June 10, 2022

Dr. Robert M. Califf
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Califf:

On March 15, 2022, the President signed into law an amendment to the Federal Food, Drug, and Cosmetic Act (FDCA) that extends the jurisdiction of the Food and Drug Administration (FDA) to tobacco products that contain nicotine not derived from tobacco (non-tobacco nicotine, or NTN). Under the new legislation, manufacturers of products containing NTN that wish to market their products must submit a premarket application (PMTA) by May 14, 2022, and obtain FDA's authorization by July 13; otherwise, the products are subject to FDA enforcement action.

The undersigned state attorneys general write to urge the FDA not to authorize the marketing of any NTN product because, based on information currently available, such products cannot satisfy the "public health" standard of Section 910 of the FDCA. Moreover, in the event FDA does not deny marketing authorization to all NTN products, we urge it to at least deny authorization to all NTN products other than those with tobacco flavor and to impose stringent regulatory requirements on those products that do receive authorization, including strict marketing limitations, strong surveillance and reporting requirements, and restrictions on claims that refer to the absence of tobacco, like "tobacco-free," absent FDA authorization to make such claims under the FDCA's modified risk tobacco product provisions. The FDA has the power to regulate these harmful products, and it should take swift, effective measures to protect the public, especially its youth.

Background

NTN products, particularly electronic nicotine delivery systems (ENDS), have grown in popularity in recent years.[1] These NTN products are little understood, have faced little-to-no regulatory scrutiny, and they present multiple public health concerns. First, these products are frequently sold in youth-friendly flavors and are growing in popularity with that age group. Second, the unexplored chemical characteristics of NTN make it potentially dangerous to its users beyond the normal negative effects of nicotine consumption. Third, using their claims of being "tobacco-free," the manufacturers of these products argue they are not subject to regulatory authority, tobacco taxation, or the tobacco product bans of major online retailers. Lack of effective national regulation of such products would all but guarantee that a new generation of young people will needlessly become addicted to nicotine and subject the public to potential harm from a product whose effect on the human body is not well understood.

[1] Nicotine produced using chemicals derived from non-tobacco sources, or a highly purified form of nicotine derived from tobacco.

Prior to the March 15, 2022 amendment to the FDCA, some manufacturers of NTN products claimed that these products were not subject to FDA regulation because they do not contain nicotine, or any other substance, that was made or derived from tobacco, citing the then-current definition of "tobacco product" in the FDCA. These manufacturers have marketed their products without complying with requirements applicable to other ENDS products, including the need to submit PMTAs, the need to obtain FDA authorization to claim that their products present a lower risk of disease or contain a reduced level of harmful substances (modified risk claims), or the need to display statements warning that nicotine is addictive. To date, FDA has not taken enforcement action directed at any of these products. However, on April 13, 2022, the FDA issued a press release regarding its new authority over products containing nicotine from any source and stating that NTN products would be subject to the FDCA and that PMTAs for those products would be due by May 14, 2022.[2]

Do Not Authorize The Marketing Of NTN Products

Section 910 of the FDCA states that a tobacco product's PMTA will be denied if the FDA finds that the application failed to show that "permitting such tobacco product to be marketed would be appropriate for the protection of the public health." Although the use of NTN products has increased sharply as the FDA has cracked down on tobacco-derived nicotine ENDS products, there has been little in the way of scrutiny directed toward NTN products. These so-called "tobacco-free" NTN products are being marketed without any regulatory constraints on what the products may contain, how they are manufactured, what effects they may have on their users, and what health claims may be made for them, all to the detriment of the public health. As the FDA evaluates the PMTAs for these products, it should find that they cannot satisfy the "public health" standard of Section 910 of the FDCA and should therefore prohibit their marketing.

