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8/18/2023

Re: **Request for Information about Cannabidiol from US Congress**

Dear Rep. McMorris Rodgers, Sen. Cassidy, Rep. Pallone and Sen. Sanders:

Thank you for the opportunity to provide input on the Congressional deliberations regarding the regulation of CBD. We are part of a research team at the USC Schaeffer Center for Health Policy & Economics that is at the forefront of analyzing cannabis policy reforms and their impacts on medical access, medical and recreational use, and positive and negative health impacts. Dr. Pacula, who leads the team, has spent more than 30 years studying cannabis and tobacco markets with funding from NIDA, NIAAA, ONDCP, the European Union and the Robert Wood Johnson Foundation. Our responses draw on our experiences and perspectives developed through this research, including evaluations of U.S., Canada, Australia and European markets as well as ongoing discussions with local, state and federal regulators.[1]

Stricter regulations of the market for non-medical CBD and the products allowed to be sold in it are required to ensure the public health and public safety of Americans. As scientists, we usually wait for clear scientific evidence before guiding policy reforms, but we feel it necessary to act because the industry is moving ahead of the science assuming that new product formulations derived from the plant are safe because the plant appears to be safe. Policymakers should consider the regulatory experiences that we have observed from tobacco, vaping products, alcohol and prescription drug industries when considering the regulation of CBD for nonmedical use. Those considerations as well as the pharmacological aspects of CBD and our current knowledge of the endocannabinoid system are reflected in the answers contained herein.

If you seek further information, please do not hesitate to contact Dr. Pacula at email below.

Sincerely,

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[1] The views expressed in this letter are those of the authors and do not necessarily reflect the views of the USC Schaeffer Center or the University of Southern California (USC).

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.

    a. Due to the lack of regulations as a whole plant (containing multiple cannabinoids with different properties) there have been ongoing product proliferation and contamination of CBD-based food, beverage, vaping and cosmetic products in the U.S. market.[1] CBD product labelling does not match product composition[2] and synthetic derivatives of the plant with potentially intoxicating and harmful effects are now sold everywhere, including edibles that look like candies and infused beverages that appeal to children and/or can inadvertently be consumed by children.[3]

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

    a. Because the 2018 Farm Bill uses a very broad definition of hemp (specifically: defining it in terms of one single cannabinoid in the plant, delta-9 THC, rather than comprehensively considering all the compounds in the plant), there has been an explosion of hemp-derived products, some of which have been synthesized and/or infused with specific cannabinoids besides delta-9 THC that are also intoxicating. Our understanding of the role played by the other cannabinoids within the plant and their impacts on our endocannabinoid system continues to evolve, but THCA – which can be legally present in hemp products and rapidly converts to delta-9 THC once heated or combusted – is just one example of a potentially relevant compound of the plant that should be regulated if the goal is to reduce the development of an unregulated intoxicant. Others include delta-8 THC and THC-O-Acetate. Products containing nontrivial amounts of these cannabinoids have been generally prohibited in state cannabis markets due to safety concerns, but are now legally permissible with the Farm Bill because they do not contain more than trace amounts of delta-9 THC. By defining hemp on a basis of single compound, the government has opened the flood gates to a bunch of new intoxicants as well as manufactured products containing large amounts of delta-9 THC because (a) other intoxicating and potentially harmful compounds exist in the cannabis sativa L plant and are not explicitly prohibited by this definition; and (b) current technology enables the extraction of even small or trace amounts of delta-9 THC from the plant to be combined and/or synthesized together or with other extracts into a manufactured products that contains far more than the naturally occurring amount of any of the cannabinoids desired, including delta-9 THC. State regulators have been grappling with the proliferation of products that are technically prohibited under their state cannabis laws,[4] as noted in the testimony provided by CANNRA's Executive

