Juul Labs®

Jose Luis Murillo
Chief Regulatory Officer

July 29, 2022

By CTP Portal and Email

Brian King, Ph.D., M.P.H.
Director, Center for Tobacco Products
Food and Drug Administration
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Request for 21 C.F.R. § 10.75 Supervisory Review of the Marketing Denial Order

Dear Director King:

Juul Labs, Inc. (JLI) requests supervisory review of the marketing denial order (MDO) issued by the Food and Drug Administration (FDA or the Agency) on June 23, 2022, for premarket tobacco product applications (PMTAs) covering currently marketed JUUL products and a new device with age-verification technology (collectively, the JUUL System or JUUL products).[1] JLI makes this request pursuant to 21 C.F.R. § 10.75, which provides that an interested person outside the agency may request internal agency review of a decision through the established agency channels of supervision or review.

JLI understands that your office has initiated its own § 10.75 supervisory review for the MDO as of July 5, 2022, based on "scientific issues unique to this application that warrant additional review."[2] To ensure a complete, fair, and efficient review, JLI requests that its § 10.75 request be consolidated with your office's review and that no decision be rendered until JLI's § 10.75 request has been fully considered.

[1] The submission tracking numbers (STNs) for these products are PM0000864 (Menthol 3.0%), PM0000872 (Menthol 5.0%), PM0000874 (Virginia Tobacco 3.0%), PM0000876 (Virginia Tobacco 5.0%), PM0000878 (JUUL Device), and PM0000879 (JUUL Locked Device).

[2] FDA Correspondence to JLI Regarding "June 23, 2022 Marketing Denial Order Related to Certain Products Under Premarket Tobacco Product Application ('PMTA') PM0000864, PM0000872, PM0000874 PM0000876, PM0000878, PM0000879; *Juul Labs, Inc. v. FDA*, 22-1123 (D.C. Cir.)" (July 5, 2022).

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I. INTRODUCTION AND REQUESTED RELIEF

The statute: In June 2009, Congress enacted the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), providing FDA jurisdiction and comprehensive authority over the manufacture, marketing, and distribution of tobacco products.[3] Central to this statutory authority was to enable the Agency to reduce tobacco-related death and disease in the United States, which stems primarily from combustible cigarettes — the most lethal consumer product ever marketed. Part of FDA's regulatory mandate was to "provide new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products."[4] That is, advance tobacco harm reduction through product innovation and regulation.

The PMTA process enables the Agency to do just that by evaluating new tobacco products under a rigorous, science- and evidence-based review to determine whether they are "appropriate for the protection of public health" (APPH). While the burden is on the applicant to provide "well-controlled investigations," "valid scientific evidence," and other relevant information to support the marketing of its products, FDA bears the statutory responsibility to undertake a complete and holistic review of the information, data, and analysis in a PMTA.[5]

Novel, well-studied noncombustible products, including electronic nicotine delivery systems (ENDS), should benefit from this regulatory approach to promote public health. Because it is the combustion — the burning of tobacco and inhalation of smoke and thousands of toxicants that come with it — that kills. While nicotine is addictive and can be harmful, it is not directly responsible for tobacco-caused cancer, lung disease, and heart disease.[6] By providing adult smokers (who otherwise have not or will not quit) a less harmful form of nicotine delivery and moving them down the continuum of risk, unprecedented public-health gains can be made while marginalizing the combustible cigarette.

Today, the Tobacco Control Act is just over thirteen years old. And today, combustible cigarettes continue to be used by approximately 31 million Americans, result in approximately 480,000 preventable deaths each year, and comprise approximately 75%

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[3] Tobacco Control Act, 21 U.S.C. § 387 *et seq.*

[4] Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, § 3(4), 123 Stat. 1782 (2009).

[5] Tobacco Control Act, 21 U.S.C. § 387j. *see also* Administrative Procedure Act, Pub. L. 79-404, 60 Stat. 237 (1946).

