Parker D. Kasmer
Regulatory Counsel

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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-2018-N-3504; "Tobacco Product Application Review"

To whom it may concern,

JUUL Labs, Inc. (JLI or the Company) is the manufacturer of JUUL products, an electronic nicotine delivery system (ENDS), with the mission of displacing combustible cigarette use among adult smokers. JLI is submitting this comment for the above-referenced docket regarding Tobacco Product Application Reviews.

On October 22–23, 2018, FDA held a two-day public meeting to discuss, among other things, the policies and processes for submitting and reviewing tobacco product marketing applications. In light of that public meeting, the Agency opened this docket to obtain further feedback on the review process for applications.

JLI believes this type of public dialogue is integral to establishing a transparent, predictable, and efficient framework for submitting and reviewing marketing applications, including Premarket Tobacco Product Applications (PMTAs) for ENDS. It is fundamentally important that FDA protect the public health when evaluating new tobacco products, and the Company believes part of this objective includes encouraging innovation in potentially less harmful products to help transition adult smokers down the risk continuum from combustible cigarettes.

The Company understands that FDA is seeking comments on general topics, including achieving greater efficiencies and transparency in the application review process, while continuing to protect the public health. JLI offers its insights below on specific points it believes FDA should consider when finalizing the tobacco product review process. Given JLI's position as an ENDS manufacturer, much of this comment is focused on the PMTA submission and review process for those products.

I. ENDS MANUFACTURERS NEED GREATER CLARITY ON REQUIREMENTS FOR APPLICATION CONTENT AND THE REVIEW PROCESS

Many manufacturers are operating in an area of unknowns for submitting PMTAs for complex alternatives to cigarettes, such as ENDS. In July 2017, the Agency acknowledged, as part of its comprehensive regulatory plan for tobacco and nicotine regulation, the need to establish foundational rules to make the product review process "more efficient, predictable, and transparent" while continuing to protect public health.[1] While the Agency has provided some insight on the PMTA process for ENDS,[2] more defined requirements and guidelines are needed for manufacturers to produce complete, scientifically-supported applications for meaningful review by the Agency.

JLI appreciates that FDA intends to promulgate regulations and issue guidance that will set forth requirements for marketing applications and the review process, akin to existing regulations for premarket applications for other FDA-regulated products. This is a critical starting point to improve clarity around application submission and review. For example, JLI believes formalized requirements on application structure and content will ensure manufacturers submit complete and consistent applications. These formalized requirements, in turn, will facilitate more efficient assessments by FDA and its technical and scientific reviewers.

The Agency also should consider means to incorporate amendments for pending applications and supplements to previously authorized PMTAs. The PMTA process for ENDS will be a rigorous one, for both manufacturers and Agency reviewers, and a structure that creates flexibility for application amendments will make it easier for applicants to ensure FDA has up-to-date product and scientific information during its review. Moreover, a supplement pathway should be established to incorporate lifecycle management principles, after PMTA authorization, similar to what has been adopted in other FDA-regulated industries (e.g., medical devices). The Company offers proposals on PMTA supplements below.

JLI believes final guidance tailored to ENDS products, particularly on the development of preclinical and clinical data, is needed to ensure a thorough understanding of the technical and scientific requirements for PMTAs. With this well-defined framework, manufacturers can develop data-driven applications, enabling FDA to better assess the population-level public health impacts of new tobacco products.

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[1] FDA Press Release, FDA Announces Comprehensive Regulatory Plan to Shift Trajectory of Tobacco-related Disease, Death (July 28, 2017).

[2] *See* FDA Guidance (Draft), Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (2016).

Below are specific topics that should be addressed as FDA develops final guidance to provide clarity for manufacturers and improve the application submission and review process:

Standardization of preclinical requirements: Rigorous preclinical testing of ENDS is critical, but manufacturers currently have little guidance on testing standards and methodologies to support marketing applications. For example, manufacturers generally understand that testing and analysis of harmful and potentially harmful constituents (HPHCs) in tobacco products is essential for both marketing applications and future regulatory compliance requiring HPHC listing.

But additional clarity on other elements of a required toxicological program, such as cytotoxicity, genotoxicity, and other advanced assays, will ensure FDA has the data it needs to review the potential health impact of new tobacco products. Similarly, FDA should consider standardizing aspects of preclinical testing, including the number of samples required for testing, replicates of testing, testing methodologies, and data presentation. The Agency also should clarify requirements around *in vivo* testing during preclinical analysis and when *in vitro* and/or *in silico* testing will be sufficient.