[1] https://www.cnn.com/2019/03/26/success/cbd-entrepreneurs/index.html
[2] See for example https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5818782/ and https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2794440
[3] See https://apnews.com/article/90274726bf9f4976b1504d47f18fcf2a, https://apnews.com/article/ut-state-wire-tx-state-wire-fl-state-wire-cbd-marijuana-7b452f4af90b4620ab0ff0eb2cca62cc, and https://oag.ca.gov/news/press-releases/attorney-general-bonta-cannabis-infused-edibles-packaged-popular-food-and-candy
[4] https://oag.ca.gov/news/press-releases/attorney-general-bonta-cannabis-infused-edibles-packaged-popular-food-and-

Director, Gillian Schauer to the House Committee on Oversight and Accountability Health Care and Finance Services Subcommittee on July 27, 2023. Auditing and enforcement of regulatory compliance also seem to be absent under our current federal regulations.

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

    a. As noted in Q2, newly manufactured products derived from the plant are proliferating, including foods, beverages,[5] dietary supplements,[6] and vaporizers.[7] Many of those new products are targeting youth[8] and pregnant women.[9] Consumers are getting untested and unsafe products because there is no enforcement of a regulatory standard of products derived from the plant considering all the compounds, only that the plant as an input in the process of producing this wide range of products meet a specific and clearly weak threshold for a single compound. Because consumers themselves are ill-informed on whether and how these products differ from cannabis products and/or the science supporting wellness claims, consumer decision making is not supported by regulatory framework that protects vulnerable individuals.(i.e. there is no agency here).[10]

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.

    The FDA's concerns raised about regulating CBD through the food and dietary supplement authorities are valid. There are known adverse events and harm that occurs even from approved pharmaceutical formulations of CBD (Epidiolex) for some individuals,[11] and there is growing research that there are potential hepatotoxic and gastrointestinal adverse effects of CBD at higher doses, as well as interactions with some medications.[12] We have insufficient data to know what thresholds are safe. Regulation as a drug, even if just an OTC drug seems to be more fitting. If CBD is to be taken as a medication, it can then be delivered in a consistent and precise dosage every time. Moreover, the device used to

candy

[5] https://www.usfoods.com/great-food/food-trends/cbd-can-be-a-profitable-ingredient.html

[6] https://www.vitaminshoppe.com/lp/cbd

[7] https://www.cbdmall.com/cbd-vape

[8] Again, we reference this news release from CA AG identifying foods/drinks that are consumed by children: https://oag.ca.gov/news/press-releases/attorney-general-bonta-cannabis-infused-edibles-packaged-popular-food-and-candy.

[9] Bayly N. Can you consumer Delta 8 Flower pre and post pregnancy? Grynny.com February 25, 2022. Accessed at: https://www.gryyny.com/news/47427/can-you-consume-delta-8-flower-pre-and-post-pregnancy/

[10] https://www.healthline.com/health/best-cbd-gummies#_noHeaderPrefixedContent

[11] Epidiolex (cannabidiol) FDA approved prescribing information. July 2020. Accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210365s005s006s007lbl.pdf

[12] Chesney E, Oliver D, Green A, Sovi S, Wilson J, Englund A, Freeman TP, McGuire P. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. *Neuropsychopharmacology*. 2020 Oct;45(11):1799-1806. doi: 10.1038/s41386-020-0667-2; Graham M, Martin JH, Lucas CJ, Murnion B, Schneider J. Cannabidiol drug interaction considerations for prescribers and pharmacists. *Expert Review of Clinical Pharmacology*. 2022 Dec;15(12):1383-1397. Doi:10.1080/17512433.2022.2142114.; Bonaccorso, S., Ricciardi, A., Zangani, C., Chiappini, S., & Schifano, F. (2019). Cannabidiol (CBD) use in psychiatric disorders: A systematic review. *Neurotoxicology*, 74, 282-298.

deliver the CBD product (e.g. vaping device) can generate harm by raising the temperature of the plant product being vaped to a temperature where otherwise benign compounds like THCA get converted to delta-9 THC.[13] All of these confounding issues and complications suggests that a new regulatory pathway may be needed.

Scope

5. How should CBD and/or cannabinoid-containing hemp products be defined? What compounds should be included and excluded from a regulatory framework?