[6] Gottlieb, S., & Zeller, M. (2017). A nicotine-focused framework for public health. *New England Journal of Medicine*, *377*(12), 1111–1114.

of the total tobacco market.[7] Meanwhile, FDA has authorized only forty-two "less harmful" new products (twelve distinct brands under multiple stock keeping units (SKUs)).[8] One of which is a combustible cigarette, albeit with "very low nicotine."[9] For ENDS products, like the JUUL System, the Agency has authorized just twenty-three new products (seven distinct brands under multiple SKUs).[10] This represents less than 3% of the total ENDS market.[11]

The submission: JLI submitted PMTAs for its currently marketed products and a new product (the JUUL Locked Device) with embedded age-verification technology to better restrict underage access. These PMTAs included information, data, and analysis from over 110 scientific studies across nonclinical (75+ studies), clinical (14 studies), and behavioral (21 studies) research programs to provide a comprehensive dataset on the health risk and net-population impact associated with the use of JUUL products.[12] JLI also assessed its products relative to combustible cigarettes, an FDA-authorized heated tobacco product (IQOS), and other marketed ENDS products.[13]

On health risks, among other findings, the JUUL System presented at least a 98% reduction in harmful and potentially harmful constituents (HPHCs) compared to combustible cigarettes, presented at least an 82% reduction in HPHCs compared to IQOS, and showed a reduction in biomarkers of exposure (BOE) to toxicants among adult

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[7] Cornelius, M., et al. (2022, Mar. 18). Tobacco Product Use Among Adults – United States, 2020, *Morbidity and Mortality Weekly Report, 71*, 399; Center for Disease Control. (2020, April). *Tobacco-Related Mortality*; Passport – Euromonitor International. (2021). U.S. Retail Sales. Retrieved from https://www.portal.euromonitor.com/. While combustible cigarettes comprise approximately 75% of the total tobacco market, all combustible products (including cigarettes, cigars, cigarillos, and roll-your-own tobacco) comprise approximately 85% of the total tobacco market. *See id.*

[8] FDA Premarket Tobacco Product Marketing Granted Orders, retrieved from https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders.

[9] FDA TPL Review of 22nd Century Group Inc.'s PMTAs PM0000491–PM0000492.

[10] FDA Premarket Tobacco Product Marketing Granted Orders, retrieved from https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-granted-orders.

[11] Internal analysis based on syndicated market data from Information Resources, Inc. (IRI) for tracked channels through the first quarter of 2022. Tracked channels are limited to convenience, food/grocery, and drug. Based on internal estimates for tracked and non-tracked channels, JLI believes that authorized ENDS products comprise approximately 1.0–1.5% of the ENDS market.

[12] PMTA Section B.1 Executive Summary (b-1-executive-summary.pdf) for an integrated summary of the evidence presented in JLI's PMTAs and key findings to demonstrate that marketing of the JUUL System is APPH.

[13] PMTA Section B.1 Executive Summary (b-1-executive-summary.pdf) for a full summary of the comparator product analyses.

smokers who completely switched to the JUUL System that was on par with no tobacco use at all.[14]

On net-population impact, among other findings, over 90% of JUUL users were current or former smokers and over 50% of JUUL purchasers completely switched from combustible cigarettes within twelve months.[15] For the remaining 50% that did not switch completely, over 80% reduced their cigarette consumption by 50% or more and thus significantly reduced their exposure to HPHCs and other toxicants in cigarette smoke.[16]

These lines of evidence converge on the conclusion that use of the JUUL System presents substantially less risk than combustible cigarettes for adult smokers and, based on JLI's understanding of the literature, is the most effective alternative product to get smokers off cigarettes.[17]

The process: On July 29, 2020, JLI submitted its PMTAs to FDA. During the nearly two-year review period, JLI received just one substantive request for additional information on its PMTAs in the form of a deficiency letter in March 2021 (Deficiency Letter). [18] In June 2021, JLI responded by addressing each question with additional information, data, and analysis to support the Agency's review (Deficiency Response). [19] From June 2021 until the MDO in June 2022, FDA did not raise any other questions or otherwise engage substantively with JLI.

