IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
Southern Division

AMERICAN ACADEMY OF PEDIATRICS, et al.,	*	
Plaintiffs,	*	
	*	**Case No.: PWG-18-883**
v.	*	
FOOD AND DRUG ADMINISTRATION, et al.,	*	
Defendants,	*	
JUUL LABS, INC.,	*	
Amicus	*	

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DECLARATION OF JOANNA ENGELKE
ON BEHALF OF JUUL LABS, INC.

I, Joanna Engelke, pursuant to 28 U.S.C. § 2746, declare:

1. I am employed by JUUL Labs, Inc. ("JLI") as its Chief Quality and Regulatory Officer. I have worked at JLI since February, 2018. During that time I have provided quality and compliance oversight to JLI's products. My more than 30 years of experience since receiving an M.B.A. from Harvard University includes executive leadership of global quality and regulatory matters at Boston Scientific and Managing Director of Halloran Consulting Group, Inc., a national consultancy to life sciences companies. The information in this declaration is based on (i) my personal knowledge;

(ii) the business records of JLI; and (iii) the personal knowledge of others at JLI from whom I received the information.

COMPANY BACKGROUND

2. JLI is a San Francisco-based company dedicated to improving the lives of the world's one billion smokers by eliminating cigarettes. To further that goal, JLI has developed a nicotine-delivery system, by pioneering vapor technology, to provide adult smokers with a viable alternative to combustible cigarettes. JLI is the number one vapor-product manufacturer in the United States.

3. The Company's founders, James Monsees and Adam Bowen, both of whom are now former smokers, conceived the idea that became JLI to provide a real alternative to traditional combustible cigarettes. Graduates of Stanford University's Design School in the mid-2000s, they pioneered groundbreaking technology that aimed to improve the lives of smokers. As smokers themselves, they saw a gap in the alternative smoking environment for adults who wanted to switch from combustible cigarettes. Mr. Monsees and Mr. Bowen saw a lack of development in the tobacco industry, and sought to leverage their own design and scientific know-how to develop an alternative for adult smokers, one that would provide a nicotine experience that was similar to cigarettes, was easy to use, and did not involve combustion.

4. The JUUL system is a closed-system vapor platform with three components: (1) an electronic device that couples with (2) a nicotine-containing liquid pod at one end and (3) a charger at the other end. The JUUL system generates a nicotine aerosol vapor for inhalation. The pod is filled with a nicotine and benzoic acid formulation ("e-liquid") that is designed to appeal to adult smokers and facilitate their switch away from combustible cigarettes.

5. JLI products have been designed for adult smokers only, for the purpose of transitioning them from combustible cigarettes.

6. Different tobacco products—cigarettes, cigars, smokeless tobacco like dip or snuff, and ENDS—have different risk profiles. The Food and Drug Administration ("FDA") has noted repeatedly that a "key piece of the FDA's approach 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," and is less harmful when delivered through ENDS. News Release, FDA, FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death (July 28, 2017) ("FDA News Release"). There is a growing global recognition of the public health benefit of moving current adult smokers down the continuum of risk from combustible tobacco to electronic nicotine. For instance, Public Health England, the British government agency principally responsible for public health, has concluded that e-cigarettes are approximately 95% less harmful than combustible cigarettes. *See* Brose, McNeil, et al., E-cigarettes: an evidence update, A report commissioned by Public Health England 5 (Aug. 2015), available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733022/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf.

7. The increase in the sales of JUUL products has corresponded with a significant population-wide transition away from combustible cigarettes. Cigarette-pack sales volumes have declined dramatically. Syndicated market data provided by the Nielsen Company's "Answers in Demand Services for the Total Store/Tobacco Category" show that in a recent four-week period, for example, cigarette sales volumes dropped by more than 11% year-over-year. This compares favorably with the compound annual decline rate of 2.7% from 2011 to 2016 according to the Alcohol and Tobacco Tax and Trade Bureau. The Nielsen syndicated data show that the trend

away from combustible cigarettes is most pronounced where JLI has high market penetration: in New York City, Portland, Oklahoma City, Seattle and Denver, declines accelerated from 3.0% year-over-year one year ago to 13.9% in a recent reporting period.