A good starting place is to specify all the naturally occurring cannabinoids and terpenes known to naturally exist in the plant as of (for example) January 1, 2018,[14] and designate maximum levels of each of those in addition to the criteria that delta-9 THC be below 0.3%. Information on these cannabinoids and terpenes can be obtained from scientific studies of the plant by industry and researchers documenting the information prior to the adoption of the Farm Bill. Furthermore, the regulation should explicitly state that no product generated or derived from hemp can be sold in non-medical markets if they contain a level of ANY cannabinoid (or terpene) beyond that which naturally occurred in the plant as of January 1, 2018, particularly if used as a food, beverage, smokable good or cosmetic. Making this second statement is what is particularly important for regulatory purposes, as it negates the incentive by the industry to further innovate in the processing and manufacture of plant derivatives. The explicit advantages of such a regulatory approach is that it (a) does not harm existing cultivators or retailers of these products, aside from requiring them to more closely monitor the whole plant being cultivated and/or the products they allow to be sold, and (2) focuses the FDA attention and resources on manufacturers and processors who are the main ones generating the innovative and potentially harmful products that should be studied and evaluated before made available to consumers in the marketplace.

Furthermore, we would recommend that the regulation prohibit synthetic cannabinoids from the legal market for hemp (some products may be desirable for medical purposes, and those can be explored through the existing FDA drug authority). The reason for this is that there is growing evidence of harm from synthetic cannabinoids more generally,[15] and synthetic cannabidiol in particular has the potential to react differently with our endocannabinoid system, particularly our

[13] https://www.scientificbulletin.upb.ro/rev_docs_arhiva/rez0e1_161311.pdf; Love, C. A., Kim, H. Y. H., Tallman, K. A., Clapp, P. W., Porter, N. A., & Jaspers, I. (2023). Vaping Induced Cannabidiol (CBD) Oxidation Product CBD Quinone Forms Protein Adducts with KEAP1 and Activates KEAP1-Nrf2 Genes. *Chemical Research in Toxicology*, *36*(4), 565-569.

[14] We suggest Jan 1, 2018, as this is a date prior to the passage of the Farm Bill, at which point additional genetic modification of the plant could have occurred. Information on the naturally occurring plant and its compounds at this time is available from NIDA grantees as well as Jazz Pharmaceutical and Bedrocan, who were engaged in cultivating for scientific purposes.

[15] Horth RZ, Crouch B, Horowitz BZ, et al. *Notes from the Field:* Acute Poisonings from a Synthetic Cannabinoid Sold as Cannabidiol — Utah, 2017–2018. MMWR Morb Mortal Wkly Rep 2018;67:587–588.
DOI: http://dx.doi.org/10.15585/mmwr.mm6720a5; Michael Geci, Mark Scialdone, and Jordan Tishler.
The Dark Side of Cannabidiol: The Unanticipated Social and Clinical Implications of Synthetic Δ8-THC.
*Cannabis and Cannabinoid Research.* Apr 2023.270-282.http://doi.org/10.1089/can.2022.0126;
https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc

CB1 and CB2 receptors, than naturally occurring CBD.[16]

a. 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?

    i. Yes, for reasons specified already above, it is important for the FDA to limit the amount of intoxicating or potentially intoxicating substances produced from the plant in food and dietary supplements, but not necessarily through authorities already granted to the FDA for those goods. The substances of concern can be addressed as recommended in response to Q5 above through a new regulatory pathway, and should include limits on all known compounds of the plant, particularly in finished consumable, ingested, or cosmetic products from the plant. As noted already in Q5, synthetic cannabinoids, including synthetic CBD, should not be permitted in any new authorities, but rather explored only through new drug pathway.

b. 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?

    i. Given the scientific literature is unable to identify a clear "healthy" amount of THC and other cannabinoids at this time, the FDA would be best served assuming that the amounts available in the natural plant, which are far less than those available in extracts, edibles, concentrates and products derived from the plant, would be good starting level. These "limits" placed on the specific compounds of the plant can and should be reconsidered every 5 years as new science becomes available. Further, the regulatory framework should consider:

The public safety and public health impacts associated with use of the product, not just the harms from prohibition

- The limits should consider the total converted THC (and/or other intoxicants or identified harmful compound) as delivered to the consumer given the product and probable mode of administration (e.g. joint, vaping device, edible), and not the bulk weight amount contained in the plant or manufactured product at the time sold.
- Adequate resources are given to the FDA and other enforcement agency for checking compliance with rules (audits of products and stores) not just initial testing of products.

c. Should FDA regulate the manufacture and sale of "semisynthetic derivatives," or

[16] https://www.tga.gov.au/sites/default/files/review-safety-low-dose-cannabidiol.pdf

"biosynthetic cannabinoids," which are still scheduled under the CSA?

The FDA should prohibit the sale of semisynthetic, synthetic derivates, and biosynthetic cannabinoids in any food, cosmetic, and tobacco product it regulates under the proposed new authority. Such products should only be considered through the FDA's drug authority until sufficient science has emerged demonstrating their safety for general uses.

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?

The cannabis plant and the cannabinoids that can be extracted from it differ substantially from other substance-specific regulatory frameworks because, by definition, cannabis is not a single substance, like caffeine. In some ways, it is more similar to kratom, which the government has outright prohibited rather than specify particular compounds of the plant that individually are allowed or not allowed. Until the scientific community understands what the plant's naturally occurring mixture of cannabinoids does within the body, and how each individual cannabinoid impacts the endocannabinoid system when exposed at various levels, it is unwise (and scientifically unfounded) to come up with a framework targeting one cannabinoid, unless that product is delivered in the same doses as we have studied and seen occur naturally in the plant.

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?

The absence of federal regulation has allowed the cannabis industry to innovate in ways that were never imagined by the voters or legislatures, by creating new products which contain higher than naturally occurring extracts of particular cannabinoids, including Delta-8 THC, THC-0 and so on. Again, if the FDA considered regulating all the compounds of the plant rather than singular cannabinoids, or at least required that all other compounds be maintained at levels naturally occurring in the plant, such innovation with respect to CBD would not be possible in the hemp market

a. What is the public health impact of these novel compounds? Our knowledge of both acute and adverse events is steadily growing, but those already identified in the literature include: poisonings, acute psychosis, respiratory depression, anxiety, vomiting, and loss of consciousness. [17]

[17] Horth RZ, Crouch B, Horowitz BZ, et al. *Notes from the Field:* Acute Poisonings from a Synthetic Cannabinoid Sold as Cannabidiol — Utah, 2017–2018. MMWR Morb Mortal Wkly Rep 2018;67:587–588.
DOI: http://dx.doi.org/10.15585/mmwr.mm6720a5; Michael Geci, Mark Scialdone, and Jordan Tishler.
The Dark Side of Cannabidiol: The Unanticipated Social and Clinical Implications of Synthetic Δ8-THC.
*Cannabis and Cannabinoid Research.* Apr 2023.270-282.http://doi.org/10.1089/can.2022.0126;
https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc;
CDC Health Alert Network (2021) "Increases in Availability of Cannabis Products Containing Delta-8 THC and Reported Cases of Adverse Events" Available at: https://emergency.cdc.gov/han/2021/han00451.asp.

b. How have FDA and state regulators enforced against products containing these compounds? They have not paid sufficient attention to these alternative compounds in products outside of providing consumers with alerts on their webpage. FDA could require that all stores post risks when such risks are identified to make consumers aware more quickly.

c. How should Congress consider the inclusion of these products in a regulatory framework for cannabinoid hemp products, if at all? As already recommended above, Congress should indeed consider the inclusion of all compounds of the plant (cannabinoids, terpenes, flavonoids, etc) and require the compounds in any products based from hemp remain at the same levels as naturally occurring in the plant in any dose or full product. This would preclude the derivation of products with unnatural levels of compounds that impose health events.