This situation is of great concern because NTN ENDS products are being used in large quantities by youth, and thus threaten to help addict another generation to nicotine to the detriment of public health. The 2021 National Youth Tobacco Survey (NYTS), conducted by the Centers for Disease Control and FDA, found that 11.3 percent of high school students reported current ENDS use. Of those students who were currently using ENDS, over 85 percent reported using flavored ENDS products and 26.1 percent reported that their usual brand was the NTN product Puff Bar.[3] Accordingly, Puff Bar, which is sold in a variety of flavors such as Watermelon, Blue Razz, Banana Ice, Strawberry, Grape, and Mango, was by far the most popular brand among high school students surveyed. The FDA, in reviewing PMTAs, has to date denied every application for flavored ENDS products on which it has made a determination, in large part because of "the known and substantial risk to youth posed by flavored ENDS." (FDA Review of PMTA for Bidi Vapor, LLC, at OA13.)

While it is bad enough that flavors entice youth to use ENDS and potentially become addicted to nicotine, the additives that create those flavors can pose their own severe health risks to users. Common

[2] FDA.gov. *Requirements for products made with Non-Tobacco Nicotine*. U.S. Food and Drug Administration. (2022, April 13). Retrieved May 2, 2022, from https://www.fda.gov/tobacco-products/ctp-newsroom/requirements-products-made-non-tobacco-nicotine-take-effect-april-14.

[3] An analysis of the popularity of JUUL and Puff Bar based on the volume of google searches for either product concluded that, "The popularity of Puff Bar on Google Search suggests that users may replace cartridge-based vaping products [i.e. JUUL] with disposable e-cigarettes [i.e. Puff Bar] in the circumvention of the partial flavour ban." Dai H., *et al.*, (2022). Online popularity of JUUL and Puff Bars in the USA: 2019–2020. Tobacco Control, 31 (7-10). doi:10.1136/tobaccocontrol-2020-055727. Although this was prior to Puff Bar transitioning to NTN, it still continues to be available in a wide variety of youth friendly flavors and the NYTS found that it is the most popular ENDS product among high school students.

ENDS flavoring additive Diacetyl, for instance, causes bronchiolitis obliterans ("popcorn lung"),[4] loss of epithelial resistance, flattening of the airway epithelium, loss of lung cilia, and increased susceptibility to SARS-CoV-2 (COVID-19).[5] Another ENDS flavoring additive, vanillin, was shown to create birth defects in animal studies.[6] One study of flavored ENDS products found that the flavoring additives therein are potentially responsible for inflammatory responses and DNA damage in lung cells.[7]

Beyond the known risks associated with flavoring additives in ENDS products there are the unknown risks of the NTN itself. There are multiple processes that can be used to create NTN[8] and they each involve a variety of chemicals such as ethyl nicotinate, niacin, ethanol, or sulfuric acid.[9] Most of these processes produce a nicotine mixture that is equal parts S-nicotine, which makes up >99 percent of the nicotine in tobacco, and R-nicotine, a less understood stereoisomer of S-nicotine.[10] While the public is most acquainted with S-nicotine and its effects, "[l]ittle is known about the pharmacological and metabolic effects of R-nicotine in humans."[11] The limited studies conducted to date have found potential differences between these two stereoisomers, but there is a lack of research in this area.

A further problem of the unregulated nature of NTN products is that the amount of S-nicotine and R-nicotine in any given NTN product is unknown. One study tested four different e-liquids[12] for their total nicotine content as well as the amounts of each stereoisomer. It found that three of these NTN products were labeled as containing 6 mg/ml of nicotine, but half of that was R-nicotine meaning they were much less potent and may encourage consumers to purchase higher nicotine content products.[13] The fourth product was also labeled as containing 6 mg/ml of nicotine, however it contained approximately twice that amount with the remaining 6 mg/ml being R-nicotine.[14] Given the relative lack of understanding of the effects of R-nicotine on the human body, exposing unwitting consumers to large amounts could result in negative health consequences.

The FDA should not authorize the marketing of any NTN product unless and until, such products satisfy the "public health" standard of Section 910 of the FDCA.

