



May 29, 2024

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

RE: Urgent public health imperative to regulate nicotine analog products

Dear Dr. Califf:

The undersigned organizations write today about a matter of great urgency. In a clear effort to circumvent any regulation by the Food and Drug Administration (FDA), companies are introducing new products that use nicotine analogs instead of nicotine from tobacco or synthetic nicotine. FDA must act to regulate these products and remove them from the market immediately.

Nicotine analogs are compounds that are structurally similar to nicotine, and include nicotine derivatives and metabolites.¹ Internal industry documents reveal that tobacco manufacturers previously studied the potential for analogs to “replace nicotine in order to create more ‘desirable’ products and to circumvent anticipated nicotine regulation.”²

We are aware that there are at least three companies marketing products made with nicotine analogs: Charlie’s Holdings, Inc.’s new e-cigarette brand, SPREE BAR;³ Outlaw Dip Company, Inc.’s tobacco-free oral snuff;⁴ and ECBlend, LLC’s e-liquids.⁵

SPREE BAR uses what the company calls Metatine, “a patented non-nicotine compound that provides adult users with a strong sense of satisfaction that is largely indistinguishable from traditional vape products.”⁶ The company further claims that Metatine is a “synthetically derived molecule that is structurally similar to, but chemically different from other vaping alkaloids” and that “Metatine is not made from, and does not contain, nicotine.” SPREE BAR is available in a variety of youth-appealing flavors, including Rainbow Fruit, Blue Razz Ice, Strawberry Apple

¹ Vagg, R., & Chapman, S. (2005). Nicotine analogues: A review of tobacco industry research interests. *Addiction (Abingdon, England)*, 100(5), 701–712. <https://doi.org/10.1111/j.1360-0443.2005.01014.x>

² *Ibid.*

³ SPREE BAR Products. <https://spreebar.com/products/>

⁴ Outlaw Dip. <https://outlawdip.com/>

⁵ ECBlend. *Shop All Nicotine Flavors*. <https://www.ecblendflavors.com/shop-all-nicotine-flavors/>

⁶ SPREE BAR. *What is Metatine?* <https://spreebar.com/metatine/>

Melon, Blood Orange Peach, Watermelon Grapefruit, Strawberry Mango, Creamy Melon, Sweet Spearmint, and Pineapple Coconut.⁷

Outlaw Dip Company claims some of its products (tobacco-free moist snuff) are made with Nixamide (which they also call Nic-Safe), “a proprietary alternate solution to nicotine.”⁸ The company claims that Nixamide is “structurally different from nicotine – independent of its stereochemistry,” “has been specially formulated to deliver the same satisfaction, pleasure and enjoyment as traditional tobacco products and nicotine vaping for adult consumers using a proprietary blend with the main ingredient being nicotinamide,” and “blends the same way as regular nicotine in manufacturing and has a smooth experience when vaped, or mixed with smokeless alternatives.”⁹ Outlaw Dip Company products marketed with Nixamide (i.e., Nic-safe) are available in a variety of youth-appealing flavors, including Wild Watermelon, Killer Vaniller, Wintergreen, Lucky Lipper, and Ramblin Rootbeer.¹⁰

Similarly, ECBlend sells e-liquids made with Nixotine - flavored Nixodine, “a unique blend of nicotinamide and other carefully selected proprietary ingredients.”¹¹ The company states that “Nixodine is carefully designed to target the same nicotinic acetylcholine receptors that traditional nicotine stimulates” and that “Nixotine provides the same great sense of satisfaction, pleasure, and enjoyment as nicotine.”¹² Nixotine products are available in numerous drink, fruit, soda, sweets and dessert flavors.¹³

FDA action is needed. First, FDA’s Center for Tobacco Products (CTP) should itself determine and not rely on the industry’s assertions whether products made with nicotine analogs qualify as tobacco products under the Tobacco Control Act. If they do contain nicotine, FDA should promptly take action to remove these products from the market. If it determines that a product does not, then for the reasons described below, the products meet the definition of a drug and FDA’s Center for Drug Evaluation and Research (CDER) should take action so these products do not escape regulatory oversight. FDA must not lose sight of the public health consequences of regulatory inaction over these nicotine analog products. These are potentially addictive products designed to avoid FDA oversight which are being marketed in youth-appealing flavors.

The aforementioned manufacturers are attempting to circumvent regulation as a tobacco product and avoiding FDA CTP’s premarket tobacco product application process.