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.).

   a. For which non-ingestible routes of administration are consumers interested in consuming CBD products? Novel routes of administration need some limitations and/or restrictions until adequate safety data is made available on the impacts of these novel routes of administration. Devices for combusting and /or vaping cannabis should be regulated under the medical device or tobacco regulation authority if they are not explicitly included under the new regulatory mechanism.

   b. How should a regulatory framework for cannabinoid products account for non-ingestible routes of administration?
   See responses to Q8a.

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. US states have largely focused on regulating access to CBD as a medication, although since the Farm Bill, some states have gone further. New York, for example, prohibits CBD injectables, inhalers, cigarettes, cigars, pre-rolls, CBD forms for the purpose of smoking, any form packaged or combined with other items designed for smoking (rolling papers, pipes).[18] New York also has packaging and labeling requirements including warnings that the product has not been evaluated by the FDA, that it may contain THC and cause a user to fail a drug test, that pregnant or nursing women should consult a healthcare provider before use, that it should be kept out of reach of children, and that if the product is intended for inhalation, smoking or vaping is hazardous to health among other requirements.[19]

   a. 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? New York standards are referenced above in Q11. Additional information on standards are likely to be available through CANNRA. It is unclear the extent to which any of these can

[18] https://cannabis.ny.gov/system/files/documents/2023/05/nys-cannabinoid-hemp-permitted-and-prohibited-product-forms-guidance.pdf.

[19] https://cannabis.ny.gov/system/files/documents/2021/11/cannabinoid_hemp_product_packaging_and_labeling_checklist_112321.pdf

be "effective at protecting consumer safety", as no careful evaluation has been done to date. However, many are modelled after successful and effective standards used in tobacco and pharmaceutical drugs.

b. Which such standards, if any, should Congress look to as models? It is our opinion that Congress should consider standards developed by Canada as a potential model for two reasons: (1) given the Canadian government has a federal cannabis regulatory system as well, it has considered issues related to the plant more broadly, not just a single compound of the plant, and (2) a stated objective of legalization of cannabis was to improve product safety and health, not just the elimination of the illicit market. As such these regulations and standards are more keenly tied to public health concerns, not just the elimination of social injustices and the illicit market.

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?

State and Federal regulators need to communicate and work together to develop a functional regulatory framework that protects vulnerable populations. The Federal government should set the minimum standards necessary to accomplish the goal of public health and public safety, and states should be allowed to adopt more stringent policies that they deem necessary in light of their own population risk factors.

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.

There is a growing body of information about the safety and risk-benefit profile of CBD and other Hemp derived cannabinoids, much of which comes from studies presented to the US and other national regulators of pharmaceuticals as Epidiolex went through its regulatory process before being approved in each region. Additional information in the scientific literature includes:


- Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 2011 Sep 1;6(4):237-49. doi: 10.2174/157488611798280924. PMID: 22129319.
- Chesney E, Oliver D, Green A, Sovi S, Wilson J, Englund A, Freeman TP, McGuire P. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacology. 2020 Oct;45(11):1799-1806. doi: 10.1038/s41386-020-0667-2. Epub 2020 Apr 8. PMID: 32268347; PMCID: PMC7608221.
- Dos Santos RG, Guimarães FS, Crippa JAS, Hallak JEC, Rossi GN, Rocha JM, Zuardi AW. Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials. Expert Opin Drug Metab Toxicol. 2020 Jun;16(6):517-526. doi: 10.1080/17425255.2020.1754793. Epub 2020 Apr 27. PMID: 32271618.
- Graham M, Martin JH, Lucas CJ, Murnion B, Schneider J. Cannabidiol drug interaction considerations for prescribers and pharmacists. Expert Rev Clin Pharmacol. 2022 Dec;15(12):1383-1397. doi: 10.1080/17512433.2022.2142114. Epub 2022 Nov 9. PMID: 36317739.