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[14] PMTA Section H.1 Summary of the Health Risks of the Tobacco Product (h-1-health-risks-introduction.pdf) for a synthesis of the data and evidence presented in JLI's PMTAs regarding the health risks of the JUUL System, including comparative data and the known health risks of cigarette smoking.

[15] PMTA Section H.2.1 Summary of Behavioral Studies and Analyses (h-2-1-behavioral-summary.pdf) for an integrated summary of the scientific data presented in JLI's PMTAs on behavioral factors relevant to use of JUUL products. These findings were based on JLI's behavioral-research program that included more than 100,00 adults.

[16] *Id.*

[17] In the marketing authorization for NJOY Daily ENDS products, CTP-OS noted that "[e]stimates by the applicant of complete switching from cigarettes to the new products for current adult smokers at three months was 26.5%, a level higher than what is typically seen in the literature for estimates of complete switching to ENDS products." FDA TPL Review of NJOY LLC's PMTAs PM0000630-PM0000631, p. 6. JLI believes these are the highest reported switch rates for an authorized ENDS product. JLI's data show that over 50% of adult smokers completely switch from combustible cigarettes to JUUL products at twelve months.

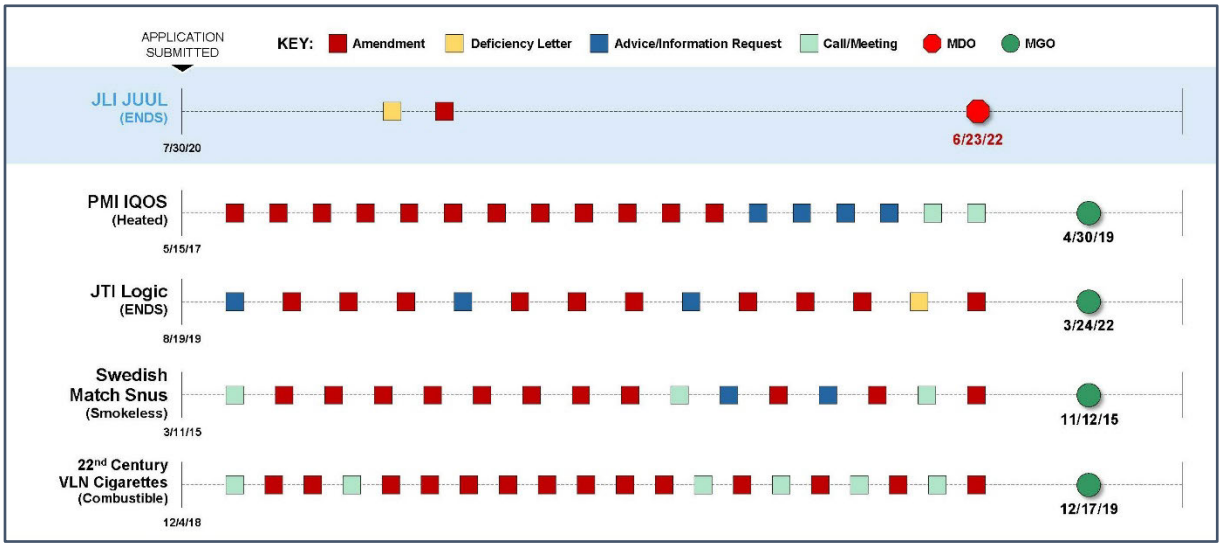
[18] FDA Deficiency Letter to JLI for PMTAs with STNs PM0000864, PM0000872, PM0000874, PM0000876, PM00000878–PM0000879.

