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Re: Docket No. FDA-2014-D-1939; Use of Investigational Tobacco Products; Revised Draft Guidance for Industry and Investigators

To whom it may concern,

JUUL Labs, Inc. (JLI or the Company) is the manufacturer of JUUL products, a closed-system vapor platform, with the mission of eliminating cigarettes among adult smokers. JLI submits this comment on FDA's draft guidance entitled "Use of Investigational Tobacco Products" (2019 Draft Guidance), which supersedes FDA's prior draft guidance of the same title issued in September 2015 (2015 Draft Guidance).

In both the 2015 and 2019 Draft Guidance documents, FDA states that because it has not yet issued regulations for investigational tobacco products (ITPs), ITPs are not exempt from premarket submission and other requirements under the Federal Food, Drug, and Cosmetic Act (FDCA). The Agency also states that it intends to exercise enforcement discretion for ITPs "on a case-by-case basis" based upon whether sponsors and investigators meet certain criteria described in the 2019 Draft Guidance.

JLI supports research of innovative tobacco products that can accelerate adult smokers' transition from combustible use to less harmful alternatives, including "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."[1] Clinical trials are a key element to understand how novel products impact the health of individual users as well as public health more broadly.

The Company, however, has concerns over FDA's current approach for ITPs and their evaluation in clinical trials — specifically, by regulating through guidance rather than promulgating actual regulations that establish binding requirements. As discussed below, FDA's use of guidance along with enforcement discretion to regulate ITPs is inconsistent

[1] *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.

with the Agency's statutory authority and precedent, and fails to establish clear and binding requirements for sponsors, investigators, and FDA staff to ensure the safe development of category-changing tobacco products.

If FDA intends to finalize the 2019 Draft Guidance before initiating rulemaking for ITPs, the Agency should further clarify the scope of a "clinical investigation," as well as its recommendations for Agency review timelines and adverse-experience reporting. In addition, JLI strongly believes that FDA should adopt a risk-based framework that adjusts the degree of Agency oversight over ITP submissions based upon the level of risk posed by the clinical investigation to human subjects, and establish express confidentiality protections for ITP submissions, consistent with FDA's framework for other investigational products.

JLI believes that this approach, as outlined below, would encourage clinical research and development of risk-reduction products that could potentially eliminate combustible cigarettes for adult smokers, while also protecting public health and making the best use of limited Agency resources.

I. FDA MUST INITIATE RULEMAKING TO ESTABLISH A REGULATORY FRAMEWORK FOR ITPS

Based on its authority under the FDCA, FDA's regulatory framework for ITPs must be established through notice-and-comment rulemaking. *See* 21 U.S.C. § 387j(g) (FDA "may exempt tobacco products intended for investigational use from the provisions of this subchapter under such conditions as [FDA] may *by regulation* prescribe.") (emphasis added).

As noted by several comments on the 2015 Draft Guidance, it is imperative that FDA promulgate regulations for ITPs that have the force and effect of law, rather than issue guidance. FDA regulations that exempt investigational products from applicable FDCA requirements are the Agency's primary legal tool for enabling research and development of new and innovative products subject to FDA oversight.

More broadly, FDA's use of guidance and enforcement discretion, rather than rulemaking, to implement tobacco-product requirements goes against express mandates under the Family Smoking Prevention and Tobacco Control Act (TCA) and, ultimately, is an ineffective way to ensure the protection of public health. In particular, several TCA provisions explicitly direct FDA to promulgate regulations to implement the underlying requirements. Even though the TCA was enacted almost a decade ago, FDA has not issued regulations to implement many of these baseline requirements.[2] Until FDA has met its

[2] *See, e.g.,* 21 U.S.C. § 387e(h) (requiring foreign tobacco product establishments to register with FDA under yet-nonexistent regulations); *id.* § 387f(e) (requiring that FDA promulgate good manufacturing practice regulations for tobacco products); *id.* § 387i(b) (requiring that FDA promulgate regulations for manufacturers and importers to promptly report market removals or corrective actions for products that are related to health risks); *id.* § 387o(a)-(b) (requiring that FDA promulgate regulations for testing and reporting

statutory obligations to establish definitive requirements that bind both industry and the Agency through *bona fide* notice-and-comment rulemaking, the regulatory framework that Congress envisioned for tobacco products — and the goals FDA seeks to achieve in promoting the development of innovative, lower-risk tobacco products — will not be fully realized.