8. JLI has reiterated many times, and it continues to maintain, that no youth and no non-nicotine user should ever use an Electronic Nicotine Delivery System ("ENDS") product. The Company does not sell "Juice Box," "Pop Corn," or any remotely similar product of the type that the Court expressed concern about in its May 15, 2019 Memorandum Opinion, D.E. 73. *See* Opinion at 3 n.5.

9. The Company has also worked proactively to prevent youth from using its products. These efforts include, among other things, creating a comprehensive action plan to address youth access, appeal, and use of JUUL products that it submitted to FDA in November 2018. Some of the elements of that plan, and some of JLI's related initiatives, include:

- JLI supports and has advocated for an increase in the minimum age to purchase tobacco products, including vapor, to 21 years old nationwide;
- JLI has ceased selling non-tobacco and non-menthol based flavored JUUL products to more than 90,000 traditional retail outlets;
- JLI has limited the sale of flavored products, other than tobacco and menthol-based, to online sales through JUUL.com, which (i) uses third-party age-verification, two-factor authentication, and facial-recognition technology to help ensure that persons ordering online are at least 21 years of age (even if state law permits tobacco purchases at age 18), and (ii) limits the amount of product that can be purchased;
- JLI has expanded its secret-shopper program that checks 2,000 stores per month to ensure compliance with age-verification and company-specific bulk purchasing requirements;
- JLI has exited U.S. Facebook and Instagram accounts;
- JLI is deploying technologically-based solutions to prevent youth access and use, including establishing full system product traceability to identify where youth are obtaining product illegally;

- JLI has developed a standard-based approach for point-of-sale systems, which includes automated scanning of government-issued identification to verify age and validity and an automated block on bulk purchases, and is partnering with retailers to deploy this technology in brick-and-mortar stores to restrict youth access to JUUL products;
- JLI uses only adults in JUUL ads;
- JLI has committed tens of millions of dollars to youth education and prevention, community engagement, and independent research on youth prevention; and
- JLI uses brand slogans that target adult smokers, such as "Make the Switch" and "The Alternative for Adult Smokers."

PMTA PROCESS

10. The Tobacco Control Act requires manufacturers of "new tobacco products" to seek FDA premarket authorization for the product to be in interstate commerce. For vapor products, this generally requires manufacturers to submit a premarket tobacco product application ("PMTA") capable of showing that allowing the marketing of such product would be appropriate for the protection of the public health. The statute requires FDA, when reviewing a PMTA, to evaluate "the risks and benefits to the population as a whole," after taking into account (i) "the increased or decreased likelihood that existing users of tobacco products will stop using such products" and (ii) "the increased or decreased likelihood that those who do not use tobacco products will start using such products." 21 U.S.C. § 387j(c)(4). This standard is not further defined in the statute.

11. In 2016, FDA released a guidance document, in draft form, regarding PMTAs for ENDS products. FDA, Draft Guidance for Industry, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (May 2016) ("Draft PMTA Guidance"). The draft guidance set forth FDA's proposed recommendations regarding the contents of an application. When FDA issues final guidance, it describes "the agency's interpretation of or policy on a regulatory issue." 21 CFR § 10.115(b). Because FDA guidance represents the agency's views,

"FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence." *Id.* § 10.115(d)(3). Yesterday (June 11, 2019), FDA issued its Final PMTA Guidance for ENDS products, which replaces the Draft Guidance. FDA, Guidance for Industry, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (June 11, 2019), available at http://bit.ly/2XFfWdy ("Final PMTA Guidance"). It will take time for JLI to review and carefully analyze the Final Guidance (which is 52 single-spaced pages), including a comparison to the Draft Guidance in order to appreciate fully what has changed, what still is missing, and how the Final Guidance will affect the work JLI has been doing so far to prepare PMTAs. In the short amount of time the Final Guidance has been available, our review has identified a number of areas in which FDA will need to provide further information—through formal guidance, FDA meetings, public meetings, or otherwise—in order for JLI to complete and submit PMTAs. The Final Guidance describes an exacting and time-consuming process that may still take years to complete.