- Huestis MA, Solimini R, Pichini S, Pacifici R, Carlier J, Busardò FP. Cannabidiol Adverse Effects and Toxicity. Curr Neuropharmacol. 2019;17(10):974-989. doi: 10.2174/1570159X17666190603171901. PMID: 31161980; PMCID: PMC7052834.
- Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res. 2017 Jun 1;2(1):139-154. doi: 10.1089/can.2016.0034. PMID: 28861514; PMCID: PMC5569602.
- Larsen C, Shahinas J. Dosage, Efficacy and Safety of Cannabidiol Administration in Adults: A Systematic Review of Human Trials. J Clin Med Res. 2020 Mar;12(3):129-141. doi: 10.14740/jocmr4090. Epub 2020 Mar 2. PMID: 32231748; PMCID: PMC7092763.
- Pauli CS, Conroy M, Vanden Heuvel BD, Park SH. Cannabidiol Drugs Clinical Trial Outcomes and Adverse Effects. Front Pharmacol. 2020 Feb 25;11:63. doi: 10.3389/fphar.2020.00063. PMID: 32161538; PMCID: PMC7053164.
- U.S. Food & Drug Administration. What You Should Know About Using Cannabis, Including CBD, When Pregnant or Breastfeeding. Available from: https://www.fda.gov/consumers/consumer-updates/what-you-should-know-about-using-cannabis-including-cbd-when-pregnant-or-breastfeeding


However, the evidence remains insufficient for regulators outside of the U.S. to conclude that new CBD products are safe, which is why the European Food Safety Authority (EFSA) decided to delay approving new products until sufficient data could be obtained to determine CBD's effects on multiple body systems, including the liver, GI tract, endocrine system, nervous system, and psychological well-being is insufficient.[20] In particular, EFSA clearly noted concern related to the evidence of adverse effects in animal studies of the effects of CBD on the reproductive system.

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

Permit and fund research on products available on the market today, not just those based on the cannabis plant that is grown for scientific research by NIDA-sponsored vendors. Encourage, facilitate and fund international collaboration on human studies in jurisdictions with different standards.

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

Consumer safety can be better protected if products are limited in terms of forms and formulations, so that the independent scientific community has more time to evaluate the potentially positive and negative impacts of the products on the market. If medical necessity demands availability of higher concentrations of a particular cannabinoid than available in the legal CBD market, then those opportunities should be provided through an Investigative New Drug authority – not through availability in the market place.

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

See Q11 above and evidence raised by FDA in its review of the request to regulate CBD as food (https://www.fda.gov/news-events/press-announcements/fda-

[20] https://www.efsa.europa.eu/en/news/cannabidiol-novel-food-evaluations-hold-pending-new-data

concludes-existing-regulatory-frameworks-foods-and-supplements-are-not-appropriate-cannabidiol). It is imperative when considering concerns raised by risks associated with CBD products that additional evidence is considered, such as: (a) the presence of other ingredients in the product that may cause unexpected interactions with CBD for some individuals, (b) the exposure (dose, mode of administration, and pharmacokinetics) of the product being used, by whom, and under what circumstances, and (c) that the product was being consumed in combination with another product (e.g. alcohol, tobacco) that may have caused an additional risk above and beyond that of the CBD product itself. All of these factors have to be considered when evaluating both therapeutic benefits and harms.

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?

    The FDA should not consider these two as the same, as there is a lack of bioequivalence data, different routes of administration, and one is a purified product versus products with additional compounds. Use of preclinical rodent data as evidence of safety and/or introduction into the market prior to human safety assessment creates a precedent for other drugs.

16. Should there be limits on the amount of CBD in foods, dietary supplements, tobacco, or cosmetics? If so:
    a. Should Congress or FDA set such limits, recognizing the time it can take to complete the legislative process and the regulatory process at FDA? Yes, there should be limits until science has indicated the amount of CBD that can be consumed without any harm in the general population. As that science is evolving, Congress could set preliminary limits that are statutorily required to be reconsidered and modified every 3-5 years based on scientific evidence and the regulatory process at the FDA. Those limits could be based on amounts known to exist in nature, without extraction and synthesis into concentrated product.

    b. How should that amount be determined? What should the amount be?