II. FDA SHOULD FURTHER CLARIFY THE MEANING OF "CLINICAL INVESTIGATION"

While the 2019 Draft Guidance more appropriately defines a "clinical investigation" to mean only those studies where an ITP is administered or dispensed to or used by one or more human subjects — rather than all studies "involving" an ITP, as defined in the 2015 Draft Guidance — further clarification is needed. Specifically, FDA should clarify the scope of a "clinical investigation" under its ITP framework and leverage how it has defined the scope of such investigations under its investigational device exemption (IDE) regulations for medical devices.

Congress modeled much of the regulatory review process for tobacco products in the TCA based upon the risk-based review process it established for medical devices. Similar to devices, Congress established a framework where: (1) numerous pre-2007 tobacco products are grandfathered and require no premarket submissions for continued marketing; (2) "new" tobacco products that are substantially equivalent to these and other predicate products require premarket notification rather than premarket tobacco product applications (PMTAs) (and in many cases should not require clinical data);[3] and (3) PMTAs are required for "new" tobacco products that are not substantially equivalent to such predicates (and generally require clinical data).[4] As it did for devices, Congress established this framework to balance certain potential competing interests. In particular, it sought to maintain the availability of tobacco products for adults, subject to FDA oversight, while also requiring that new products undergo a risk-based review that, in part, assesses their public-health impact against currently marketed products.[5] FDA, likewise, has recognized

tobacco product constituents, ingredients, and additives, including smoke constituents); *id.* § 387t(b) (requiring that FDA promulgate recordkeeping regulations for tracking and tracing purposes).

[3] *C.f.* 84 Fed. Reg. 12,740, 12,743 (Apr. 2, 2019) ("[S]ection 910(a)(3)(A) of the FD&C Act authorizes FDA to issue an order finding substantial equivalence when FDA finds that the new tobacco product is in compliance with the requirements of the FD&C Act and either: (1) Has the same characteristics as the predicate tobacco product or (2) has different characteristics and the information submitted contains information, including clinical data if deemed necessary by FDA, that demonstrates that it is not appropriate to regulate the product under (the premarket tobacco application or 'PMTA' provisions) because the product does not raise different questions of public health.").

[4] *See* 21 U.S.C. §§ 387e(j), 387j(a)(1)–(3).

[5] *See* TCA § 3, *codified at* 21 U.S.C. § 387 note.

that tobacco products should be "put through an appropriate series of regulatory gates to maximize public health benefits and minimize harms."[6]

Under FDA's regulations for IDE studies (codified at 21 C.F.R. Part 812) a "clinical investigation" is defined to include a "clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device."[7] Moreover, FDA has exempted certain studies from the "clinical investigation" definition including, in relevant part, "[a] device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk."[8]

Accordingly, the IDE regulations, in practice, only apply to device studies involving human subjects that are conducted to demonstrate safety and effectiveness supporting premarket approval (PMA) for a new use, or certain section 510(k) premarket notifications.[9] As such, FDA's IDE regulations were purposefully designed to avoid unnecessary burdens on scientific research and innovative product development, while also ensuring appropriate oversight to protect human subjects.[10]

FDA should adopt a similar framework for ITPs, in that only studies in human subjects that are conducted for the purposes of evaluating harm reduction, protection of public health, and other factors required for marketing authorization under the FDCA should be covered. In particular, clinical investigations subject to ITP regulations should include only studies in which an ITP is administered to, dispensed to, or used by one or more human subjects to determine whether the product would: (i) reduce harm and the risk of tobacco-related disease; or (ii) be appropriate for the protection of public health or otherwise not raise different questions of public health compared to a predicate tobacco product.[11]

This approach focuses Agency resources on studies evaluating safety and potential impacts on public health, consistent with the approval standards for marketing orders for

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[6] *See, e.g.,* FDA, FDA Voices, Commissioner Scott Gottlieb, M.D., Spring Unified Agenda: FDA's Anticipated Upcoming Regulatory Work (May 9, 2018), available at https://bit.ly/2UTpjF3.

[7] 21 C.F.R. § 812.3(h); *see also id.* § 812.2(a).

[8] *Id.* § 812.2(c)(4).

[9] *See, e.g.,* FDA, Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Frequently Asked Questions about Medical Devices, at 8 (Jan. 2006), available at https://bit.ly/2ZbZF17 (Medical Devices FAQ Guidance); FDA Presentation, Clinical Trials for Medical Devices: FDA and the IDE Process, available at https://bit.ly/2v4w0ZU.