12. As detailed in the Final PMTA Guidance, any PMTA should contain a comprehensive assessment of each product that includes, among other things, manufacturing methods and standards, clinical and non-clinical studies, human health surveys, and a population health model. The Final Guidance confirms that manufacturers are encouraged to include "detailed technical information and analysis concerning" the product's manufacturing facilities. Final PMTA Guidance at 25. FDA also continues to recommend in its new Final PMTA Guidance validation and accreditation to ensure that a company manufactures a consistent product over time and meets the specifications listed in the application. *Id.* at 26, 30-31. The Final PMTA Guidance, like the Draft Guidance, states that FDA will provide "tobacco product manufacturing practices, which will be set forth in a future rulemaking," to help manufacturers

satisfy various criteria. *Id.* at 11. FDA has not stated when it expects to complete the rulemaking that sets forth these recommended tobacco product manufacturing practices. It appears from the Final Guidance, though, that FDA may apply future requirements that result from such rulemaking to a PMTA that is begun before, but submitted after, the rulemaking is completed. *Id.* at 11 n.18.

13. FDA also recommends that manufacturers undertake non-clinical studies. *Id.* at 31. Non-clinical studies include, for example, *in vitro* (outside of a living organism, such as in a culture dish) studies that test cytotoxicity (whether the components are toxic to cells) and genotoxicity (whether the components affect genetic material). Final PMTA Guidance at 34-35. The Final PMTA Guidance also refers to *in vivo* (inside a living organism, such as a mouse) studies to determine toxicity levels. *Id*. at 35. These tests, which FDA traditionally expects for non-tobacco products, should be performed by accredited laboratories, which is usually accomplished by hiring a third-party laboratory inspected and approved by FDA.

14. The Final PMTA Guidance confirms that the manufacturer must include in its application "a full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation" of the product. Final PMTA Guidance at 26. "FDA interprets this requirement" from the Tobacco Control Act "to mean that [an applicant] should provide a complete list of uniquely identified components, ingredients, and additives by quantity in the new product, as well as the applicable specifications and a description of the intended function for each." *Id.* The new Final Guidance also recommends that any testing "reflect the range of operating conditions," such as different temperatures and settings, as well as different "use patterns (e.g., intense and non-intense use conditions) within which consumers are likely to use" the product, and the "types of products that consumers are likely to use in conjunction with"

applicant's products. *Id.* at 27-28. The practical effect is that manufacturers will need to test the product's components under a wide range of use and operating condition assumptions, not only at the time that the product is created, but also after 3, 6, 9, and 12 months to determine whether the product's characteristics (such as their chemical composition) are stable or, instead, change over time.

15. FDA's Final Guidance also states that when a product "has not yet been sufficiently reviewed, new nonclinical and clinical studies may be necessary." Final PMTA Guidance at 46. FDA says it does not expect "long-term" clinical or non-clinical studies, where "long-term" is defined as lasting six months or longer, to be included in PMTAs. *Id.* at 13, 31, 37. But the Final Guidance further states: "To evaluate the acute and chronic health effects associated with the product, FDA recommends including studies, other scientific evidence, or both, that identify biomarkers of exposure, biomarkers of harm, and health outcome measurements or endpoints." *Id.* at 37, 40. In a section about "[h]ealth outcomes" FDA recommends data measuring changes to "heart rate and blood pressure" as well as longer-term effects such as "changes in lung, cardiac, and metabolic function. *Id.* at 40-41. Under the Final PMTA Guidance, FDA interprets the Tobacco Control Act to require inclusion of "a full narrative description of the way in which a consumer will use the new tobacco product, including a description of how a consumer operates the product, how the manufacturer reasonably believes a consumer could change the product characteristics, adjust the performance, or add or subtract ingredients." *Id.* at 30.

16. The Final PMTA Guidance also suggests that an evaluation of product use patterns consider, among other things, "the trends by which users consume the product over time." Final PMTA Guidance at 38-39. "FDA recommends that information and data on product use, including use in conjunction with other tobacco products, be assessed, when possible, by factors

that may be expected to influence such patterns, such as age group (including youth and young adults), sex, race, ethnicity, and education." *Id.* at 39. The Final PMTA Guidance recommends, when conducting studies, to "ensure, to the extent possible, that the study findings are generalizable to the population of U.S. users and nonusers of" the new tobacco product. *Id.* at 41. Evaluations of consumer perception should identify consumer perceptions of the product, both in an absolute sense and in comparison to other categories of tobacco products or quitting tobacco use. *Id.* at 38. Evaluations should also address the likelihood of initiation and cessation by both users and nonusers of tobacco products. *Id.*

17. As alluded to above, the Tobacco Control Act requires that the manufacturer make a "showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." 21 U.S.C. 387j(c)(2)(A). This suggests that manufacturers may need to create a population health model to assess the net-population impact of their products, including use by current and new users of tobacco products. FDA's Final PMTA Guidance does not offer insight into how to construct a proper population health model for ENDS products.