Bridging studies across similar tobacco products: Many ENDS are based on a central product platform that can be used with several other tobacco products, such as e-liquid cartridges. While these individual components may differ slightly — for example, in nicotine content or flavor — they generally are produced under the same manufacturing methods, comprise similar ingredients, and share performance characteristics, including theory of operation. Given these similarities, robust preclinical and clinical testing for each individual component would be unnecessary to demonstrate performance characteristics and health effects need to support a PMTA.

JLI appreciates that FDA should have a comprehensive data set to support its review, but believes bridging studies among similar tobacco product components will establish needed efficiencies. This approach will align with FDA's "least burdensome principle" adopted across other Centers. For example, manufacturers should be able to utilize representative clinical data across similarly-situated products, accounting for any differences in composition through bridging studies or preclinical development. If structured correctly, FDA will have visibility into the potential public-health impact of similar tobacco products and their components, while reducing redundancies in product testing and preclinical and clinical development.

Bundled submissions for multiple tobacco products: JLI anticipates that many ENDS PMTAs will incorporate various tobacco product components that are all used within a product platform. For example, manufacturers may seek authorization for multiple e-liquids that differ only in nicotine weights or multiple devices that differ only in slight technological attributes. These minor differences are likely to have shared regulatory and scientific considerations, and performance characteristics and clinical data likely would not

vary substantially. In such cases, bundling of multiple product components into a single application would be appropriate.

Currently, there is limited structure and precedent for such submissions, and manufacturers would benefit from understanding how such applications should be developed — from preclinical and clinical testing requirements to content and application formatting. Guidance also should incorporate a mechanism to cross-reference data sets and related information within a single PMTA or across multiple PMTAs for similarly-situated products.

Principles to assess nicotine effects among the adult smoker population: Critical to FDA's review and authorization of a PMTA is whether the tobacco product is appropriate for the protection of the public health, incorporating a risk-benefit, net-population assessment.[3] For many ENDS products, this should include an analysis of their respective impact among adult smokers and against combustible cigarette use. The effectiveness of an ENDS product lies in its ability to provide a similar satisfaction or alternative to the adult smoker, namely in nicotine delivery and uptake.

FDA should consider these real-world concepts in its final guidance and provide insight on how ENDS manufacturers can compare nicotine effects among adult smokers, including switching effects and reference timepoints for comparative effectiveness research. For example, as nicotine delivery and absorption rates can be analyzed through various measures, including pharmacokinetic analysis, manufacturers would benefit from a standardized approach for assessing this critical attribute in ENDS. JLI also suggests that FDA consider using combustible cigarettes as the benchmark for any nicotine-effects analysis for the adult smoker.

Environmental Assessments: JLI understands that an Environmental Assessment (EA) will be required for PMTA submissions, to enable FDA to conduct an environmental-impact analysis associated with the use, manufacturing, and disposal of tobacco products. The Company believes additional guidance is needed to identify specific requirements and considerations for ENDS, including their components, to assess their potential environmental impact throughout the life of the product. FDA can utilize EA guidance for other regulated products, including new drug and biologic applications.

Reliance on non-sponsor studies: All PMTAs, and FDA's review thereof, should be data-driven. While many ENDS manufacturers will develop their own preclinical and clinical programs to support PMTA submissions, there is an opportunity to utilize other data not developed by the application sponsor. FDA should outline best practices and specific requirements for incorporating these non-sponsor studies; that way, ENDS manufacturers can present a holistic review of their products and enable FDA to consider the best evidence available to support PMTA authorization.

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[3] *See* Tobacco Control Act, § 910(c)(4).

II. FDA Should Develop a Streamlined Review Process for Minor, Low-Impact Changes to Advanced Tobacco Products

When creating foundational rules and finalizing guidance for PMTAs, the Agency has the opportunity to revisit, and provide further insight on, product changes that can be made without obtaining traditional premarket authorization. JLI acknowledges that there already is a statutory provision limiting certain "modifications" of tobacco products.[4] This restriction largely results from skepticism around historical changes to other tobacco products which made them more appealing to youth or increased the risk of negative health effects (e.g., the addition of filter ventilation in combustible cigarettes).[5] But tobacco products on the market today, which include complex, technologically advanced nicotine delivery systems, are far different from what was on the market in 2009 during enactment of the Tobacco Control Act. As with any complex, highly technical device, minor changes beyond those that impact essential performance characteristics will be necessary to ensure product reliability and safeguard *against* potential adverse health effects.

In light of these considerations, FDA should deploy several regulatory tools to permit minor, low-impact changes to certain tobacco products:

Application of SE Exemption process: JLI believes FDA should explain in writing its current practice for Substantial Equivalence Exemption (SE Ex) Requests. Under current practice, and as articulated during the October Public Meeting, JLI understands that FDA has applied the SE Ex process to any tobacco product that can be sold under the Tobacco Control Act, extending it beyond those products eligible for SE premarket review. The Agency also should provide further detail on the types of minor modifications that are eligible for SE Ex requests, including expectations or requirements for comparative performance testing to demonstrate the minimal impact of the minor modification.