[10] *See, e.g.,* 45 Fed. Reg. 3,732, 3,735 (Jan. 18, 1980).

[11] *See* 21 U.S.C. § 387j(a)(3)(A) (definition of "substantially equivalent"); *id.* § 387j(c)(2) (approval standard for PMTAs); *id.* § 387k(g) (approval standards for MRTPAs).

Modified Risk Tobacco Product Applications (MRTPAs) under section 911, PMTAs under section 910(b), and certain Substantial Equivalence (SE) reports under section 910(a)(3)(A)(ii) of the FDCA. Other types of testing — such as design validation, consumer-preference testing or in-house flavor or sensory testing for product development or quality control — would not be subject to ITP requirements, consistent with FDA's framework for investigational devices. Indeed, under FDA's IDE regulations, such studies would be excluded as long as the purpose of the study was not to evaluate safety or effectiveness.[12] Where such testing involves inhalation of nicotine by study participants, application of requirements for human subject protection under 21 C.F.R. Part 50 and Institutional Review Board (IRB) review under 21 C.F.R. Part 56 would be appropriate to ensure informed consent and other applicable safeguards. Consistent with FDA's IDE regulations, there would, however, be no cause to impose separate ITP requirements.

This approach also ensures that all studies intended to support a marketing application for an ITP are subject to oversight. As FDA acknowledges in the 2019 Draft Guidance, it is essential for FDA regulations to ensure that the studies relied upon by sponsors to support marketing of new tobacco products are conducted safely, ethically, and in a manner that ensures the integrity of the data generated.[13] The proposal described above does exactly that.

III. FDA SHOULD APPLY A RISK-BASED FRAMEWORK TO ITPS COMPARABLE TO IDE REGULATIONS

JLI urges FDA to adopt a risk-based framework for ITPs, comparable to FDA's IDE regulations (codified at 21 C.F.R. Part 812), and provide guidance on applicable requirements and conditions, as discussed further below.

A. Overview of IDE Framework

Clinical studies for medical devices are subject to differing levels of regulatory control depending upon the level of risk of the study. FDA regulations distinguish between significant risk (SR) and nonsignificant risk (NSR) device studies, and the procedures for obtaining approval to initiate the study differ accordingly. An SR device presents a potential for serious risk to the health, safety, or welfare of a human subject.[14] SR devices may include devices that are substantially important in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health; implants; or devices that support or sustain human life, where a study of such a device would pose a significant

[12] *See* 21 C.F.R. § 812.2(c)(4).

[13] *See* 2019 Draft Guidance, at 6.

[14] 21 C.F.R. § 812.3(m).

risk to human subjects.[15] Conversely, an NSR device is a device that does not meet the SR device definition — meaning the device does not pose a significant risk to human subjects.

Sponsors are responsible for making the initial risk determination and presenting it to the reviewing IRB for study approval.[16] The risk determination should be based on the potential harm related to the proposed use of the device in the clinical study, as well as any additional procedure the subject would have to undergo as part of the study, such as a surgical procedure.[17] Unless FDA has already made a risk determination for the clinical study, the IRB will review the sponsor's SR or NSR determination and modify the determination if the IRB disagrees with the sponsor.[18]

Sponsors must meet different requirements before initiating a clinical study depending on whether the study involves an SR or NSR device. For an SR device study, the sponsor must obtain approval from both FDA and the IRB prior to initiation of the study.[19] To obtain approval from FDA, the sponsor must submit to the Agency an IDE application that contains detailed information, including a description of the study and the device; copies of all labeling for the device; information regarding the investigators and IRB; copies of all forms, informational materials to be provided to subjects to obtain informed consent; and other information, including any other relevant information requested by FDA.[20] Unless FDA expressly notifies a sponsor otherwise, an IDE study may begin on the 30th day after FDA's receipt of the IDE application or upon FDA approval of the application, whichever is earlier.[21]

By contrast, an NSR device study requires only IRB approval. To obtain IRB approval, the sponsor must provide the IRB an explanation of why the device is not an SR

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[15] *Id.*

[16] FDA, Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, Significant Risk and Nonsignificant Risk Medical Device Studies, at 3 (Jan. 2006), available at https://bit.ly/2v9TCMy (SR and NSR Device Studies Guidance).

[17] *Id.* at 6.