18. FDA asserts that "[t]he recommendations made in [the Final] guidance document are substantially similar to those set forth in the draft guidance issued on May 5, 2016" and that if a manufacturer has "taken measures consistent with the draft guidance, they will generally be consistent with the recommendations herein." Final PMTA Guidance at 2. Yet there are some material changes in FDA's position in the Final PMTA Guidance, including the agency's expectations on the duration and form of the studies required to support a PMTA. *Compare*, *e.g.*, Final PMTA Guidance at 14 *with* Draft PMTA Guidance at 14 (regarding the specific comparisons recommended for the assessment of health risks between a new tobacco product and marketed products); Final PMTA Guidance at 13, 31, 37 *with* Draft PMTA Guidance at 44

(regarding the agency's position on "long-term" studies in such contexts as clinical studies of biomarkers of exposure). Moreover, FDA repeatedly acknowledged that its draft guidance provided insufficient information for regulated entities to prepare a compliant PMTA. In July 2017, FDA stated that an extended compliance policy was necessary "to issue foundational rules to make the product review process more efficient, predictable, and transparent for manufacturers," "to issue regulations outlining what information the agency expects to be included in Premarket Tobacco Applications," and to "finalize guidance on how it intends to review PMTAs." *See* FDA News Release. The Commissioner at that time explained during a November 2017 speech that FDA "pushed off product application deadlines for certain of the newly deemed products in particular to allow the ENDS to continue to advance while we got in place foundational reg[ulation]s that would define how we would require product applications to come into FDA." Scott Gottlieb, Address at National Press Club, at 32:16-34 (Nov. 3, 2017).[1] He explained that FDA intended to advance regulations that "are going to lay out what that product application process is. The foundational regulations for the tobacco program were never put in place, and so we are going to take the time to put those in place." *Id.* at 33:08-20. In August 2018, FDA repeated that "foundational proposed rules" were needed "regarding the basic 'rules of the road,' especially when it comes to what's expected in premarket applications." FDA, *Advancing Tobacco Regulation to Protect Children and Families: Updates & New Initiatives from the FDA on the Anniversary of the Tobacco Control Act & FDA's Comprehensive Plan for Nicotine* (Aug. 2, 2018).

[1] *Available at* https://www.c-span.org/video/?436197-1/fda-commissioner-scott-gottlieb-addresses-national-press-club

19. The new deadlines that FDA set in August 2017 for submitting a PMTA have significantly affected JLI's planning for various studies and other work that the Company is performing, and will be performing, for use in connection with PMTAs. In order to prepare a high-quality PMTA – one that contains the quantity and quality of information most helpful to FDA's review process – the durations of the studies and other work that the Company is performing, and will be performing, were chosen in line with having the application completed and submitted by August 2022 (the date set forth in the August 2017 guidance for ENDS products). For example, as explained more below, the Company's human health surveys and nonclinical stability testing were designed to fit within a timetable under which the application would be submitted in August 2022 or earlier.

20. The brief filed by Plaintiffs on May 29, 2019, states that no further PMTA guidance was needed from FDA, but FDA's subsequent release of Final Guidance, which differs from the Draft Guidance, shows otherwise. Plaintiffs' brief gives the example of products manufactured for the IQOS Tobacco Heating System that recently received an FDA marketing order based on a PMTA. Pl's Opening Br. On Remedies, D.E. 78, at 10-12 & n.11. The IQOS Tobacco Heating System products are not ENDS products. Instead, as the FDA release cited in footnote 11 of Plaintiffs' brief describes them, they are part of a device that heats tobacco-filled sticks wrapped in paper to generate a nicotine-containing aerosol. *See* News Release, FDA, FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway (Apr. 30, 2019), *available at* https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway. Because of this composition, IQOS products "meet the definition of a cigarette in the Federal Food, Drug and Cosmetic Act." *Id.* The manufacturer of the IQOS products did not need guidance from

FDA for PMTAs for ENDS products, because they are not ENDS products. Moreover, it took FDA more than two years to complete its review of the application for the IQOS products. FDA announced its decision on April 30, 2019. Although, as just noted, FDA review did not involve an ENDS product, FDA made a number of statements in connection with issuing its IQOS marketing order that JLI is considering in an effort to understand how FDA might approach its review of PMTAs for ENDS products. These statements are apart from, and in addition to, the new Final Guidance.

