similar to what they did with monacolin K, the same ingredient that is in the prescription cholesterol-lowering drug lovastatin[3], which is found in Red Yeast Rice. The reality is natural products occupy space in both the drug and supplement (food) categories, including caffeine, folate, niacin, lovastatin, and lithium. The critical differences in those cases are 1) the type of claims that can be made and (2) the dosage. While FDA has said that CBD is different, it most parallels lovastatin which was debated in court. To this day, lovastatin is available on the market, and it contains monacolin K. FDA at present only enforces when it finds a lovastatin product at approximately half the effective lowest dose of lovastatin. They do this based on a Health Hazard Evaluation (HHE), which the FDA has failed to produce for CBD. A more direct solution is contained within the last part of the approved drug/investigational drug exclusion from the definition of a dietary supplement unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act." In FDA's Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues IV.D. 8 (July 2011), FDA provides its interpretation of this language as follows:

The general rule is that an article that has been authorized for investigation as a new drug or as a biologic before being marketed as a food or as a dietary supplement cannot be marketed as a dietary supplement if substantial clinical investigations of the article have begun and the existence of such investigations has been made public. FDA can create an exception to this prohibition by regulation, but only if the agency finds that the use of the article in dietary supplements would be lawful. To date, no such regulations have been issued. The appropriate mechanism to request such a regulation is to file a citizen petition under 21 CFR 10.30.

There is also precedent for enforcement discretion via the N-acetyl cysteine case.

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7) How has the absence of federal regulation over CBD created a market for intoxicating, synthetically-produced compounds, such as Delta-8 THC, THC-O, THC-B, HHC-P, and others? What is the public health impact of these novel compounds? How have FDA and state regulators enforced against products containing these compounds? How should Congress consider the inclusion of these products in a regulatory framework for cannabinoid hemp products, if at all?

Delta-8 THC is a psychoactive cannabinoid from the cannabis plant that can be synthetically converted from CBD. Most states permit the full or restricted sale of hemp and hemp-derived CBD products, and therefore, delta-8 THC products are on the rise. Delta-8 THC consumption can cause intoxication. Products are often sold in edible form and occasionally in packaging that appears like candy.

Delta-8 THC is one of several psychoactive THC isomers in the cannabis plant, although most of cannabis's psychoactive effect is ascribed to delta-9 THC. Although CBD is a non-psychoactive cannabinoid of the cannabis plant, CBD can be synthetically converted into psychoactive delta-8 THC to produce larger amounts of delta-8 THC than found naturally in the cannabis plant.

In May 2022, a federal appeals court issued a ruling that delta-8 THC is not a Schedule 1 substance under federal law (AK Futures LLC v. Boyd St. Distro, LLC, 35 F.4th 682 (9th Cir. 2022)). Until the federal government clarifies its position, the regulation of delta-8 THC falls under the purview of the states, with many states banning or restricting the sale of these products. Several studies have documented increases in unintentional youth cannabis exposures following the expansion of cannabis legalization over the past decade, with edibles being the most frequent route of exposure. With the increased availability of delta-8 THC, including in states that have not passed laws to allow medical and/or non-medical adult cannabis use, there is concern that unintentional youth ingestions could continue to increase.

Delta-8 THC-containing products for consumption have highlighted a recurrent regulatory issue surrounding the legality of hemp-derived products at the federal level. In September 2021, the FDA issued and updated a consumer advisory outlining consumer safety concerns related to delta-8 products. The consumer advisory highlighted that no delta-8 THC products have been evaluated or approved by the FDA, and many of the methods used to derive delta-8 THC synthetically involve potentially harmful chemicals. The Centers for Disease Control and Prevention issued similar guidance warning consumers of the rise in hospitalization reports and adverse event incidents related to delta-8 THC. In a response letter to the Alabama Board of Pharmacy, the U.S. Drug Enforcement Administration (DEA) clarified the control status of delta-8 THC under the Controlled Substance Act (CSA). DEA explained in its letter that "cannabinoids extracted from the cannabis plant that have a Δ9-THC concentration of not more than 0.3 percent on a dry weight basis meet the definition of 'hemp' and thus are not controlled under the CSA." Furthermore, DEA highlighted that THC "synthetically produced from non-cannabis materials" is controlled.