       An expert scientific review panel consensus decision may be able to identify dosing that is known to be safe for CBD alone based on existing evidence. Given that the plant naturally contains additional compounds that may also interact with how natural CBD operates in the body, we think that limits on CBD should not be thought of in terms of only CBD, but also in terms of the other compounds with which it is delivered or consumed. As mentioned above, one way to do that is to set limits on all the known compounds and not allow the creation of any product that when delivered through a specific formulation or mode of administration would deliver more than what we know naturally occurs in the plant and take into account how the mode of administration may influence compounds (e.g. smoked products) and their bioavailability. Any limits beyond those known by science should be tied to what occurs in nature until the scientific evidence supports a change in those limits based on both short and long term impacts of consumption.

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

Both. It is way too easy to get around serving limits if packages are not also limited.

d. 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? No, for the reasons specified by the FDA, it cannot set such limits under its current statutory regulatory authorities. See: https://www.fda.gov/news-events/press-announcements/fda-concludes-existing-regulatory-frameworks-foods-and-supplements-are-not-appropriate-cannabidiol

e. How should the experience of states inform the setting of limits on amounts of CBD in products? Experience of states in terms of limits effective for safe consumption is limited because observational data is inadequate to identify actual harms or benefits from those using due to all sorts of confounding. That said, information from the states in terms of difficulty regulating these products and industry's innovation can and should be considered, as represented by CANNRA.

17. 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.)?

We would recommend that the regulatory framework be restrictive and not allow any combination products until we have better data and science on CBD itself as it naturally occurs with other cannabinoids. Once we have a better understanding of this, then we can make informed decisions about CBD in combination with other products. Regulating interactive effects will be minimal if the amounts of CBD in a product are capped at very low levels commonly observed in the natural plant. The problem is that extracts and concentrates contain significantly higher amounts and it is the exposure to these concentrated products that raise serious concern.[21]

18. 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?

No response given.

19. What functional ingredients combined with cannabinoids raise safety concerns?

Any compound that increases bioavailability or confers a drug interaction that increases plasma concentrations or causes potential toxicity should be carefully evaluated in terms of safety concerns.

Quality

20 How should Congress create an FDA-implemented framework to ensure that manufacturers provide appropriate consumer protections and quality controls?

Congress should consider best practices used by U.S. states, Canada, Australia,

[21] https://pubmed.ncbi.nlm.nih.gov/33951339/ ; https://jamanetwork.com/journals/jama/fullarticle/2804077

and Israel in the monitoring of both adult-use cannabis as well as plant-based medical cannabis. Testing and GMP must be part of the regulatory process, but rigorous standards for product content, design and marketing or equally or more important. Furthermore, funding a systematic approach of auditing (compliance checks) with firm implications for non-compliance e.g. fines, companies required to remove products from markets, loss of license is necessary to ensure compliance with any framework developed.

a. How should such a framework compare to the current Good Manufacturing Practice (GMP) requirements that apply to food, dietary supplements, and cosmetics?

The U.S. FDA would be best placed to address this question.

b. Are those food, dietary supplement, and cosmetics GMP frameworks adequate for regulating quality in CBD? Why or why not?

We concur with the assessment of the FDA that the current frameworks are inadequate for the reasons they specify.

21 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?

Left blank intentionally.

Form, Packaging, Accessibility, and Labeling

22. 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.

Only claims that can be substantiated with independent and robust scientific evidence should be permitted. Any claim of wellness and/or low risk based on being a "natural product" should be prohibited unless explicitly referencing a risk for which there is sufficient scientific evidence to warrant such claim.

23. 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?

Research from Canada and the US shows that plain packaging and warning labels on cannabis products make products less appealing for consumers, particularly youth.[22] Additionally, this research in Canada shows that awareness of specific

[22] Samantha Goodman, Cesar Leos-Toro & David Hammond (2022) Do Mandatory Health Warning Labels on Consumer Products Increase Recall of the Health Risks of Cannabis?, *Substance Use & Misuse*, 57:4, 569-580, DOI: 10.1080/10826084.2021.2023186; Goodman, S., Leos-Toro, C., & Hammond, D. (2019). The impact of plain packaging and health warnings on consumer appeal of cannabis products. *Drug and Alcohol Dependence*, 205, 107633; Leos-Toro, C., Fong, G. T., & Hammond, D. (2021). The efficacy

potential health harms was greater in jurisdictions with mandated warning labels. These findings are not surprising in light of similar evidence from tobacco products, including the effectiveness of conveying risk with symbols and markings.[23]

In coordination with states, we recommend a single, unified symbol to represent both cannabis and hemp products so that these products are recognizable to consumers.