JLI'S PMTA EFFORTS BEFORE THE RELEASE OF FINAL GUIDANCE

21. Notwithstanding a lack of finalized PMTA guidance for ENDS products before yesterday, JLI had already been at work on the necessary studies, and had gathered the required information, to the extent possible. To that end, JLI has dedicated 87 full-time employees to conducting the work necessary to, and to preparing, its PMTAs. The number of employees working on the PMTA process is expected to grow to more than 150 by the end of this year. JLI has already dedicated more than $50 million to preparing the applications, and it plans to spend a total of more than $125 million by the end of 2019. The absence of sufficient information from FDA on what specifically those applications must include has caused JLI to be conservative in its preparations in order to guard against FDA penalizing it for a lack of thoroughness. This necessarily means that progress has been slower, and will take longer, than if JLI had more specific instructions.

Meetings with FDA for Information on Survey and Test Design

22. In an effort to address the issues and questions left unresolved by the Draft PMTA Guidance, JLI availed itself of an FDA process for submitting questions about the preparation and review of PMTAs for ENDS products. For example, JLI used the feedback at one of the

earlier meetings, in January 2018, to help inform its understanding of FDA's expectations for its PMTA.

23. Further meetings have been necessary. FDA's process for requesting, planning, participating in, and receiving feedback following such meetings is involved. For example, another meeting with FDA occurred in February 2019. A total of four months passed between the date JLI requested the meeting (in November 2018) and FDA's written feedback following the meeting. Before JLI could attend the meeting it needed to submit, at least 45 days before the meeting date, a detailed "briefing document," known as a Meeting Information Package for Premarket Tobacco Product Application. The document, 29 pages plus attachments, contained required product information and a list of 13 detailed, multi-part questions for the agency. JLI's stated purpose for this meeting was to receive FDA feedback on the specific questions it had about preparing JLI's PMTA submission.

24. JLI received written feedback from FDA in March 2019. That feedback was important to JLI on a number of fundamental issues. For example, FDA responded to questions with factors and approaches that JLI should consider in determining how many permutations of product flavors and nicotine concentrations it should subject to a number of different types of clinical, nonclinical, and analytical chemistry testing. FDA also suggested that, in identifying the physical characteristics of each e-liquid subject to the PMTA, JLI should add at least five metrics to the list that was proposed by JLI. As another example, FDA advised JLI that, before undertaking a particular type of toxicology study, it should request a follow-up meeting with the agency to discuss specific design parameters to be incorporated into such a study. FDA also referenced its May 2016 draft PMTA guidance, and explained that, when finalized, it would represent the Agency's current thinking on this issue.

25. On another topic at the February 2019 meeting, FDA stated that, while it does not have specific requirements governing the types of experimental models and toxicity endpoints to be measured in a PMTA for tobacco products, JLI should consider a number of specific things to include in the PMTA relevant to those tests, and FDA identified four non-FDA guidance documents that may be useful. FDA also provided responses on important questions about how to determine, under the Draft PMTA Guidance at the time, when "batches" used in sampling are "different," and what constitutes a "replicate" for each batch. This information was needed to satisfy the proposed recommendation in the Draft PMTA Guidance that data sets span "a minimum of three different batches with a minimum of ten replicates per batch, with date and time sampling points." Draft PMTA Guidance at 24; *see also* Final PMTA Guidance at 25-26 (changing the number of suggested replicates to "generally seven or more"). FDA responded by explaining, with examples, that the answers vary according to the purpose of each test. FDA also clarified that, while the sampling protocol described in the relevant section of the Draft PMTA Guidance operates as a minimum, a number of factors which it set forth at the meeting could raise or lower the numbers. FDA also suggested how to go about justifying the choice and clarified that, in the absence of FDA guidance regarding replicate and batch testing for tobacco products at this time there are multiple ways to conduct batch testing. This was all information that FDA provided for the first time in connection with the February 2019 meeting.