According to an FDA Consumer Update, the vast majority of delta-8 THC products on the market are produced through the conversion process of CBD, and some have interpreted DEA's statements to suggest that delta-8 products produced from hemp-derived CBD are excluded from the CSA. Furthermore, this statement at the federal level does nothing to hinder the banning or restriction on the use of delta-8 products at the state level, where many states have already enacted legislation to restrict access to such products.

In addition, on May 4, 2022, the FDA issued five warning letters to companies for selling products containing delta-8 THC. This marked the first time the FDA has issued warning letters for products containing delta-8 THC. Similar to the FDA's enforcement actions surrounding CBD products, the warning letters focus on the illegal marketing of unapproved delta-8 THC products by companies as treatments for medical conditions or other therapeutic uses. The letters cite violations of the Food, Drug, and Cosmetic Act (FDCA) relating to marketing unapproved new drugs, drug misbranding, and using delta-8 THC as an unapproved food additive.

The cited warning letters targeted companies that allegedly violated the FDCA by including delta-8 THC in either a food or dietary supplement, including unlawful drug claims about those products' efficacy and

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utility in treating medical conditions.

FDA concluded through these warning letters that the cited drug claims classify these products as unapproved new drugs because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and/or intended to affect the structure or any function of the body. In addition to labeling the products as unapproved new drugs, the warning letters emphasize these products are also misbranded because they are not labeled with adequate directions for use. Finally, FDA concluded that the addition of delta-8 THC in the case of food products classified the ingredient as an unapproved food additive, as the companies did not submit safety data to the FDA for the ingredient to be approved as a generally recognized as GRAS, and therefore, lawful ingredient.

As stated, prior, for conventional food and dietary supplement products, by definition can't be intoxicants. Similar to alcohol, it would appear that intoxicants are best left to the states to maintain jurisdiction of a marketplace, not the FDA. FDA does have authority to remove unapproved new drugs/street drug alternatives that are not licensed by the states or do not fit into those "intoxicants" categories, should the states make those decisions.

8) CBD products are not limited to just ingestible routes of administration—some are interested in products with alternative routes of administration (e.g., inhalable, topical, ophthalmic drops, etc.). For which non-ingestible routes of administration are consumers interested in consuming CBD products? How should a regulatory framework for cannabinoid products account for non- ingestible routes of administration?

Topical products, usually bear disease claims which would mean they are regulated as drugs. For topical products containing hemp but don't make a claim on CBD those would fit in the cosmetic space at FDA. Ophthalmic drops claiming CBD would also be regulated as a drug. Inhalable or vaped products, depending on intended use, if they were "intoxicants" then that would fall to the states to regulate.

Federal-State Interaction

9) In the absence of federal regulation or enforcement over CBD products, many states have established state regulatory programs to safeguard public health and create market certainty for industry participants. Which product standards relating to warning labels, minimum age of sale, manufacturing and testing, ingredient prohibitions, adverse event reporting, and others, have states adopted to protect consumer safety? Which such standards, if any, should Congress look to as models?

CBD is fully legal in Alaska, Arizona, California, Colorado, Connecticut, the District of Columbia, Maine, Massachusetts, Michigan, Montana, Nevada, New Jersey, New York, Oregon, Vermont, Virginia, and Washington. Meanwhile, CBD is conditionally legal in the remaining states, meaning that it may be legal under certain circumstances, such as for medical use or with a prescription, but otherwise illegal.
It is worth noting that states in the West and Northeast tend to have more relaxed laws on CBD, with more states fully legalizing its use. On the other hand, states in the South and Midwest tend to have stricter laws on CBD, with most states only conditionally legalizing it. However, these trends are not absolute, and there are exceptions in both regions.

The state-led regulatory environment for CBD has resulted in a complicated — and constantly changing — state patchwork of laws that is challenging for businesses and consumers to navigate. Businesses selling CBD products must not only comply with this patchwork of state laws, but also with applicable FDCA provisions, which in some cases may conflict with state laws.

Advertising restrictions, including product claim limitations, are common. Many states, such as New York, impose product labeling requirements that go above and beyond the FDA's regulations. California's Proposition 65 requires certain warning statements for products containing any amount of THC.