[18] 21 C.F.R. §§ 812.60; 812.5. FDA, nonetheless, retains authority as the final arbiter in determining whether a device study is SR or NSR. SR and NSR Device Studies Guidance, at 4 (citing 21 C.F.R. § 812.2(b)(1)).

[19] 21 C.F.R. §§ 812.2, 812.20(a), 812.42.

[20] *Id.* § 812.20(b).

[21] *Id*. § 812.30(a)(1) ("An investigation may not begin until: (1) Thirty days after FDA receives the application . . . for the investigation of a device . . ., unless FDA notifies the sponsor that the investigation may not begin; or (2) FDA approves, by order, an IDE for the investigation."). IND regulations similarly state that "[a]n IND goes into effect (1) Thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under §312.42; or (2) On earlier notification by FDA that the clinical investigations in the IND may begin. FDA will notify the sponsor in writing of the date it receives the IND." *Id.* § 312.40(b).

device, along with information that may help the IRB in evaluating the risk of the study.[22] If the IRB disagrees with the sponsor's NSR determination and determines that the device poses a significant risk, the sponsor must report this finding to FDA within five working days.[23] FDA considers an investigation of an NSR device to have an approved IDE when the IRB concurs with the NSR determination and approves the study.[24]

SR device studies must comply with all IDE regulations, as well as regulations for human subject protection and IRBs.[25] NSR device studies must comply with abbreviated IDE requirements and the regulations for human subject protection and IRBs.[26]

B. FDA Should Adopt a Risk-Based Framework in ITP Regulations

FDA should adopt a similar risk-based approach in its ITP regulations. Such an approach would reflect FDA's scientific understanding of the risks associated with tobacco products, while also allowing the Agency to more appropriately allocate its limited resources. As the Agency has repeatedly recognized, there are different types of tobacco products, and these products present varying levels of risks to users. Indeed, "[a] key piece" of FDA's approach to regulating tobacco "is demonstrating a greater awareness that nicotine — while highly addictive — is delivered through products that represent a continuum of risk and is most harmful when delivered through smoke particles in combustible cigarettes."[27]

Additionally, as noted previously, Congress modeled the regulatory process for tobacco products under the TCA based upon the risk-based process it had established for medical devices. FDA should draw from Congress's approach, as well as its own IDE regulations, to establish a risk-based framework for ITP regulations. This would allow the Agency to focus on ITP studies that pose more than an insignificant risk to human subjects, comparable to the framework FDA established for IDEs. Thereafter, FDA should issue guidance on the differences between SR and NSR ITP studies, and update the guidance to include specific examples, as it also has done for investigational devices.[28] This level of clarity and transparency would facilitate the development of innovative products, while maintaining appropriate oversight by FDA and ensuring the protection of human subjects.

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[22] *Id.* § 812.2(b)(1)(ii).

[23] *Id.* § 812.150(b)(9).

[24] *Id.* § 812.2(b)(1).

[25] *See generally id.* Part 812.

[26] *See id.* § 812.2(b).

[27] FDA, FDA News Release, FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (July 28, 2017), available at https://bit.ly/2YiMwD5.

[28] *See* SR and NSR Device Studies Guidance.

C. Specific Recommendations for a Risk-Based ITP Framework

As with investigational devices, FDA should differentiate between SR and NSR ITP studies. FDA should similarly define an SR ITP as an ITP that presents a potential for serious risk to the health, safety, or welfare of a human subject.[29] And, as a corollary, an ITP that does not meet the definition of an SR ITP should be considered an NSR ITP.

FDA also should establish prior approval requirements for both NSR and SR ITP studies that are consistent with those for NSR and SR device studies:

NSR ITP Studies	SR ITP Studies
• NSR ITP studies should require approval by IRBs	• SR ITP studies should require approval from FDA and the appropriate IRB
• Sponsors must report to FDA when an IRB disagrees with their NSR determination and obtain prior approval from the IRB and FDA as appropriate	• SR ITP studies may begin 30 days after FDA receives the ITP application or upon FDA approval, whichever comes first, unless FDA expressly notifies the sponsor that it has disapproved the application[30]

For IDEs, FDA's decision to establish different prior approval requirements for NSR and SR device studies stems from the goal of allocating scarce Agency resources based on risk to human subjects and balancing the need for oversight with the burden on industry and on researchers.[31] The same calculus applies to ITPs. Absent a risk-based ITP framework, FDA will not be able to effectively foster innovation in less harmful tobacco products and, as a result, will not maximize related public-health benefits and minimize harms, in line with the Agency's goals.[32]

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[29] *Cf.* 21 C.F.R. § 812.3(m).