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[4] White, A. V., *et al.*, (2021). Risk assessment of inhaled diacetyl from electronic cigarette use among teens and adults. Science of The Total Environment, 772, 145486. https://doi.org/10.1016/j.scitotenv.2021.145486

[5] Langel, S. N., *et al.*, (2022). E-cigarette and food flavoring diacetyl alters airway cell morphology, inflammatory and antiviral response, and susceptibility to SARS-COV-2. Cell Death Discovery, 8(1). https://doi.org/10.1038/s41420-022-00855-3

[6] Dickinson, A. J. G., *et al.*, (2022). E-liquids and vanillin flavoring disrupts retinoic acid signaling and causes craniofacial defects in xenopus embryos. Developmental Biology, 481, 14–29. https://doi.org/10.1016/j.ydbio.2021.09.004

[7] Muthumalage, T., *et al.*, (2019). E-cigarette flavored pods induce inflammation, epithelial barrier dysfunction, and DNA damage in lung epithelial cells and monocytes. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-019-51643-6

[8] Although Puff Bar claims its NTN products are created using a "patented manufacturing process," the company does not disclose the source of its NTN or the process by which it is manufactured. Additionally, a Google Patent search for "NTN" and "'Puff Bar'" did not return any patents held by the Puff Bar company.

[9] Johnson, L., Ashtray Blog. *NTN: Could it save vaping?* Retrieved April 25, 2022, from https://www.ecigarettedirect.co.uk/ashtray-blog/2016/12/synthetic-nicotine-vaping.html#:~:text=Synthetic%20nicotine%20is%20the%20term,nicotine%20after%20several%20intermediate%20steps.

[10] Jordt, S.-E. (2021). NTN has arrived. *Tobacco Control*. https://doi.org/10.1136/tobaccocontrol-2021-056626.

[11] Jordt, S.-E. *at* 3.

[12] Liquid used in ENDS which can contain nicotine, THC, flavor additives, etc..

[13] Hellinghausen, G., Lee, *et al.*, (2017). Evaluation of nicotine in tobacco-free-nicotine commercial products. *Drug Testing and Analysis*, *9*(6), 944–48. https://doi.org/10.1002/dta.2145.

[14] *Id.*

Impose Stringent Regulatory Requirements On NTN Products

Should the FDA not deny marketing authorization to all NTN products, it must at least deny authorization to all NTN products other than those with tobacco flavor and to impose stringent regulatory requirements on those products that do receive authorization. There is no justification for regulating NTN any differently than tobacco-derived nicotine and the recent amendment to the FDCA makes that clear. If anything, NTN's obscure origins, unexplored chemical characteristics, and use in flavored products that appeal to youth call for heightened vigilance.

As noted above, NTN products are currently being sold without any regulatory constraints on their contents, their manufacturing, their effect on users' health, and what health claims may be made for them. They are also more widely available than tobacco-derived nicotine products as they can sidestep some retailers' ban on selling tobacco products. A recent Stanford study analyzed the sale and marketing of NTN products and found that Google shopping, Target, Kmart, eBay, and Amazon all sold multiple NTN products and Walmart sold one.[15] None of these retailers sell established tobacco products online.[16] This increases youth access to NTN products, which are available in a wide range of flavors that appeal to youth. For instance, an individual could purchase "20ne" brand NTN pouches on Amazon.com in flavors such as Very Berry, Gin and Tonic, and Glacier Mint and with a variety of nicotine strengths.[17]

The companies marketing and selling these NTN products are also making the type of health claims the FDA rigorously monitors on established tobacco products. The CEO of one NTN company said its product, "is cleaner than naturally derived nicotine because it has no [tobacco specific nitrosamines]. These nitrosamines have the potential to turn into carcinogens. [Our NTN] will not have any nitrosamines and is 100 percent carcinogenic-free by design."[18] The ENDS product retailing site VaporDNA.com has a guide on "tobacco free nicotine" that claims it is a "safe alternative to use in the replacement of naturally harvested [n]icotine," that it is "healthier for you than traditional tobacco products are," and that it can help you quit smoking.[19] These are claims that the FDA requires tobacco product manufacturers to submit evidence for.