26. This need for meetings to gain clarification and further guidance still exists even now that Final PMTA Guidance has been published. In fact, the Final Guidance recommends requesting such a meeting in multiple circumstances. *See, e.g.*, Final PMTA Guidance at 36 (suggesting a meeting before conducting non-animal based tests); 37 (suggesting a meeting if planning to conduct any computational modeling); 13 (suggesting a meeting to discuss

alternatives to well-controlled investigations); 26 (same, specific to demonstrating appropriateness for human health); 22 (suggesting a meeting to discuss product samples before submitting them); 28 (suggesting a meeting to consult on which harmful and potentially harmful constituents (HPHC) testing is appropriate to a particular application).

Validation of Manufacturing Machines and Facilities

27. In addition to JLI meeting with FDA about its study designs and other aspects of the PMTA, the Company has taken extensive steps to validate its manufacturing lines. As explained above, FDA recommends that companies manufacture their tobacco products through validated machines (also referred to as "qualified lines"). Qualified lines are necessary so that JLI can demonstrate that the facility produces a consistent product, which is necessary to ensure that the pods it tests share the characteristics of pods that consumers use. If pods are produced on machines that do not create a consistent product, then the different samples will vary, and the results of the testing may differ between batches.

28. For other (*i.e.*, non-tobacco) products that FDA regulates, the agency has published "good manufacturing practice" requirements that inform manufacturers of the Agency's view about how to create qualified lines and ensure consistent and quality-controlled product manufacturing. As noted above, FDA stated in its Draft PMTA Guidance document that it will set forth tobacco product manufacturing practice requirements for ENDS in a future rulemaking. *See* Draft PMTA Guidance at 12. In November 2017, FDA requested comments on "updated recommendations for regulations on good manufacturing practice for [ENDS]," *see* 82 Fed. Reg. 55,613, 55,613 (Nov. 22, 2017), but it has yet to initiate a rulemaking. Furthermore, because ENDS are a new product, there are no readily identifiable standards for manufacturing or production. JLI therefore does not know the agency's view about what is necessary to create a

qualified line. JLI expected that the recently released Final Guidance would include recommendations on product manufacturing to support a PMTA, but the Final Guidance states that "tobacco product manufacturing practices . . . will be set forth in a future rulemaking." Final PMTA Guidance at 11. Thus, no discernible clarity on manufacturing requirements will be known until FDA finalizes that rulemaking.

29. To fill this gap, JLI has looked at how manufacturers in other areas regulated by FDA, such as the pharmaceutical and medical device industries, have set up their manufacturing process. JLI also evaluated whether its manufacturing procedures comport with what other ENDS manufacturers are doing, and based on a "best guess" about what FDA will want. Due to the lack of clarity from FDA, however, JLI has been forced to take extra precautions that have delayed qualifying the lines.

30. In addition to manufacturing facilities, JLI needs to establish controls over supplier quality systems and product specifications to verify the raw materials and facilities of suppliers, because supply variations could lead to an inconsistent product used in the PMTA process.

31. Despite the lack of final guidance on the topic, JLI went ahead with validating its facilities and qualifying its lines, using its best estimate of what FDA will require. This was a time-intensive process, still under way across the entire supply chain base, with specific lines used to manufacture PMTA test samples to be completed later this month (June 2019). In choosing when and how to qualify its lines, JLI relied on FDA's extended compliance policy to ensure that JLI could comply with the August 2022 deadline.

JLI's Extensive Nonclinical Studies

32. JLI has also designed non-clinical studies to gather required data on the products' chemical attributes and components. Designing an effective study is a labor intensive and

challenging process that frequently requires time consuming back-and-forth with FDA. For example, as explained above, JLI added to the attributes it tests after FDA recommended adding to the list during the February 2019 meeting. The proper definition of a "different batch," also clarified at the February 2019 meeting, was needed before JLI could begin some of the required nonclinical testing.

33. As another example, JLI has been in dialogue with FDA over the proper inhalation profile for its toxicological studies. An inhalation profile measures the length of inhalation, how long the vapor is held, and the volume of vapor. FDA has not informed regulated entities what inhalation profile should be used during testing. JLI originally proposed to FDA that it use a standard puff – one representative of how consumers use the product. After extensive communication, FDA recommended using a different inhalation profile. Again, determining the proper inhalation profile is a prerequisite to conducting certain nonclinical tests, yet even the Final PMTA Guidance does not provide concrete guidance on this foundational point.