[30] *Cf. id*. §§ 812.2, 812.20, 812.30(a), 812.42, 812.150.

[31] *See, e.g.,* 45 Fed. Reg. 3,732, 3,736 (Jan. 18, 1980) ("By dispensing with the submission to FDA of applications conserving nonsignificant risk devices, the regulatory system will avoid an unnecessary and costly paperwork burden on sponsors, an excessive processing burden on FDA, and delays in approval, without sacrificing protection of human subjects.").

[32] *See, e.g.,* FDA, FDA Voices, Commissioner Scott Gottlieb, M.D., Spring Unified Agenda: FDA's Anticipated Upcoming Regulatory Work (May 9, 2018) ("One goal of our efforts is to encourage innovation of less harmful products. We will ensure that all tobacco products, whatever their nicotine content or delivery mechanism, are put through an appropriate series of regulatory gates to maximize any public health benefits and minimize harms."); FDA, FDA Statement, Statement from FDA Commissioner Scott Gottlieb, M.D., on pivotal public health step to dramatically reduce smoking rates by lowering nicotine in combustible cigarettes to minimally or non-addictive levels (Mar. 15, 2018), available at https://bit.ly/2DuKHXX ("... our plan demonstrates a greater awareness that nicotine, while highly addictive, is delivered through products on a continuum of risk, and that in order to successfully address cigarette addiction, we must make it possible for current adult smokers who still seek nicotine to get it from alternative and less harmful sources. To that end, the Agency's regulation of both novel nicotine delivery products such as e-cigarettes and traditional tobacco

Requiring prior FDA approval for SR studies while allowing IRBs to be the primary backstop for NSR studies provides for an efficient but well-controlled management of clinical research. Dual pre-initiation oversight by FDA and IRBs is necessary where the study may pose a serious risk to human subjects based on information known or unknown about an ITP. In contrast, FDA can and should allow IRBs to take primary responsibility for overseeing studies for which there is a sufficient corpus of information to ensure human subjects are adequately protected.

After initiation, both NSR and SR studies should comply with remaining requirements for ITPs. These include (1) ITP labeling requirements; (2) prohibition of commercialization, promotion, and other practices; (3) human subject protection and informed consent; (4) monitoring; and (5) recordkeeping and reporting. As is the case for NSR device studies, NSR ITP studies should be subject to more streamlined recordkeeping and reporting requirements than SR ITP studies.[33]

Given FDA's many competing priorities and the varying risk of harm posed to human subjects by different ITPs, this paradigm allows FDA and IRBs to focus more oversight resources on IDE studies for which there is a greater potential for harm to human subjects. It also balances the need for such oversight with the burden on industry and researchers, which, in turn, will spur innovation in less harmful products for a market that is dominated by combustible products.

IV. FDA SHOULD CLARIFY ADVERSE-EXPERIENCE REPORTING REQUIREMENTS FOR ITP STUDIES

While part of FDA's recommendations for adverse-experience reporting in the 2019 Draft Guidance bears some similarity to requirements for IDE and IND studies, the reporting recommendations depart from requirements for investigational devices and drugs in key aspects. JLI urges FDA to adopt adverse-experience reporting recommendations for ITPs that are more consistent with the Agency's IDE and IND regulations.

A. Threshold for Reportable Adverse Experiences

In the 2019 Draft Guidance, FDA recommends that sponsors inform FDA, the appropriate IRB(s), and all participating clinical investigators of adverse experiences that are both "serious **and** unexpected" *and* "serious **or** unexpected."[34] This dual-reporting

products will encourage the innovation of less harmful products while still ensuring that all tobacco products are put through an appropriate series of regulatory gates to maximize any public health benefits and minimize their harms.").

[33] *See* 21 C.F.R. §§ 812.2(b)(1)(v), 812.140(b), 812.150(b).

[34] 2019 Draft Guidance, at 12–13 (emphasis in original).

scheme departs from adverse-event reporting requirements for IDEs and INDs, without much explanation.