The manufacturer of SPREE BAR believes that its product is not subject to FDA jurisdiction as a tobacco product. Its website states:

“Metatine does not meet the definition of nicotine as stated in the Family Smoking Prevention and Tobacco Control Act, is not a salt or complex of nicotine, and is not itself derived from nicotine or tobacco; accordingly, Metatine is not subject to FDA

⁷ SPREE BAR Products. <https://spreebar.com/products/>

⁸ Outlaw Dip. *Blog. What is Nixamide? A Nicotine Alternative.* <https://outlawdip.com/blogs/blog/what-is-nixamide>

⁹ Outlaw Dip. *Blog. What is Nixamide? A Nicotine Alternative.* <https://outlawdip.com/blogs/blog/what-is-nixamide>

¹⁰ Outlaw Dip. <https://outlawdip.com/>

¹¹ ECBlend. *Nixotine—Flavored Nixodine.* <https://helpdesk.ecblendflavors.com/knowledgebase.php?article=156>

¹² *Ibid.*

¹³ ECBlend. *Shop All Nixotine Flavors.* <https://www.ecblendflavors.com/shop-all-nixotine-flavors/>

tobacco requirements. Metatine products are not required to obtain FDA premarket authorization (often known as a PMTA).¹⁴

SPREE BAR's manufacturer, Charlie's Holding, clearly is attempting to circumvent regulation by the FDA, as it explicitly states in marketing SPREE BAR. The company claims that it is "PMTA exempt",¹⁵ "6,000-puff SPREE BAR flavor pods have a retail price that is LESS THAN HALF the price of leading 5,500-puff disposables,"¹⁶ "Metatine products are exempt from nicotine excise taxes in many states, which can result in massive savings for retailers and consumers,"¹⁷ and "Metatine can be combined with many flavors and is legal to sell in nearly all 50 states."¹⁸

Likewise, in a YouTube video, Outlaw Dip Company's founder states that the company began using a nicotine analog in its products in order to avoid FDA's premarket tobacco product application process.¹⁹

Additionally, Outlaw Dip's website states:

"Made from a proprietary alternative solution to nicotine (patent pending), Nixamide is structurally different from nicotine – independent of its stereochemistry – and not falling under the TCA (Tobacco Control Act)."²⁰

"We at Outlaw Dip have researched and tested Nic-Safe™ (aka Nixamide™) over the last year to "bring back the buzz" safely, legally, and better than ever before."²¹

Nicotine analog products must be regulated as either tobacco products or drugs.

FDA should not allow these companies or any other company to market new potentially addictive products unless the products are reviewed and authorized by CTP or CDER, particularly since little is known about the potential health risks of exposure to nicotine analogs via inhalation and oral absorption. The agency's premarket review process is designed to require companies that market new tobacco products or new drugs to undergo FDA review prior to exposing the public to their products. Whether regulated as drugs or as tobacco products, these products are on the market illegally and must be removed immediately through prompt enforcement action.

If CTP determines that it cannot regulate nicotine analogs as tobacco products, they clearly fit within the definition of a drug and must be regulated as such.

The definition of a drug, 21 U.S.C. § 321(g)(1), includes, "articles (other than food) intended to affect the structure or any function of the body of man or other animals." The "structure-function" portion of the definition covers products such as tranquilizers, birth control pills, and products to stimulate hair growth. It also makes the sale of imitations of stimulants illegal.

¹⁴ SPREE BAR. *What is Metatine?* <https://spreebar.com/metatine/>

¹⁵ SPREE BAR. *Products.* <https://spreebar.com/products/>

¹⁶ SPREE BAR. *What is Metatine?* <https://spreebar.com/metatine/>

¹⁷ *Ibid.*

¹⁸ *Ibid.*

¹⁹ Outlaw. *Setting the Record Straight.* <https://www.youtube.com/watch?v=3A7luDBD400>

²⁰ Outlaw Dip. *Blog. What is Nixamide? A Nicotine Alternative.* <https://outlawdip.com/blogs/blog/what-is-nixamide>

²¹ *Ibid.*

For example, while cocaine is an illegal, controlled substance, imitation cocaine products are not. Nevertheless, an imitation cocaine product is an illegal drug because the seller intends it to have the same stimulant effect as illegal cocaine.²² Had FDA not used its drug authority, imitation cocaine could be freely sold in the United States.