34. JLI's nonclinical testing has been hampered by the lack of concrete guidance in other ways as well. For most products that FDA regulates, the product formulations and test methods are well established. The pharmaceutical industry, for example, has international standards that inform regulated industries how to perform certain tests, and how to interpret those test results. Similar standards do not exist in the ENDS industry. There is no consensus about how to set up sample units, what tests to use to measure chemical components, or how to interpret the results. Furthermore, because test results may vary depending on the test method used, the absence of standardized methods makes it difficult to compare products. Although JLI is not waiting before it conducts nonclinical testing, JLI expected that the Final PMTA Guidance would include standardized testing methods, but it does not. In addition, the Final Guidance recommends

considering a list of more than 30 constituents or chemicals in the analysis of potential health risks, with a dozen added to the list that appears in the Draft Guidance. *Compare* Final PMTA Guidance at 28-29 *with* Draft PMTA Guidance at 26-27. The Final Guidance also states that this list is only FDA's "current thinking" on which constituents or chemicals to consider. Final PMTA Guidance at 28 n.35. "FDA intends to establish a revised list of harmful and potentially harmful constituents (HPHCs) that include HPHCs in ENDS products and publish it in the *Federal Register*." *Id.* The Final Guidance gives no expected publication date.

35. Another factor that affects the timing to complete nonclinical testing is the availability of space at accredited laboratories. Qualified laboratory space is severely limited, however, both because relatively few accredited laboratories perform work on ENDS products and because manufacturers are competing for the limited space.

36. Notwithstanding these challenges, and even before receiving the Final PMTA Guidance, JLI has (1) set up testing parameters that it believes FDA will accept, (2) arranged for the delivery of product from qualified lines, and (3) secured laboratory space.

37. These efforts have been made in reliance on the timeline the FDA announced in 2017. The tests of other remaining work will still take a significant amount of time, and there are serious limitations on shortening the process. For example, one critical component of a PMTA is stability testing. Stability testing is akin to determining a use-by date for groceries. JLI must test whether and how the product changes over various time periods (3, 6, and 12 months, for example) and under various conditions (such as various temperatures or exposure to light). By definition, these tests take time. The only way to determine, for example, how its product changes over a one-year period is to test it a year after it was manufactured on a qualified line.

Furthermore, neither the Draft nor the Final PMTA Guidance explains whether the stability testing should account for 6 months, 12 months, or some other duration.

JLI's Clinical Studies

38. JLI is already conducting clinical, human-based studies in support of its PMTA. Five clinical studies that it began in April 2018 concluded in February 2019.

39. The clinical studies that JLI has conducted to date are helpful for test-design purposes, and will assist in planning and carrying out studies for use in the PMTA. (These concluded trials pre-dated the existence of a qualified line.)

40. Similar to the process for nonclinical studies, JLI has met with FDA to attempt to ascertain whether its planned clinical studies would comport with FDA's expectations. During those meetings, FDA has told JLI that it expects certain types of clinical studies that do not appear in the Draft PMTA Guidance and that JLI did not have reason to believe were necessary for a PMTA.

41. For example, during the meeting process FDA requested clinical research on "third-hand" exposure. (First-hand exposure is when a consumer uses the product directly; second-hand exposure is similar to the phenomenon of second-hand smoke for combustible tobacco products; and third-hand exposure refers to vapor that a non-user might come into contact with after it condenses on a surface). Neither the Draft PMTA Guidance nor the Final Guidance mentions this type of exposure. To JLI's knowledge, there also is no research in the literature about third-hand exposure testing and no other party has ever submitted research on third-hand exposure as part of a PMTA. Based on FDA's statements outside of the formal written guidance process, JLI plans to design and conduct third-hand exposure clinical trials.

JLI's Long-Term Adult Survey

42. JLI is also engaged in surveys to determine how adults use its products, as well as their use of other tobacco products. Among other things, these surveys cover frequency of use of JLI's products, use concurrently with other tobacco products, use as an alternative to other tobacco products, and changes in usage over time.

43. JLI began designing these surveys more than a year ago. Due to the dearth of experience conducting significant behavioral research on ENDS products, these surveys needed to be designed with minimal guidance from past practice. That lack of experience has slowed the entire process down, from engaging research firms that could conduct preliminary testing and design a proper survey, to obtaining institutional review board approval, to implementing the survey.