FDA also does not clearly define "unexpected" or "serious." Instead, FDA states that "an adverse experience would be unexpected, if *for example*, the nature, severity, or frequency of an effect of using an [ITP] was not consistent with known or foreseeable risks associated with such product or the research procedures."[35] Further, FDA provides only one example of a "serious and unexpected" adverse experience—specifically, "burns resulting from an exploding battery in an [ENDS]."[36]

In contrast, in the IDE and IND contexts, FDA generally requires adverse-event reporting only for events that are both serious *and* unexpected. In addition, the Agency more clearly defines relevant terms within the context of such reporting requirements. In the IDE context, for example, FDA requires sponsors to report "unanticipated adverse device effects" to the Agency, all reviewing IRBs, and participating investigators.[37] FDA defines an "unanticipated adverse device effect" as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."[38]

In the IND context, FDA requires sponsors to notify the Agency and all participating investigators of "any suspected adverse reaction that is both serious *and* unexpected."[39] In addition, FDA expressly defines a "serious adverse event" and an "unexpected adverse event":

> *Serious adverse event or serious suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death,

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[35] *Id.* at 12 n.18 (emphasis added).

[36] *Id.* at 12–13.

[37] 21 C.F.R. § 812.150(b)(1).

[38] *Id.* § 812.3(s).

[39] *Id.* § 312.32(c)(1)(i) (emphasis added). In addition to "serious and unexpected suspected adverse reaction[s]," IND sponsors must also report: findings from any other epidemiological studies, pooled study analyses, or other clinical studies, that suggest a significant risk in humans exposed to the drug; findings from any animal or in vitro studies suggesting a significant risk in humans exposed to the drug; and increased rate of occurrence of serious suspected adverse reactions. *Id.* § 312.32(c)(1)(i)–(iv).

> be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
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> *Unexpected adverse event or unexpected suspected adverse reaction*. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.[40]

FDA should assure greater consistency across its adverse-event reporting approaches for investigational products and more clearly define the meaning of "serious" and "unexpected" adverse experiences for ITPs to minimize uncertainty.

B. Reporting Timelines

FDA's recommendations on the timing for reporting adverse experiences in the Draft Guidance are nebulous and noticeably shorter than applicable timelines in other investigational settings. FDA recommends that sponsors inform FDA, the appropriate IRB(s), and all participating clinical investigators of:

- "serious and unexpected" adverse experiences, "[w]ithin a few days after initial receipt of the notification;"

[40] *Id.* § 312.32(a).

- "serious or unexpected" adverse experiences, "[w]ithin a few weeks after initial notification."[41]

FDA should establish clearer timelines for adverse-experience reporting for ITPs, as it has done for IDEs and INDs. For IDE studies, sponsors are required to submit to FDA and the reviewing IRB a report of any unanticipated adverse device effect as soon as possible, but no later than 10 days after the investigator first learns of the effect.[42] For IND studies (involving drugs that are not marketed), sponsors must notify FDA and all participating investigators of serious and unexpected suspected adverse reactions as soon as possible, but no later than 15 calendar days after the sponsor determines the event requires reporting.[43]

The absence of clear reporting timelines makes it difficult for sponsors and investigators of ITP studies to assess whether they are submitting adverse-event reports in a timely fashion. Establishing reporting timelines for ITP studies by regulation creates clear obligations for sponsors and investigators, alerts FDA and reviewing IRBs to important safety signals in an efficient manner, and provides investigators and sponsors sufficient time to investigate serious and unexpected adverse events that could have a significant impact on the study or the public health.

In addition, it is not clear why ITP sponsors have shorter reporting timelines for serious and unexpected adverse experiences compared to IDE and IND sponsors, who have 10 working days and 15 calendar days respectively to notify FDA.[44] Although FDA does not define exactly how many days "a few days" means within the ITP context, it presumably refers to a shorter period than the IDE and IND timelines. FDA should apply timelines for adverse-experience reporting in ITP studies that are consistent with its requirements for IDE or IND studies, unless it can articulate a logical basis for imposing a significantly shorter timeline for ITPs alone.

V. FDA SHOULD INCLUDE THE SAME APPLICATION REVIEW AND RECORDKEEPING TIMELINES FOR ITPS AS IT CURRENTLY REQUIRES FOR IDES AND INDS

The 2019 Draft Guidance provides timelines for Agency review of ITP applications and for investigator and sponsor recordkeeping that depart from corresponding timelines in the IND and IDE regulations. Absent a clear justification, FDA's review and recordkeeping timelines for ITPs should align with the timelines it requires in other investigational contexts.