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While FDA has failed to make determinations for CBD, other countries, such as the United Kingdom, Canada, and Australia have adopted such limits. Several states have elected to impose serving size limits that mimic these countries and have used public data to make these determinations. New York proposed regulations, for example, that would impose a limit of 25 mg per individually packaged products if the product was a food or beverage and 75 mg per individual serving if the product is a supplement. An increasing number of state hemp laws expressly prohibit synthetic cannabinoids or intoxicating cannabinoids, controlled substance analogues or cannabinoids created through isomerization including delta8-THC and delta 10-THC. In many states, synthetic substances are also prohibited under state-controlled substances laws.

10) How should Congress consider federal preemption as it works towards a regulatory pathway? Should states be able to continue to build upon federal regulation of CBD products?

The FD&C Act expressly preempts any state law that establishes "any requirement respecting any claim of the type described in section 343(r)(1) … made in the label or labeling of food that is not identical to the requirements of section 343(r) of this title." 21 U.S.C. § 343-1(a)(5). The FDA's preemption of state labeling standards seems straightforward: a state can establish standards where the FDCA is silent, but where the FD&C Act has spoken, the state-law standard must be identical. Ninth Circuit's 2019 decision in *Dachauer v. NBTY*: the court held that the FD&C Act's regime of structure/function claims preempts a plaintiff's attempt to impose additional substantiation requirements on such claims. If a product's "immune health" structure/function claim is appropriately substantiated under the FD&C Act's standards, there is no path for a plaintiff to insist that a defendant must *also* provide proof that the product reduces the risk of all-cause mortality.

The Ninth Circuit followed this same logic in its 2021 decision in *Greenberg v. Target*. The plaintiff bought a biotin supplement hoping that it would slow or reverse his hair loss, owing to a "helps support healthy hair and skin" structure/function claim made for the product. The Ninth Circuit had little difficulty finding that the FD&C Act's preempted state-law deceptive advertising claims where the claim met the FD&C Act's requirements for structure/function claims. Because the FD&C Act's provides the requirements for such claims, and because the company met those requirements, the company could not face state-law liability for the claim. For conventional foods and dietary supplements containing CBD the states should be pre-empted by FDA in carrying out its mandate.

Safety

11) What is currently known about the safety and risk-benefit profile of CBD and other hemp derived cannabinoids? What safety and toxicity data are available to support this knowledge. Please include in your answer any relevant information about safety with regard to specific populations, such as children and pregnant individuals.

The safety data for daily exposure to healthy populations for orally ingested CBD is very well established. Other governments, most notably the UK and Health Canada have established daily exposure limits to CBD. A nine-member panel called the Science Advisory Committee on Health Products Containing Cannabis for Health Canada concluded that CBD is "safe and tolerable for short-term (maximum of 30 days) at doses from 20 milligrams per day to a maximum dose of 200 mg per day."[5] The United Kingdom's Food Safety Authority's recommends that healthy adults do not take more than 70mg of CBD a day unless a doctor agrees to more.[6] Clearly a daily amount can be established and likely in the range of 70-200 mg daily, which will allow for a significant safety factor. Most products are currently labeled to address population specific

[5] https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/health-products-containing-cannabis/review-cannabidiol-health-products-containing-cannabis.html

[6] https://www.food.gov.uk/safety-hygiene/cannabidiol-cbd#:~:text=As%20a%20precaution%2C%20we%20recommend,potentially%20be%20seen%20above%20this.

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concerns, in this case, not for use by those under 18 and by pregnant/expecting women. This would be material and consistent with FDA's authorities where conditions of use are required in the labeling of a dietary supplement.

Additionally, if today FDA determined that CBD is not excluded from the definition of a dietary supplement under 21 U.S.C. 321 (ff)(3)(B) or exercised enforcement discretion in over individual CBD or extracts containing CBD such products would require an NDI notification on an individual dietary supplement product submitted consistent with 21 CFR Part 190.6. The FDA's authorities for supplements would be a product-by-product review, giving comprehensive assurance of what is in the marketplace has been evaluated for safety specific to that products composition. Additionally, the NDI requires that conditions of use are given in the notification, where FDA could withhold an "good day letter" from a company if they do not ensure conditions of use that restricts use by those under 18 and by pregnant/expecting women.