In addition to the risk of youth initiation, the regulatory gap these products create also has harmful impacts. A lack of enforcement has created an unlevel competitive playing field, as this one category of ENDS products has, so far, evaded regulatory burdens and restrictions, while its competitors undertake the expense and effort required to conform to FDA requirements. This regulatory disparity creates incentives for more ENDS manufacturers to claim they use or have switched to NTN, expanding the problem.

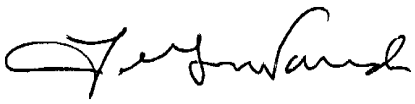
* * *

The FDA has now been granted the authority to regulate NTN products in the same manner as established tobacco products. We therefore urge the FDA to protect consumers, and particularly our

[15] Ramamurthi, D., *et al*., (March 8, 2022). Marketing of "Tobacco-Free" and "NTN" Products. *Stanford Research into the Impact of Tobacco Advertising: White Paper* (22) from, https://tobacco.stanford.edu/wp-content/uploads/2022/03/Synthetic-Nicotine-White-Paper-3-8-2022F.pdf.
[16] *Id*.
[17] Amazon.com, *Amazon 2One Store*, Retrieved April 11, 2022, from https://www.amazon.com/stores/page/7A2EAD9D-820C-4698-BC8C-78486B33AD67?ingress=2&visitId=c8e91c06-496b-4807-980d-29cead7d8e9e&ref_=ast_bln.
[18] Donahue, T. S. (2020, October 12). Vapor Voice. *Disruptive science*. Retrieved April 27, 2022, from https://vaporvoice.net/2020/10/12/disruptive-science/.
[19] VaporDNA.com. *Tobacco free nicotine (tfn)*. Retrieved April 27, 2022, from https://vapordna.com/collections/tobacco-free-nicotinetfn.

youth, from the threat of harm from an unregulated class of tobacco products and use the authority granted to it by Congress to deny marketing authorization for any NTN product because such products cannot satisfy the "public health" standard of Section 910 of the FDCA, or, if the FDA does approve marketing authorization for some NTN products, it should at least deny authorization to all NTN products other than those with tobacco flavor and to impose stringent regulatory requirements on those products that do receive authorization.

Respectfully,



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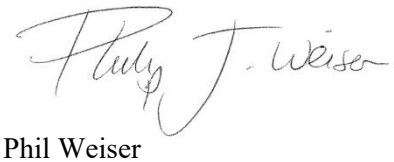

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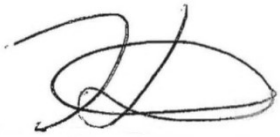

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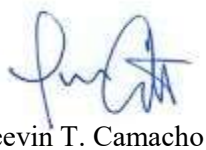

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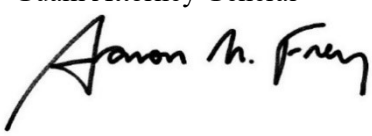

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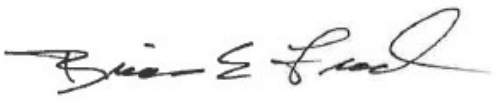

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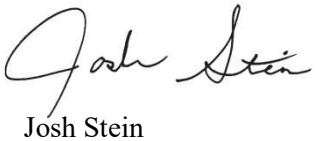

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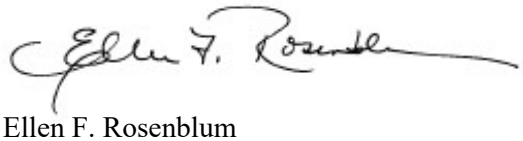

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