24. 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?

All edible CBD products or those containing other cannabinoids should have a Nutrition Facts Label and Supplements Label. These products should also comply with allergen labeling requirements for foods. Additionally, a standardized label panel should be created to inform consumers about the content of all potentially intoxicating cannabinoids (e.g. mg CBD, mg THC, mg THCA) contained in the product. All liquids should be labeled with %THC (similar to % alcohol for beverages). FDA approved inserts should be included in packages to explain potential adverse health effects and interactions with medications.

25. 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?

We recommend graphic warning labels for all intoxicating hemp products based on precedent set for other public health goods, including:

- Tobacco use: https://www.fda.gov/tobacco-products/labeling-and-warning-statements-tobacco-products/cigarette-labeling-and-health-warning-requirements
- Children's toys (due to potential choking hazards, for children under 3): https://www.stanfordchildrens.org/en/topic/default?id=toy-safetyprevention-90-P02999
- Alcohol use (among pregnant women): https://www.ttb.gov/labeling-wine/wine-labeling-health-warning-statement

Moreover, we recommend that Congress and the FDA acknowledge that industry has interfered with the implementation of such requirements, including requirements for tobacco warning labels despite well-established scientific evidence of health harms, and that it take action to prevent such interference.

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of health warnings and package branding on perceptions of cannabis products among youth and young adults. *Drug and alcohol review*, 40(4), 637-646; Mutti-Packer, S., Collyer, B., & Hodgins, D. C. (2018). Perceptions of plain packaging and health warning labels for cannabis among young adults: findings from an experimental study. *BMC public health*, 18, 1-10.

[23] Hiilamo, H., Crosbie, E., & Glantz, S. A. (2014). The evolution of health warning labels on cigarette packs: the role of precedents, and tobacco industry strategies to block diffusion. *Tobacco Control*, 23(1), e2-e2; Cunningham, R. (2022). Tobacco package health warnings: a global success story. *Tobacco Control*, 31(2), 272-283.

The FDA should assess warning statements and labeling appropriate and effective for CBD only products as well.

26. 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?

Yes, it is possible that total THC content could be unknown in a particular consumable product for the reasons described above in responses to Q2 and Q4. Our colleagues at the Public Health Institute have shared with us that many states are now using specific formulas to calculate "Total THC" or total potential delta-9 THC that might exist in a consumable product. For example, the California Department of Cannabis Control currently uses the following formula: Total THC (mg/g) = [(delta 8-THCA concentration (mg/g) + delta 9-THCA concentration (mg/g)) x 0.877] + [delta 8-THC concentration (mg/g) + delta 9-THC concentration (mg/g)]. The validity of such a formulation depends on the process in creating the product and/or mode of administration (will it be heated or not).

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27. 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?

Such access should be made as is deemed appropriate from scientific investigation of therapeutic CBD and adverse events for children. Until scientific evidence is available, children under 21 should only be able to access CBD products by prescription. To enforce this, adults should only be able to access CBD products in age-gated retailers similar to how states allow cannabis.

28. 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.

None of these products, until demonstrated safe for children, should be allowed to be marketed, packaged or labeled in a manner that makes them enticing for kids. There is lots of precedence for such restrictions, including from tobacco and e-cigarettes. Specific additional restrictions pertain to marketing. It should also be restricted, as has been done historically for alcohol and tobacco.

29. 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?

We do this with candy bars, cookies sold in packages, and all sorts of children snacks, as well as beer (6-packs) and cigarettes. Edible products should be required to be physically separate into individual doses with dose size clearly labeled.