PMTA supplement pathway: FDA should establish a supplement pathway to enable a streamlined review for minor changes to PMTA-authorized products. Product or process-related changes may be needed after PMTA authorization, particularly for complex ENDS, to safeguard product performance over time and account for failure modes that become apparent after design development, verification, and validation. To do this, JLI believes that FDA can adopt concepts similar to supplements for Premarket Approval (PMA) applications for medical devices.[6] For example, the Agency can distinguish product changes that require review before implementation and those that do not — such as changes to improve quality controls or manufacturing processes that would reduce potential adverse health effects associated with the product. Such an approach would encourage product

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[4] *See* Tobacco Control Act, § 910(a).

[5] *See, e.g.*, H.R. REP. NO. 111-58, Pt. I, at 4 (2009) ("The manipulation of nicotine and other chemical levels increases addictiveness and harm. H.R. 1256 grants FDA the authority to require product changes in current and future tobacco products, such as the reduction or elimination of ingredients, additives, and constituents (including smoke constituents).").

[6] *See, e.g.*, 21 C.F.R. § 814.39.

lifecycle management, while also providing transparency to the Agency for more critical changes.[7]

Changes required by tobacco product standards: To the extent FDA promulgates tobacco product standards, through regulation, that would require changes to currently marketed products, FDA should consider how best to ensure efficient and transparent adoption. For example, FDA may consider requiring specifications for ENDS batteries or purity requirements for e-liquid ingredients. Such product standards would necessarily be driven by public-health considerations. To encourage efficient implementation of any such tobacco product standard, FDA could create an abbreviated review mechanism outside of the traditional review and authorization process where manufacturers can provide notice of the change and comparative-testing data limited to that change. Or, for currently marketed products that have yet to obtain PMTA authorization but are subject to FDA's current compliance policy, the Agency could permit the changes to be made and continue to exercise enforcement discretion.

III. FDA Should Accelerate the Review of Technologically-Based Solutions to Improve Public Health

JLI is a technology-focused company, using innovative solutions to provide an effective alternative for adult smokers. The current legal and regulatory framework, however, may restrain these innovations from coming to market as efficiently as possible. While JLI acknowledges the need for a rigorous review of new tobacco products, FDA should create a framework to encourage innovation, especially when it clearly benefits the public health. The Company believes such a framework should consider:

Accelerated review for innovative products: FDA already has signaled the potential for abbreviated or accelerated review for certain e-cigarettes that include features restricting access and use among youth.[8] JLI commends the Agency for this approach, and the

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[7] JLI suggests that FDA consider a PMTA supplement process in tandem with the Agency's rulemaking on Tobacco Product Manufacturing Practice (TPMP) requirements. The Company believes TPMP should be product-based, and requirements should incorporate unique manufacturing principles associated with a particular tobacco product. For example, while combustible cigarettes are manufactured in an automated process that has not changed materially for decades, ENDS products involve complex componentry that range from plastic molding to highly technical hardware and firmware capabilities. For ENDS, concepts derived from the Quality System Regulation (QSR) for medical devices should guide the Agency's thinking, including design verification and validation principles during development and design change control thereafter. Similar design change-control concepts, particularly those that could impact product performance, can be reviewed and authorized through a PMTA-supplement pathway or other mechanisms. While other changes, such as those relating to product specifications, process, or procedure, need not be evaluated by FDA so long as quality assurances are in place. JLI understands FDA will initiate rulemaking on TPMP soon, and the Company looks forward to providing feedback and participating in substantive dialogue with the Agency and other stakeholders.

[8] *See, e.g.*, FDA Statement, Statement from Commissioner Scott Gottlieb, M.D., on Proposed New Steps to Protect Youth by Preventing Access to Flavored Tobacco Products and Banning Menthol in Cigarettes (Nov.

Company already has begun pursuing this initiative, including the development of user-level access restrictions through technological capabilities. As part of finalizing guidance for ENDS PMTAs or through other guidance, JLI believes FDA should define the process for an accelerated premarket review, including which product features may be eligible, in order to provide additional transparency and enable others in the industry to follow suit. Where manufacturers can utilize innovation and technology to significantly improve public health, such as limiting youth access, an abbreviated pathway to market should be available.

