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By Electronic Submission
Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2019-D-0297; Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products; Draft Guidance for Industry

To whom it may concern,

JUUL Labs, Inc. (JLI or the Company) is the manufacturer of the JUUL system, a closed-system vapor platform, with the mission of eliminating cigarettes among adult smokers. JLI submits this comment on FDA's draft guidance entitled "Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products" (Draft NRT Guidance).

JLI supports FDA's commitment to shift the trajectory of tobacco-related disease and death by promoting innovative products that help adult smokers stop combustible use and ultimately can reduce nicotine dependence. As the Agency has emphasized, cigarette smoking "remains the leading cause of preventable death in the U.S., responsible for 480,000 premature deaths each year."[1] This is because "cigarettes are incredibly addictive," and "[w]hile nicotine keeps smokers addicted, it's the smoke and the 7,000 chemicals contained in it that causes the disease and death."[2] A key element of FDA's comprehensive approach, therefore, "is recognizing that nicotine, while highly addictive, is delivered through products along a continuum of risk with combustible cigarettes at one end, and nicotine replacement therapy (NRT) products at the other."[3]

While the Draft NRT Guidance includes welcome insights on the clinical development of NRTs generally, the discussion is limited to the study of NRT products comparable to those currently available on the market. There is no discussion in the

[1] FDA, Statement from FDA Commissioner Scott Gottlieb, M.D., on additional steps by the Agency to support the development of safe and effective novel nicotine replacement therapies to help smokers quit cigarettes (Feb. 21, 2019), available at https://bit.ly/2NnobH8.

[2] *Id.*

[3] *Id.*

document on the use of vapor products as NRTs, even though FDA has recognized the potential of these products to be developed and approved as NRTs.[4]

Vapor products present a significant and unprecedented public health opportunity for adult smokers. While containing nicotine, vapor products do not produce the thousands of harmful constituents linked to tobacco-related cancers and cardiovascular and respiratory diseases. Unlike virtually all currently marketed NRTs, vapor products utilize highly engineered delivery systems to provide nicotine to adult smokers. This delivery system has the unique potential to offer adult smokers innovative and personalized tools not only to transition them away from combustible cigarettes in the first instance, but also to address their nicotine dependence over time. The Draft NRT Guidance, however, fails to discuss vapor products or FDA's current thinking on the complex regulatory issues these products may raise as potential medical therapies when intended to be used for the treatment of nicotine addiction, ultimately reducing consumption to zero.

Accordingly, for the reasons elaborated further below, JLI requests that FDA issue a separate guidance document that explains the Agency's current thinking on the development and use of vapor products as NRT products. Consistent with FDA's good guidance practices (21 C.F.R. § 10.115), we urge FDA to provide this separate guidance in draft form to solicit comment from interested stakeholders before issuing a final guidance on the specific subject. In addition, JLI urges FDA to adhere to the Federal Food, Drug, and Cosmetic Act (FDCA) and follow its own interpretation regarding the types of clinical studies and marketing claims that indicate a tobacco-derived product is intended to be used as a tobacco product versus a medical product.

I. FDA SHOULD PROVIDE SPECIFIC GUIDANCE ON THE CLINICAL DEVELOPMENT OF VAPOR PRODUCTS AS NRTS

FDA has devoted considerable energy over the past several years to the concept of continuum of risk for tobacco products, but there has been no clear focus on the continuum of technology available for vapor products, including how these products could be developed into NRTs and the regulatory process for such development.

In today's marketplace, the delivery systems in advanced vapor products are designed to aerosolize e-liquid, regulate the heating temperature, and control the amount of vapor discharged. This technology, as already recognized by FDA, provides "new forms of nicotine delivery that could allow currently addicted adult smokers to get access to nicotine without all the risks associated with lighting tobacco on fire."[5] While transitioning

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[4] *See* FDA, Draft Guidance, Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products (Aug. 2018), available at https://bit.ly/2ADRYsd; FDA, Statement from FDA Commissioner Scott Gottlieb, M.D., *supra* note 1.

[5] *See* FDA, FDA in Brief: FDA advances framework for enabling the study of new tobacco products as part of the Agency's ongoing commitment to improve the efficiency and effectiveness of tobacco product regulation (Feb. 20, 2019), available at http://bit.ly/2DfJg29.

adult smokers from combustible cigarettes to less harmful alternatives, alone, would provide tremendous public health benefit, vapor technology offers even more promise to impact nicotine consumption if the user so chooses. This includes the ability to: (1) enable the user to track nicotine consumption over time; (2) facilitate user control over nicotine consumption; and (3) ultimately provide the user tools to reduce nicotine consumption on a step-wise basis down to zero.