12) What actions, if any, should the Federal government take to better understand the potential benefits or harms of CBD products and other cannabinoids?

For conventional foods and dietary supplements, the FDA doesn't have a mandate to examine efficacy. Harms are addressed by the current statutory and regulatory authorities as outlined above.

13) How should a new framework for CBD products balance consumer safety with consumer access?

No new framework is necessary. With the passage of DSHEA, Congress recognized the importance of nutrition and the benefits of dietary supplements in promoting public health. Products sold as dietary supplements come with a Supplement Facts label that lists the active ingredients, the amount per serving, as well as other ingredients, such as fillers, binders, and flavorings. The FDA has established good manufacturing practices (GMPs) that companies must follow to help ensure their dietary supplements' identity, purity, strength, and composition. These GMPs can prevent adding the wrong ingredient or too much or too little of the correct ingredient and reduce the chance of contamination or improper packaging and labeling of a product.

14) Some stakeholders have raised concerns that CBD products have inherent risks. What are those inherent risks, and at what levels of CBD do those risks present themselves?

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What data and other evidence support the existence of such risks, and from which products are such data and evidence derived?

We are unaware of any inherent risk attributable to CBD as a conventional food or dietary supplement that wouldn't be attributable to any other ingredient that FDA currently regulates. Should something emerge in the marketplace, there are post market surveillance requirements. Serious adverse event reporting for dietary supplements and the reportable food registry for conventional foods.

15) FDA approved Epidiolex, a drug containing CBD, based in part on a data package that included preclinical data from rodent safety models, as well as clinical trials. FDA has received safety data on CBD products from several manufacturers also based on rodent models. How should FDA consider data submitted for a CBD-containing drug as evidence to support that CBD is safe for human consumption in non-drug products, recognizing the inherent differences in the intended uses of such products?

There are different standards for evaluating data for a CBD-containing drug versus CBD-containing supplements. Recently, The Office of Food Additive Safety, Center for Food Safety and Applied Nutrition (CFSAN) has published its review the oral toxicity of cannabidiol (CBD). The authors of the review stated: "The toxicological profile of CBD raises safety concerns, especially for long-term consumption by the general population." This is a prime example of the agency using drug standards to conduct a dietary supplement study which at the very least is disingenuous and at worst, very harmful to the regulatory process on CBD. Instead of using actual dietary supplement data and research like the data supplied in NPA's citizen petition, the FDA chose to use drug data to draw conclusions three times the dose of the CBD drug Epidiolex.

As noted in NPA's citizen petition, cbdMD studied CBD's safety so that it could further demonstrate the untenability of the Agency's historical treatment of CBD and its corresponding safety data. cbdMD spent $1,000,000 to prepare identity and safety data to answer all safety questions posed by the Agency, and the Agency has no proper justification for refusing the review of cbdMD's data or NDI submission under the pretense that CBD is excluded from the definition of a dietary supplement under DSHEA, or by dodging the consideration of convincing safety data. cbdMD has compiled a dossier of identity and safety data for submission as a novel food ingredient for the European Union and for submission in support of a new dietary ingredient notification to FDA. The United Kingdom and the European Union have already reviewed and approved this data.

Unfortunately, cbdMD and others are forced to submit CBD-specific NDIN without the full scope of safety data it has compiled unless the Agency agrees to review the data and provide the submitter, in the form of an NDIN response letter, with its determination of whether it agrees or objects to it on scientific merits and not on a broad policy statement on drug exclusion. After all, submitting confidential data to the Agency without the guarantee that it will be reviewed and appropriately replied to does nothing other an expose the submitter's risk of disclosure of the data along with potential misrepresentation of the data without any benefit to the submitter. A CBD NDI submitter should not be forced to expose itself to this risk after spending substantial resources to study CBD unless it receives a substantive response from FDA. Without the pathway for the Agency to review the safety data consistent with the statute, the Agency has effectively reversed the marketplace, providing an advantage to companies who will never conduct the required safety studies, meet GMPs and other regulatory requirements.