Mobile applications associated with ENDS: Many ENDS products are technologically-driven and can work in tandem with mobile applications or other software-based programs that could benefit the public health. For example, applications could facilitate user-level restrictions to limit youth access; enable pre-defined limits on product usage; or even allow the user to alter and reduce vapor and nicotine intake. Other applications, although linked to ENDS products, may have less product impact. FDA should provide guidance on how mobile applications will be regulated, accounting for both the variety of applications potentially available in the future and their innovative features that could provide significant public-health benefits. The Agency also should outline requirements for software validation and related quality-control concepts as part of PMTA review to ensure consistent performance of the mobile application.[9]

Where features could impact product performance and be subject to regulation as a component of a tobacco product, FDA should consider a framework that incentivizes innovation and applies full PMTA review only when the application or its features significantly alter the risk profile of the ENDS product.[10] The Agency can borrow risk-based concepts for mobile medical applications and limit regulatory requirements to those features that present higher risk profiles.

FDA also should account for normal update cycles for mobile applications following PMTA authorization. Typically, software-based programs, including mobile applications, require minor periodic updates to fix software bugs and address other non-product features that do not impact the core function of the application. Changes of non-product features would include, among others, updates in aesthetics (e.g., changes in text and color schemes) or the collection of user-information (e.g., changes in product registration). Such changes would not affect application functionality, and premarket review would be both unnecessary and freeze the mobile application in an unworkable state. FDA should provide clear guidance

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15, 2018); Angelica LaVito, FDA Chief Says Agency Is Considering Fast-track Review for New E-cigs with Tech to Prevent Youth Use, CNBC (Sept. 20, 2018), https://goo.gl/dzpxib.

[9] In addition to considering software requirements as part of the PMTA process, FDA should incorporate these concepts in TPMP and establish a framework that contemplates software development for tobacco products.

[10] Some mobile applications for deemed products will instead be "accessories" and thus not subject to FDA regulation. 21 C.F.R. § 1100.1.

on the types of post-PMTA changes that can be made to mobile applications, without triggering additional regulatory review.[11]

IV. FDA Should Use the PMTA Process, in Addition to Other Controls, to Restrict Appeal, Access, and Use of Certain Products among Youth

JLI acknowledges that the potential benefit of ENDS products for adult smokers is offset by use among other populations, specifically youth. As FDA continues to finalize and fine-tune the application submission and review process for these types of products, JLI believes that appropriate restrictions on sales, distribution, and marketing should be in place to limit youth appeal, access, and use, and can be implemented through the PMTA process.

As JLI has previously described in prior comments, flavors remain critical to switch adult smokers from combustible cigarettes, and behavioral data will continue to demonstrate the role flavors play to initiate and maintain adult smokers on ENDS. But these products also may appeal to youth. JLI already has voluntarily implemented a restricted distribution system to limit the availability of flavored JUUL products to adults aged 21 years and older (21+ RDS). Within its 21+ RDS, JLI will sell certain flavored JUUL pods where compliance with enhanced, and automated, age-verification and bulk-purchasing requirements can be assured. As a result, the Company has stopped selling non-tobacco and non-menthol-based flavored products to over 90,000 retail outlets. JLI will continue to advocate for similar industry-wide practices, through regulation or otherwise, across all flavored tobacco products, including ENDS.

The Agency can implement similar restrictions through the PMTA process. For example, FDA can reject certain categories of flavors outright — e.g., those that mimic kid-appealing brands of candy or soda — during PMTA review. FDA also can implement certain postmarket sales and distribution controls through its PMTA review process, limiting how certain products, which may be more appealing to youth based on actual data, can be sold after authorization.[12] Such actions on a PMTA can restrict how and where certain flavored products can be sold in traditional retail, providing accessibility to adults but limiting availability to youth. In addition, FDA should consider formalizing an approach that informs other tobacco product manufacturers on best practices and policies to restrict access of their flavored products to youth. All of these potential measures should be data-driven and inform appropriate regulation and policy to eliminate combustible cigarette use among adult smokers, while simultaneously limiting use among youth.

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[11] Similar to an accelerated review for innovative products that present a clear public-health benefit, FDA should consider a streamlined review for certain post-PMTA changes to mobile applications — such as those that enhance user-level restrictions to limit youth access.

[12] *See* Tobacco Control Act, § 910(c)(1)(B).

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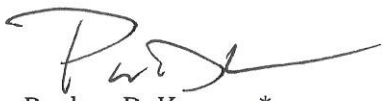
JLI supports FDA's ongoing efforts to provide a transparent, predictable, and efficient submission and review process for new tobacco products, including ENDS. The Company believes FDA can ensure that ENDS are evaluated rigorously, while preserving an innovative marketplace so adult smokers have access to the most effective alternative products to eliminate combustible cigarette use.

Sincerely,



Parker D. Kasmer*
Regulatory Counsel
JUUL Labs, Inc.

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