Most existing NRT products were approved over thirty years ago and have seen little innovation since then. Indeed, as FDA notes in the Draft NRT Guidance, NRT products "to date have involved single treatment regimens that begin on the patient's quit day."[6] Currently available NRT products therefore generally employ a one-size-fits-all approach, are not fully compatible with individualized quit plans, and have not incorporated electronic or programmable technologies to facilitate nicotine reduction. As FDA notes in the Draft NRT Guidance, other products and treatment regimens could be developed to help smokers quit, including novel products with different characteristics or routes of nicotine delivery, pretreatment before quit day, quitting by gradual reduction, and using two NRT drug products together.[7] These potential products, as well as treatment regimens, could include vapor products, which have the potential to transition adult smokers down the nicotine spectrum.

Because vapor products deliver nicotine in a manner that is uniquely different from currently available NRTs, a range of unanswered questions may arise relating to their clinical development. Presumably, the electronic delivery system would be regulated as a medical device constituent component, but FDA has not addressed other issues, including:

- What special considerations, if any, apply to the evaluation of a vapor combination product NRT? For instance, what does FDA regard as the primary mode of action for these products, especially those that may rely on technological advancements in the device component to regulate, control, and limit nicotine consumption?

- How will FDA evaluate the software components of the delivery system? What kinds of studies does FDA expect with respect to these software applications? What kinds of human factors studies, if any, does FDA expect?

- What kinds of CMC studies does FDA expect for e-liquids that are contained in vapor products intended to be used as NRTs?

- What special considerations, if any, should apply to nicotine step-down regimens that reduce nicotine consumption but do not eliminate it altogether?

[6] Draft NRT Guidance at 2.

[7] *Id.*

- How must these products be packaged or labeled given vapor products without NRT claims will continue to be sold as tobacco products in the marketplace?

- Can a sponsor rely on parts of its Premarket Tobacco Product Application (PMTA) submission or, if applicable, its Modified Risk Tobacco Product Application (MRTPA) as part of an NRT submission?

These questions, while non-exhaustive, underscore the complexity and tremendous promise of vapor products as NRTs. To help promote innovation in novel NRT products, JLI urges FDA to provide specific guidance for clinical developmental programs to support vapor products as NRTs.

II. FDA SHOULD ADHERE TO ITS OWN STATUTORY INTERPRETATION FOR CLAIMS ABOUT SWITCHING ADULT SMOKERS FROM COMBUSTIBLE USE

In the Draft NRT Guidance, FDA notes that NRT products are approved as drugs "for cessation of *cigarette* smoking," and describes endpoints for smoking cessation trials that evaluate the "proportion of subjects who are abstinent from *cigarette use*" over a certain efficacy ascertainment period.[8] This language, along with its focus on abstinence from cigarette use, contradicts FDA's own interpretation of the dividing line under the FDCA between tobacco products and medical products based upon the product's intended use.

FDA maintains that a clinical study involving a product made or derived from tobacco would be considered a clinical investigation involving a "drug," if the product is being investigated for a purpose that suggests that the product is intended to be used as a "drug."[9] Further, FDA regulations state that a product made or derived from tobacco would be regulated as a medical product (i.e., a drug, device, or combination product) if the product is intended:

> (1) for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease; or
>
> (2) to affect the structure or any function of the body in any way that is different from effects related to nicotine that were commonly and legally claimed in the marketing of cigarettes and smokeless tobacco products prior to March 21, 2000.[10]

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[8] *Id.* at 2, 11 (emphasis added).

[9] *See* 82 Fed. Reg. 2193, 2213 (Jan. 9, 2017). FDA also maintains that to determine if a product made or derived from tobacco is being investigated for a drug/device purpose, "FDA generally would review the protocol for the study, including the proposed methods and measures," which "provide insight into the purposes for which a product is being investigated." *Id.*

[10] 21 C.F.R. § 1100.5; *see also* 82 Fed. Reg. at 2213.

With respect to the first prong (i.e., the "disease prong"), FDA has stated that it considers "claims related to smoking cessation in the context of curing or treating nicotine addiction and its symptoms to bring products within FDA's 'disease prong' jurisdiction."[11]

With respect to the second prong (i.e., the "structure/function prong"), FDA has stated that manufacturers, including vapor manufacturers, can make many types of claims regarding the effects of nicotine that do *not* bring the products within FDA's medical product jurisdiction under the structure/function prong.[12] Critically, FDA has stated that it considers claims "suggesting that a tobacco product provides an alternative way of obtaining the effects of nicotine, or that a tobacco product will provide the same effects as another tobacco product" to be tobacco product claims and *not* medical product claims.[13]

Consequently, the Draft NRT Guidance's discussion on abstinence from cigarettes as a "drug" indication or study endpoint erroneously suggests that the use of a vapor product by adult smokers as a noncombustible alternative that allows them to completely switch from the use of combustible cigarettes — whether evaluated as part of a clinical study or made as part of a marketing claim — indicates that the product is intended to be used as "drug." JLI urges FDA to adhere to its own interpretation that such use of a vapor product, as well as marketing claims and studies concerning such uses, do not subject the product to FDA regulation as a drug (or medical device or combination product).