16) Should there be limits on the amount of CBD in foods, dietary supplements, tobacco, or cosmetics? If so: should Congress or FDA set such limits, recognizing the time it can take to complete the legislative process and the regulatory process at FDA?

Through the scientific review process, the FDA can establish dosage limits. Section 201 (ff) (21 U.S.C. 321 (ff), which defines dietary supplements, and by adding section 413(a) (21 U.S.C. 350b (a), provides, among other things, for the notification of the Secretary of Health and Human Services and by delegation the FDA at least 75 days before the introduction or delivery for introduction into interstate commerce of a dietary

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supplement that contains a new dietary ingredient. Section 413(a) of the act states that a dietary supplement that contains a new dietary ingredient shall be deemed adulterated unless it meets one of two requirements. One requirement is that ``*the dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered*." The alternative requirement is that: There is a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the Secretary with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

It is not possible to have a reasonable expectation of safety without knowledge of the level of the new dietary ingredient in the supplement. The dietary ingredient may be safe under certain conditions of use, but it may be unsafe under other conditions of use. For example, the essential trace mineral selenium is safe when consumed in amounts necessary to meet a person's nutrient requirements, but it is toxic when consumed at high levels. Some dietary ingredients contain constituents that have potent pharmacologic actions that could cause the dietary ingredient to present a significant or unreasonable risk of injury or illness under the labeled conditions of use. The bark of *Pausinystalia yohimbe* (K. Schumann) (commonly called yohimbe) contains the indolalkylamine alkaloid yohimbine, which is a potent alpha-2-adrenergic antagonist that may be toxic when ingested in high doses.

Thus, if the notification does not contain the level of the dietary ingredient in the product, the notification would not contain a piece of information that is necessary if the manufacturer or distributor is to conclude that the dietary supplement will reasonably be expected to be safe under the conditions of use recommended or suggested in its labeling. Without this information, the dietary supplement would be adulterated under section 402(f)(1)(B) of the act (21 U.S.C. 342(f)(1)(B)).

17) How should that amount be determined? What should the amount be?

Through the NDIN process. The FD&C Act requires that manufacturers and distributors who wish to market dietary supplements that contain "new dietary ingredients" notify the Food and Drug Administration (FDA) about these ingredients. Generally, the notification must include information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling.

The FD&C Act provides that a dietary supplement that contains a new dietary ingredient shall be deemed adulterated under section 402(f) of the FD&C Act (21 U.S.C. 342(f)) unless it meets one of two requirements:

The dietary supplement contains only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered; or There is a history of use or other evidence of safety establishing that the dietary ingredient when used under the conditions recommended or suggested in the labeling of the dietary supplement will reasonably be expected to be safe and, at least 75 days before being introduced or delivered for introduction into interstate commerce, the manufacturer or distributor of the dietary ingredient or dietary supplement provides the FDA with information, including any citation to published articles, which is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such dietary ingredient will reasonably be expected to be safe.

18) Should such limits be applied on the amount per serving, and/or per package?

That would be required by existing labeling regulations, per serving the amount would be disclosed.

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19) Could FDA set such limits under its current statutory regulatory authorities for foods and dietary supplements to potentially address safety concerns, notwithstanding exclusionary clause issues?

FDA can today, under current authorities, be compelled by Congress to set a daily consumption level (which will address the major public health concerns) in foods and dietary supplements, establishment of such a level would trigger other authorities dealing with labeling and product quality (cGMP) which the agency can use to effectively regulate the marketplace. They can do this through enforcement discretion which has precedence for dietary supplements or through notice and comment rulemaking, which has been in the statute since 1994 but has never been used by FDA.

20) How should the experience of states inform the setting of limits on amounts of CBD in products?

The tension between state and federal positions is quite clear. Dozens of states currently allow the sale of hemp-derived products. While many states have established their own guidelines, it is imperative that Congress mandate the FDA to establish dosage recommendations along with an official method of analysis for CBD products. The implementation of these regulations would serve as the uniform standard for testing products that purport to contain CBD. Science should drive the establishment of limits, just like it does for other ingredients like caffeine.