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[41] 2019 Draft Guidance, at 13.

[42] 21 C.F.R. § 812.150(a)(1).

[43] *Id.* § 312.23(c)(1).

[44] *Id.* §§ 812.150(b)(1), 312.23(c)(1).

First, FDA should respond to an ITP application within 30 days of receipt, consistent with Agency review timelines for IND and IDE applications. Under its IND and IDE regulations, FDA has 30 days to provide a written determination regarding whether a clinical investigation may or may not proceed after receiving the IND or IDE.[45] Unless FDA objects, an IND or IDE application is deemed approved after the 30-day period.[46] The 2019 Draft Guidance inexplicably affords the Agency twice as much time (60 days) to respond to an ITP application.[47] FDA, however, has articulated no logical reason as to why it needs double the amount of time to review ITP applications than IND or IDE applications.

Second, FDA should recommend (and via rulemaking require) that ITP investigators and sponsors retain records for two years, consistent with its requirements for IDEs or INDs. FDA requires IND investigators and sponsors to retain records for two years after a marketing application is approved, or if an application is not approved, after shipment and delivery of the investigational drug is discontinued and FDA has been notified.[48] Similarly, FDA requires IDE investigators and sponsors to (in relevant part) retain records for two years after the termination or completion of the investigation or the date the records are no longer required to support a premarket approval application.[49]

The 2019 Draft Guidance, however, recommends that ITP investigators and sponsors maintain records for twice as long — four years — after the termination or completion of the study, or after the records are no longer necessary to support marketing of a product.[50] Unless FDA provides an adequate justification for recommending or requiring a record retention period that is twice as long in the ITP context as it requires for IND and IDE studies, the Agency should apply the same two-year recordkeeping timeline in ITP regulations.

VI. FDA SHOULD MAKE CLEAR AND ENSURE THAT CONFIDENTIAL INFORMATION IN ITP SUBMISSIONS WILL NOT BE DISCLOSED TO THE PUBLIC

ITP applications and study-related submissions will contain confidential information that should not be publicly disclosed by FDA, either on its own initiative or in response to a Freedom of Information Act (FOIA) request. This information could include trade secrets, confidential commercial information, and medical or other personal information of human subjects.

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[45] *Id.* §§ 312.20(c), 812.20(a)(4)(i).

[46] *See id.* §§ 812.20, 812.30(a) (for IDE applications); *id.* §§ 312.20(b), 312.40(b) (for IND applications).

[47] 2019 Draft Guidance, at 8.

[48] 21 C.F.R. § 312.57(c).

[49] *Id.* § 812.140(d).

[50] 2019 Draft Guidance, at 14.

Such information is protected from disclosure under various authorities, including the Federal Trade Secrets Act (FTSA) (18 U.S.C. § 1905), the FDCA (21 U.S.C. §§ 301(j), 387f(c), 387k(e)), FOIA (5 U.S.C. § 552(b)(4) and (b)(6)), and FDA's implementing regulations at 21 C.F.R. part 20. FDA should make clear that it will not disclose such information and specify the procedures it will employ to ensure that such information is not disclosed to the public.

For example, the 2019 Draft Guidance recommends that sponsors submit, in relevant part, a detailed description of the ITP's product design (with schematics) and specifications; components, parts, and ingredients; manufacturing methods and controls; and stability data, including:

- "A description of the product design with schematics of the complete product and product components, a description of the design features (e.g., location of ventilation holes, heat source, paper porosity, coatings, nicotine concentration gradient), and performance specifications;"

- "A complete list of, or a reference to the manufacturer's complete list of, components or parts, ingredients, and additives by quantity in the tobacco product, including product chemistry and a table of any harmful or potentially harmful constituents, as well as the applicable specifications and a description of the intended function of each;"

- "The name and address of the manufacturer(s) of the tobacco product and components or parts;"

- "A description of the methods, facilities, and controls used for the manufacture, processing, packing, and storage of the investigational tobacco product;"

- "Data and information sufficient to demonstrate the investigational tobacco product will be stable during the conduct of the study."[51]

Such data and information could include trade secrets or confidential confirmation information and, as such, must not be publicly disclosed.[52]

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[51] *Id.* at 9–10.