Clinical studies or claims involving adult smokers completely switching from combustible cigarettes to vapor products (hereinafter, "switch studies" or "switch claims," respectively) do not fall within either prong of the "drug" definition. First, switch claims indicate that a vapor product provides an alternative way of obtaining the effects of nicotine, which FDA has expressly stated is a permissible tobacco product claim.[14] Second, switch claims do not state or suggest that the vapor product will cure or treat nicotine addiction or its symptoms, prevent relapse, or relieve nicotine withdrawal symptoms.[15] In addition, it is worth noting that FDA itself has recognized the potential public health benefits of vapor products, regulated as tobacco products — and not drug products — in "providing adult smokers noncombustible options to allow them to *completely switch from the use of combustible options*," and that some adult smokers are already using vapor

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[11] 82 Fed. Reg. at 2198. *See also id*. at 2205 ("Claims such as ''to reduce withdrawal symptoms,'' ''helps reduce symptoms including things like [list of withdrawal symptoms]'' and ''relieve withdrawal symptoms when you are prohibited from smoking'' would be associated with an intended use for relief of nicotine withdrawal symptoms, and would also fall within the intended uses described in § 1100.5(a)").

[12] *Id.* at 2203.

[13] *Id.* at 2200. In contrast, FDA considers claims such as "sedation," "relieve tension," "stimulation," "restore mental alertness," "weight loss" and "maintain memory" to be medical product claims, absent evidence that these claims are structure/function effects related to nicotine and were commonly and legally claimed in marketing cigarettes or smokeless tobacco products prior to March 21, 2000. *Id*.

[14] *Id.* at 2203.

[15] *See* 21 C.F.R § 1110.5.

products with the "goal of *ceasing combustible tobacco* use to obtain health benefits at the individual level."[16]

Furthermore, claims concerning quitting the use of cigarettes must now be understood in context given the expansion of vapor products in the marketplace. The term "quit" has long been associated with cessation, and thus with NRTs, on the grounds that a smoker who "quit" cigarettes was once thought to be quitting the use of nicotine-based tobacco products altogether. As alternative forms of nicotine consumption from products made or derived from tobacco have evolved, however, the term no long carries the same meaning. Indeed, an adult smoker who transitions from combustible cigarettes to a vapor product may well have "quit" cigarettes, but he or she has not stopped the use of nicotine (nor was the product necessarily intended to do that). The form of consumption has changed, and potentially the commensurate health impacts, but there has been no cessation of nicotine use and thus no cure from nicotine addiction.

This evolution in meaning reinforces the degree to which FDA must carefully consider context when evaluating whether a claim or clinical study renders a vapor product an NRT. Indeed, FDA itself recognized this phenomenon in promulgating its rule on "Clarification of When Products Made or Derived from Tobacco Are Regulated as Drugs, Devices, or Combination Products."[17] There, FDA acknowledged "that public perception can change and evidence may be developed showing that, in some situations, 'smoking cessation' is understood in context as referring to ending the use of traditional cigarettes and switching to a non-combustible product made or derived from tobacco."[18] FDA further stated that it would "closely scrutinize 'smoking cessation' claims to ensure that consumers are not misled about the intended use of a product made or derived from tobacco."[19] JLI believes that now, a full two years since that rule was finalized, public perceptions have evolved further, and a claim that one has "quit" smoking cigarettes does not necessarily mean that one has stopped using nicotine or that the product was intended to address nicotine addiction.

JLI urges FDA to adhere to its previous statements indicating that the use of switch claims in the promotional materials for a vapor product would not subject the product to FDA regulation as a drug (or medical device or combination product), and switch studies likewise would not require INDs. For vapor products that are being developed into NRTs to cure or treat nicotine addiction or its symptoms, JLI strongly agrees that product claims and clinical studies to that effect would fall within FDA's medical product jurisdiction. As

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[16] FDA, Draft Guidance, Modifications to Compliance Policy for Certain Deemed Tobacco Products, 18 (Mar. 2019), available at https://bit.ly/2FaWMpd (emphasis added).

[17] *See* 82 Fed. Reg. 2193 (Jan. 9, 2017).

[18] *Id.* at 2214.

[19] *Id.*

discussed above, the Company asks that FDA provide specific guidance on the clinical development of vapor products for such critical uses.

III. Conclusion

JLI welcomes FDA decision to issue guidance on the important issue of clinical development programs for NRTs, and we appreciate the opportunity to comment. While the Draft NRT Guidance offers helpful insight into FDA's current thinking on NRTs, it fails to address the unique regulatory issues associated with developing vapor products as NRTs. Advancements in technology have the potential to enable vapor products of the future to track and control nicotine consumption with precision, reduce nicotine levels in the same device over time, and give consumers the flexibility to program personalized cessation plans that give them the best chance to address their nicotine dependence if they so choose.

For all the reasons stated above, we urge FDA to issue another guidance, in draft form, that specifically covers NRT vapor products and explains the Agency's current thinking on how clinical programs for such products should be developed. In addition, it is critical that in any final guidance FDA apply its own interpretation of the dividing line under the FDCA with respect to the types of clinical studies and marketing claims for tobacco-derived products that indicate that the product is intended to be used as a tobacco product as opposed to a medical product.

Regards,

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