21) How should a regulatory framework account for CBD products marketed in combination with other substances that may alter or enhance the effects of CBD (e.g., caffeine, melatonin, etc.)?

This is already accounted for in the NDIN process. This is part of the required conditions of use of the ingredient or extract in combination with other new ingredients or pre-DSHEA ingredients.

22) What precedent is there for FDA restricting certain otherwise allowable ingredients in legally marketed products? What amount and type of evidence has been required/demonstrated to support any such restrictions?

FDA's authority comes from products either being misbranded or adulterated, that would be the level of evidence FDA needs to restrict anything. Various aspects of the statute and regulations lay out what the violations are to support restriction.

23) What functional ingredients combined with cannabinoids raise safety concerns?

None specifically that I am aware of. However, it's expected that any company in the conventional food or dietary supplement space has data to establish a reasonable expectation of safety of their product prior to going to market. A company would have to have substantiation to support their product and its combination of ingredients is safe.

Quality

24) How should Congress create an FDA-implemented framework to ensure that manufacturers provide appropriate consumer protections and quality controls? How should such a framework compare to the current Good Manufacturing Practice (GMP) requirements that apply to food, dietary supplements, and cosmetics? B. Are those food, dietary supplement, and cosmetics GMP frameworks adequate for regulating quality in CBD? Why or why not? Are those food, dietary supplements, and cosmetics GMP frameworks adequate for regulating quality in CBD? Why or why not?

The framework established for dietary supplement GMPs is more than adequate for dietary supplements containing CBD. On June 25, 2007, FDA published in the Federal Register a final rule that established a regulation (21 CFR part 111) entitled Current Good Manufacturing Practice (CGMP) In Manufacturing, Packaging, Labeling, Or Holding Operations for Dietary Supplements (72 FR 34752). The Dietary Supplement (DS) CGMP rule in 21 CFR part 111 ("the DS CGMP rule") requires persons who manufacture,

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package, label, or hold a dietary supplement to establish and follow current good manufacturing practice to ensure the quality of the dietary supplement and to ensure that the dietary supplement is packaged and labeled as specified in the master manufacturing record. If you manufacturer, package, label, or hold a dietary supplement you are subject to 21 CFR 111.1(a).

The general food CGMPs in part 110 (21 CFR part 110) largely address practices designed to ensure that food is manufactured, processed, packed, and held under sanitary conditions and that the food is safe, clean, and wholesome. Although the general food CGMPs in part 110 apply to a variety of food products, including dietary supplements, they do not address the unique characteristics of certain specific types of food products. The agency has implemented separate, and more specific, CGMPs for various types of food products to provide for process controls in manufacturing that are not captured by the more general part 110 food CGMPs. (See discussion in section V of this document ("Legal Authority") on product specific CGMP requirements). At the time DSHEA was enacted, there were four such additional, specific food CGMP regulations: Those for infant formula (part 106 (21 CFR part 106)), thermally processed low-acid canned food (part 113 (21 CFR part 113)), acidified food (part 114 (21 CFR part 114)), and bottled water (part 129 (21 CFR part 129)).

Dietary supplements are a type of food product for which specific food CGMPs also are needed. Manufacturing process controls are needed to ensure that a dietary supplement contains what the manufacturer intends. Unlike most foods, the majority of dietary supplements are packaged into tablets, gelcaps, and capsules. Some dietary supplements may contain bioactive ingredients for which certain, controlled amounts are intended to be in each tablet or capsule. The process controls that must be in place to ensure the tablet or capsule contains what it purports to contain are different than those that must be in place to ensure a food is manufactured, processed, packed, and held under sanitary conditions. Process controls for dietary supplement manufacture include establishing and meeting specifications to ensure the finished dietary supplement contains the correct ingredient, purity, strength, and composition intended.

Vitamins can present a concentrated source of biologically active components. A vitamin, for example, that contains too high a concentration, such as vitamin D at levels that are many times greater than intended, can lead to illness and hospitalization. A manufacturer must establish a process for manufacturing a dietary supplement product in order to produce the product consistently and reliably each time. In order to achieve consistency and reliability, there must be process controls in place to ensure, for example, that appropriate tests and examinations are conducted, a master manufacturing record is prepared, each batch production follows the master manufacturing record, and the finished tablet or capsule is placed in the intended package with the intended label.