Similarly, FDA used its drug authority to prohibit the sale of *Catha edulis* or “khat,” shrub leaves that act as a stimulant when chewed or used as tea.²³ Other products that FDA has regulated as drugs in the absence of claims include: hormone topical cream;²⁴ fluoride in dentifrice products;²⁵ and thyroid containing food supplements (based on the recognized effect of thyroid).²⁶ Likewise, in its review of over-the-counter vaginal products, FDA recognized that “[i]f an active ingredient is present in a therapeutic concentration, the product is a drug”²⁷

Because nicotine analogs have inherent, known pharmacological effects, which is exactly what manufacturers are promoting and consumers are seeking and thus what manufacturers intend to deliver, FDA has authority to regulate them as a drug. Their own promotional materials demonstrate that these manufacturers are aware of the pharmacological effects of these nicotine analogs:

“Metatine, when delivered via SPREE BAR, provides the same satisfaction, pleasure and enjoyment as traditional tobacco products and nicotine e-cigarettes. Of note, while Metatine is chemically distinct from nicotine, it may still be addictive, may have a toxicity profile similar to nicotine, and should only be used by current adult tobacco users and vapers, and never by minors (persons under the age of 21).”²⁸

“Metatine may be addictive, may be acutely toxic and, like nicotine, should be used with caution.”²⁹

“Nixamide™ is not a nicotine product but the same natural effects as nicotine do apply. Therefore, a safer alternative to nicotine consumption. Nixamide™ effects are as noted but not limited to: lightheadness [*sic*], “nicotine buzz,” elated mood, relaxation, ease of mind, focus, and in some cases spurts of energy.”³⁰

Nicotine analog products could undermine a potential product standard to establish a maximum nicotine level in tobacco products.

²² *United States v. Storage Spaces Designated Nos. 8 and 49*, 777 F.2d 1363, 1366–67 (9th Cir. 1985); see also 60 Fed. Reg. 41453, 41527–28 (Aug. 11, 1995) (describing other instances when FDA took action against similar products).

²³ 60 Fed. Reg. at 41,527.

²⁴ 58 Fed. Reg. 47,611–12 (Sept. 9, 1993).

²⁵ 59 Fed. Reg. 6084, 6088 (Feb. 9, 1994).

²⁶ 60 Fed. Reg. at 41,529 (citing FDC 64270, Case No. B-C-84-61 (E.D. Ark. 1984)).

²⁷ 48 Fed. Reg. 46,694, 46,701 (Oct. 13, 1983); see also 59 Fed. Reg. 5226, 5226 (Feb. 3, 1994).

²⁸ SPREE BAR. *What is Metatine?* <https://spreebar.com/metatine/>

²⁹ SPREE BAR. *Additional Warnings.* <https://spreebar.com/additional-warnings/>

³⁰ Outlaw Dip. *Blog. What is Nixamide? A Nicotine Alternative.* <https://outlawdip.com/blogs/blog/what-is-nixamide>

The tobacco industry has researched and investigated nicotine analogs as far back as the 1970s in order to circumvent potential regulation from the federal government.³¹ FDA should be concerned, especially as it plans to develop a proposed product standard that would establish a maximum nicotine level to reduce the addictiveness of cigarettes and certain other combusted tobacco products with the goal of the potential rule being to reduce youth use, addiction, and death.³² The introduction of unregulated nicotine analog products on the market could seriously undermine such a product standard. While we are aware of just these three manufacturers using nicotine analogs in their products, we are deeply concerned that other companies could follow suit. Nicotine analogs are now available for purchase wholesale by the gallon online, and theoretically any manufacturer can now add these chemicals to consumer products.³³

Conclusion

If FDA has authority to regulate nicotine analogs as tobacco products, it should immediately remove these products from the market. For any nicotine analog products where the Agency determines that it does not have this authority, it must make clear that nicotine analog products are drugs under the Federal Food, Drug, and Cosmetic Act and it must vigorously enforce the law against any such product and remove them from the market immediately. Agency inaction will jeopardize the public health and will undermine the regulatory system established by Congress, both for tobacco products and for drugs. And it will allow the manufacture, sale, and widespread availability of flavored products – exactly the products that caused the youth e-cigarette epidemic and nicotine addiction – to flourish. It will also undermine any progress that a maximum nicotine level product standard would make. We urge your immediate attention to this urgent matter.

Sincerely,

American Cancer Society Cancer Action Network
American Heart Association
American Lung Association
Campaign for Tobacco-Free Kids
Parents Against Vaping e-cigarettes (PAVe)
Truth Initiative

cc: Dr. Patrizia Cavazzoni, Director, Center for Drug Evaluation and Research, Food and Drug Administration
Dr. Brian King, Director, Center for Tobacco Products, Food and Drug Administration

³¹ Vagg, R., & Chapman, S. (2005). Nicotine analogues: A review of tobacco industry research interests. *Addiction (Abingdon, England)*, 100(5), 701–712. <https://doi.org/10.1111/j.1360-0443.2005.01014.x>

³² US Food and Drug Administration. (2022). *FDA Announces Plans for Proposed Rule to Reduce Addictiveness of Cigarettes and Other Combusted Tobacco Products*. <https://www.fda.gov/news-events/press-announcements/fda-announces-plans-proposed-rule-reduce-addictiveness-cigarettes-and-other-combusted-tobacco>

³³ *Ibid.*