[52] *See, e.g.,* 5 U.S.C. § 552(b)(4); 21 C.F.R. § 20.61(a) and (b); *see also Appleton v. FDA*, 451 F. Supp. 2d 129, 141 (D.D.C. 2006) (holding that "product manufacturing information, including manufacturing processes or . . . chemical composition and specifications" were trade secrets); *Heeney v. FDA*, 1999 WL 35136489, at *7 (C.D. Cal. Mar. 16, 1999) ("Design and testing data, including specification of the materials used in constructing the product . . . fall squarely within Exemption 4's reference to 'trade secrets'."), *aff'd*, 7 F. App'x 770 (9th Cir. 2001); *Rozema v. U.S. Dep't of Health and Human Servs.*, 167 F. Supp. 3d 324, 330, 339-40 (N.D.N.Y. 2016) (holding that tobacco product formulations, including ingredient quantities, constitute trade secrets).

In addition, sponsors and investigators may submit medical and other personal information about subjects for which disclosure "would constitute a clearly unwarranted invasion of personal privacy," and therefore is exempt from public disclosure.[53] For example, the 2019 Draft Guidance recommends that sponsors submit completed case report forms for serious or unexpected adverse tobacco product experiences to FDA, and retain adverse experience reports as part of their recordkeeping for ITP studies.[54] These reports could contain medical or other personal information regarding subjects, which would be protected from disclosure.

Despite this, neither the 2019 Draft Guidance, nor the 2015 Draft Guidance, include any provisions for confidentiality. This approach stands in stark contrast to FDA's IND and IDE regulations, both of which include regulations specifically addressing confidentiality concerns. Under longstanding policy, FDA generally does not disclose the existence of an IND or IDE application unless its existence has been previously publicly disclosed or acknowledged.[55] FDA regulations for INDs and IDEs also specify that disclosure of information submitted by sponsors and investigators under IND or IDE applications to support a marketing application will be governed by the same procedures as those that apply to information submitted as part of the marketing application itself. Generally, for INDs, FDA disclosure of data and information is governed by the same regulations that would apply to a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA), as appropriate.[56] Likewise, for IDEs generally, FDA disclosure of data and information is governed by the same regulations that would apply to a PMA.[57] IND and IDE confidentiality regulations also include specific details on FOIA requests for information from investigations involving exceptions from informed consent under 21 C.F.R. § 50.24.[58]

Moreover, FDA's failure to include recommendations for confidentiality in the 2019 Draft Guidance is unique within the Agency's guidance for the premarket review of tobacco products. Guidance documents for PMTAs, MRTPAs, and SE reports all include confidentiality recommendations.[59]

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[53] *See* 5 U.S.C. § 552(b)(6); 21 C.F.R. § 20.63.

[54] 2019 Draft Guidance, at 14–15.

[55] *See* 21 C.F.R. §§ 312.130(a), 812.38(a); *see also* 47 Fed. Reg. 3,732, 3,745 (Jan. 18, 1980) (for IDEs); 52 Fed. Reg. 8,798, 8,831 (Mar. 19, 1987) (for INDs).

[56] 21 C.F.R. § 312.130(b); *see id.* § 314.430 (governing confidentiality for NDAs and ANDAs); *id.* §§ 601.50, 601.51 (governing confidentiality for BLAs).

[57] *Id.* § 812.38(d); *see id.* § 814.9 (governing confidentiality for PMAs).

[58] *Id.* §§ 312.130(d), 812.38(b)(4).

[59] *See* FDA, Draft Guidance, Modified Risk Tobacco Product Applications, at 46–47 (Mar. 2012), available at https://bit.ly/2DqrAkp; FDA, Draft Guidance, Applications for Premarket Review of New Tobacco Products, at 22-23 (Sept. 2011), available at https://bit.ly/2MJ3wz3; FDA, Guidance for Industry and FDA

FDA should ensure that its ITP regulations and guidance make clear that FDA will protect confidential information submitted by sponsors and investigators as part of ITP submissions. In addition, JLI urges FDA to promulgate regulations regarding the confidentiality of data and information in ITP submissions that are consistent the Agency's regulations for IDEs and INDs.[60] It is imperative that the Agency establish processes for handling submissions of confidential information and responding to FOIA requests in a manner that ensures confidentiality is preserved in accordance with the law.

Regards,

Parker D. Kasmer
Regulatory Counsel
JUUL Labs, Inc.

Staff, Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products, at 13 (Jan. 2011), available at https://bit.ly/2VZ85GS.

[60] *Cf.* 21 C.F.R. § 312.130(b); *id.* §§ 812.38(b)(1)–(3), (d).