These same types of controls are needed for herbal and botanical dietary supplements. Botanicals are often complex mixtures that can vary in composition depending on factors such as the part of the plant used, the location of harvesting and growing conditions that can vary from year to year even in the same location. It can be difficult to distinguish between closely related species of botanicals, and the biological activity of components of an incorrectly identified species can lead to adverse consequences. In addition, different species may be present in different ratios or blends in a particular product. Various products might contain different parts of the plant—flower, leaf, root, stem, extract—and the test methods for each can vary in the nature, sensitivity, and specificity of the test.

Well-established principles of CGMP require process controls at each step of the manufacturing process as early in the production process as possible. Quality cannot be tested into the product only at the end. Instead, the quality of the dietary supplement must be built into the product throughout the manufacturing process; quality begins with the starting material and continues with the product being manufactured in a reproducible manner according to established specifications. It is not sufficient, nor effective, to rely solely on end-product testing to assure the quality of the individual dietary supplement product sold to the consumer.

CGMPs are intended to establish a comprehensive system of process controls, including documentation of

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each stage of the manufacturing process, that can minimize the likelihood of, or detect, problems and variances in manufacturing as they occur and before the product is in its finished form. These process controls that are a part of CGMPs are essential to ensure that the dietary supplement is manufactured, packaged, held, and labeled in a consistent and reproducible manner.

Manufacturing according to CGMP means that the manufacturing process incorporates a set of controls in the design and production processes to assure a quality finished product. CGMPs specific to dietary supplements are necessary to help ensure that these products have the identity, purity, strength, and composition that meet specifications established in the master manufacturing record and that they are not adulterated.

As defined, quality means "that the dietary supplement consistently meets the established specifications for identity, purity, strength, and composition and has been manufactured, packaged, labeled, and held under conditions to prevent adulteration under section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the Federal Food, Drug, and Cosmetic Act." Ensuring the quality of the dietary supplement means that you consistently and reliably manufacture what you intend and that you establish manufacturing controls to prevent the dietary supplement from being adulterated under section 402(a)(1) of the act due to the presence of contaminants, under section 402(a)(2) of the act, for example, if it bears or contains any unintentionally added poisonous or deleterious substance, under section 402(a)(3) of the act if the dietary supplement consists in whole or in part of any filthy, putrid, or decomposed substance, or if it is otherwise unfit for food, or under section 402(a)(4) of the act if the dietary supplement has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. The definition of quality limits to section 402(a)(1), (a)(2), (a)(3), and (a)(4) of the act the types of adulteration that you must control for in this CGMP final rule. The definition applies to the controls that are designed to prevent contamination of the product that you intend to manufacture.

25) What are alternative quality approaches that Congress should consider for CBD products? For example, how should third parties be leveraged for the creation and auditing of manufacturing and testing requirements?

Several independent organizations, including the Natural Products Association, offer quality testing and allow products that pass these tests to display a seal of quality assurance that indicates the product was properly manufactured, contains the ingredients listed on the label, and does not contain harmful levels of contaminants.

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Form, Packaging, Accessibility, and Labeling

26) What types of claims should product manufacturers be permitted to make about CBD products? Please reference how such permitted claims compare to the types of claims that may be made about drugs, foods, dietary supplements, and cosmetics.

If a CBD dietary supplement manufacturer or marketer is able to substantiate the claims, they should be able to make structure/function or qualified health claims. The Federal Trade Commission (FTC) and the FDA work together under a long-standing liaison agreement governing the division of responsibilities between the two agencies. As applied to dietary supplements, the FDA has primary responsibility for claims on product labeling, including packaging, inserts, and other promotional materials distributed at the point of sale. The FTC has primary responsibility for claims in advertising, including print and broadcast ads, infomercials, catalogs, and similar direct marketing materials. Marketing on the internet is subject to regulation in the same fashion as promotions through any other media.