44. Because a well-designed survey must be representative of the United States population, the sample size must be large. These surveys, which began in May 2018, currently have roughly 70,000 participants who have signed up over time.

45. In addition to needing a proper methodology and a large sample size, these surveys must take place over a sufficient length of time. Especially when evaluating behavior relating to an addiction, results—such as whether a person has switched from combustible cigarettes to ENDS products—are more reliable the further out they are measured. JLI therefore intends to follow survey participants for at least one year to determine rates of cigarette abstention and regression. Because survey participants have enrolled over time, results will continue to come in over the course of this year. As discussed below, there will be more to do after the survey data are compiled.

JLI's Youth Surveys

46. The PMTA process requires information about youth usage and perceptions. JLI has therefore also commissioned youth surveys. In addition to questions about usage, the surveys attempt to determine prevalence, patterns of use, and perceptions regarding the addictiveness of ENDS and other tobacco products. The surveys are conducted by an independent provider.

47. Youth surveys differ from adult surveys in important ways and raise special challenges. JLI did not want to commission a youth study until it could meet with FDA to ensure that any youth surveys were conducted in a manner that FDA would approve. Before the youth surveys were started, JLI therefore met with FDA in August 2018. FDA provided feedback in October 2018, and the first round of surveys was launched the following month.

48. For ethical reasons, dual consent is required for these surveys—consent of the participant and a parent. The logistics of a youth survey also make the process more time-consuming, in part because of the need to find a survey provider experienced in and capable of locating a representative sampling of participants.

49. The youth surveys that JLI commissioned are cross-sectional and conducted at six-month intervals. Each survey is conducted with a new cohort of participants, and the answers are compared to the results of previous surveys.

50. Although cross-sectional youth surveys will have been conducted by the end of 2019, JLI needs additional information to support a PMTA. Youth perceptions of ENDS products are highly dynamic, in part because of the recent increased emphasis on initiatives to prevent usage by youth, including through educational outreach. This makes the results of only two or three surveys (for example) more difficult to use as a predictive device.

JLI's Efforts To Create A Population Health Model

51. JLI is also developing a population health model. Such a model is important in preparing the PMTA because, as noted earlier, the standard for approving an application is whether there is a showing that permitting the product to be marketed would be appropriate for the protection of the public health.

52. In contrast with combustible tobacco products, because ENDS products are relatively new JLI has not been able to look to prior studies to develop a population health model. Creating a public health model requires balancing benefits and costs without any clear guidance on how either should be measured. For example, by statute the model must weigh the cost of a person who had never previously used tobacco products becoming addicted to ENDS against the benefit of a cigarette smoker transitioning to non-combustible products. *See* 21 U.S.C. § 387j(c)(4). There is no established, accepted model informing regulated parties how to measure and compare those or other possible effects.

53. Importantly, even with the issuance of Final PMTA Guidance, FDA has not provided guidance or insight into how it intends to construct or evaluate a population model that accounts for the relevant costs and benefits of ENDS products. This is a foundational component of the PMTA, yet regulated entities have little insight into how FDA intends to evaluate whether a product is appropriate for the protection of the public health.

54. Even if FDA were to inform regulated entities about how it plans to evaluate a population health model, a reasonably situated applicant like JLI could not complete the model until its non-clinical, clinical, and survey results are complete.

55. In sum, JLI has already devoted substantial resources to the preparation of a PMTA. It embarked on the process without clear guidance from FDA, as the industry waited for the

Agency to finalize a draft from 2016. FDA has finally issued its Final PMTA Guidance, but it leaves important questions unanswered and amends recommendations made in the Draft PMTA Guidance. Even with Final Guidance, a number of the remaining steps for completing a PMTA will require time to conduct and complete studies and other work. By their nature, these studies and other analyses will take time. In addition, under FDA's submission rules a manufacturer must submit a "fileable" application. This means that if FDA decides the application should have contained additional elements or information, it can reject (decline to file) the application. With all of this in mind, JLI has designed studies and other work in reliance on FDA's guidance stating that JLI has until August 2022 to complete its PMTA. Although JLI will endeavor to meet an earlier deadline, the many factors set forth above will limit the ability of JLI to submit an application more quickly.

I declare under penalty of perjury that the foregoing is true and correct. Executed on June 12, 2019 in San Francisco, CA.

Joanna D. Engelke

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