In 1994, DSHEA significantly changed the FDA's role in regulating supplement labeling. These claims are commonly referred to as structure/function claims. Although DSHEA does not directly apply to advertising, it has generated many questions about the FTC's approach to dietary supplement advertising. The answer to these questions is that advertising for any product, including dietary supplements, must be truthful, not misleading, and substantiated. The FTC's approach to supplement advertising is best illustrated by its Enforcement Policy Statement on Food Advertising (Food Policy Statement). Although the Food Policy Statement does not specifically refer to supplements, the principles underlying the FTC's regulation of health claims in food advertising are relevant to the agency's approach to health claims in supplement advertising. In general, the FTC gives great deference to an FDA determination of whether there is adequate support for a health claim. Furthermore, the FTC and the FDA will generally arrive at the same conclusion when evaluating unqualified health claims. Supplement marketers are cautioned that the FTC will require both strong scientific support and careful presentation for such claims. Supplement marketers should ensure that anyone involved in promoting products is familiar with basic FTC advertising principles. The FTC has acted not just against supplement manufacturers, but also, in appropriate circumstances, against ad agencies, distributors, retailers, catalog companies, infomercial producers and others involved in deceptive promotions. Therefore, all parties who participate directly or indirectly in the marketing of dietary supplements have an obligation to make sure that claims are presented truthfully and to check the adequacy of the support behind those claims.

27) What is the evidence regarding the potential benefits of including a symbol or other marking on product labeling to provide clarity for consumers who would purchase products that contain CBD? What are the potential benefits or drawbacks of an additional or substitute standardized label panel for CBD products, compared to the current Nutrition Facts Label and Supplements Label? What precedent exists in foods, dietary supplements, tobacco, and cosmetics for requirements of labeling to present risks to special populations in labeling (e.g., children, pregnant and lactating women, consumers taking certain drugs, etc.)? What amount and type of evidence has been required to support such requirements?

Any added labeling or material to the label would have to meet certain first amendment tests (e.g. *Zauderer, Central Hudson*). Caffeine serves as a good benchmark here. Naturally present in coffee, tea, chocolate, cola-type beverages, caffeine may serve as a primary example of a precedent existing in foods and dietary supplements. Caffeine has a long history of safe use and is in both foods and dietary supplements with two different regulatory tracks. Whether it's CBD, caffeine or any other dietary ingredient, FDA should be evaluating exposure and collection toxicology data. Added, a number of firms have taken it on themselves to add statements of how much caffeine is in the product, which may not be

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required by law given the product category. CBD would be different as the amount for dietary supplements would have to be disclosed in the supplement facts panel.

A practical application of this is when energy drink products are marketed as foods ingredients are approved food additives or GRAS for their intended use. When energy drink products are marketed as dietary supplements, they are subject to DSHEA and must be labeled as dietary supplements. According to 21 CFR 182.1180, caffeine up to a level of 200 ppm is GRAS for use in coly-type beverages consistent with GMPs. The regulation does not automatically preclude other uses of caffeine from being considered GRAS nor does it automatically give GRAS status to other uses and or higher tolerances. FDA regulations require beverage companies to list caffeine on product labels' ingredients list. Additionally, most voluntarily label cautionary statements. Some products contain advisories against use by children, pregnant women, or individuals sensitive to caffeine.

28) Some suggest requiring labels for CBD products to include "potential THC content." Would THC content be unknown in a particular product? Is there precedent for such a labeling requirement? How should access to CBD products by children be regulated? For example, would it be appropriate to have an age restriction on the purchase of CBD products? If so, what is an appropriate age limit? What specific additional restrictions should apply to CBD products regarding their appeal to or use by children with regard to marketing, packaging, and labeling? Is there precedent in the food, dietary supplement, tobacco, or cosmetics space for restricting certain product features that would make products appealing to children? Please describe. Some suggest requiring packages with multiple servings to be easily divisible into single servings. Does a framework like this exist today for any other product or substance?

THC content should be known and controlled for per cGMPs. Disclosure of THC will likely initially be voluntary, but FDA does have authority to write a regulation through notice and comment rulemaking for disclosure of THC content, if it is a material fact, similar to the gluten allergy threshold and disclosure. Regarding the age of use, most companies currently have a label statement that CBD shouldn't be used by children. As all would go through the NDI process, FDA would also be able to influence conditions of use regarding age through those evaluations.