In November 2020, CTP's Office of Compliance and Enforcement (OCE) asked JLI to verify information and data contained in the PMTAs to facilitate inspections of certain manufacturing and research sites. JLI discussed the request with OCE via a teleconference and provided a written response with additional information to facilitate the inspections of its contract manufacturers and research sites. See Section III.B for additional information on FDA's administration of JLI's PMTAs.

[19] JLI Response to Deficiency Letter for PM0000864, PM0000872, PM0000874, PM0000876, PM00000878–PM0000879.

This limited engagement is in direct contrast to the Agency's usual, iterative process that defines a full and complete review of product applications generally and how it has managed other PMTAs specifically.

Figure 1 Differences in FDA Engagement and an Iterative Review for JLI's PMTAs Compared to Other Authorized Applications[20]



For JUUL products, there was the Deficiency Letter and Deficiency Response. And then the MDO.[21]

The leak: A day before the MDO, JLI already knew of the marketing decision. But not from FDA. The decision was leaked by agency officials to the Wall Street Journal on or before June 22.[22] Based on the article, "[FDA] is preparing to order Juul Labs Inc. to take its e-cigarettes off the U.S. market, according to people familiar with the matter" and that "FDA could announce its decision as early as this week, the people said."[23] The Agency announced its decision the next day.

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[20] FDA TPL Review of U.S. Smokeless Tobacco Company LLC.'s PMTAs PM0000470–PM0000473; FDA TPL Review of Philip Morris S.A.'s PMTAs PM0000424–426, PM0000479; FDA TPL Review of Logic Technology Development LLC's PMTAs PM0000529–PM0000531, PM0000535.PD1–PM0000537, PM0000540–PM0000541; FDA TPL Review of 22ndCentury Group Inc.'s PMTAs PM0000491–PM0000492.

[21] It seems that FDA has abandoned an iterative review process during this more recent PMTA-cycle for currently marketed products. FDA has rescinded several other MDOs after overlooking critical information in the applications during this review cycle.

[22] Maloney J. (2022, June 22) FDA to Order JUUL E-Cigarettes Off U.S. Market: Agency Has Cleared Way for Rivals Reynolds American, NJOY Holdings to Keep Selling Tobacco Flavored E-Cigarettes. *Wall Street Journal*, retrieved from https://www.wsj.com/articles/fda-to-order-juul-e-cigarettes-off-u-s-market-11655904689.

[23] *Id.*

JLI has found no other instance where a decision on a pending product application within FDA was communicated to a third party, including media, before being officially issued to the applicant.

The decision: On June 23, 2022, the Agency issued the MDO for all of JLI's PMTAs.[24] The MDO provided four deficiencies that collectively formed the basis for the marketing decision and which purportedly precluded a determination of APPH for all JUUL products. The deficiencies all relate to a subset of toxicological data provided by JLI.

The MDO is flawed both substantively and procedurally.

First, the MDO's analysis for each deficiency is substantively flawed. The conclusions and supporting findings in the MDO are inconsistent with the information, data, and analysis provided in JLI's PMTAs. Each deficiency rests on an incorrect or incomplete assessment of the data.

For example, for Deficiency 1, the MDO asserted that JLI identified certain leachable constituents of potential toxicological concern in simulated e-liquid studies but did not evaluate the mainstream aerosol yields of those constituents to determine whether and at what level users could be exposed. But JLI did provide these data — over 6,000 pages of it. Through a non-targeted analysis of the JUUL System aerosol, the PMTAs showed that the leachables in question were not detected in the aerosol and thus would not pose a health risk to the user.

For Deficiency 4, the MDO asserted that JLI provided data from an in vitro Ames assay that showed that the Menthol 5.0% product is potentially mutagenic. But the MDO only arrived at this conclusion by applying the wrong study guidelines and testing criteria. Applied correctly, the assay confirms that Menthol 5.0% is not mutagenic.

Second, the MDO's "do-not-pass-go" approach tied to toxicology is inconsistent with the requirement for a complete and holistic review of PMTAs under § 910 of the Tobacco Control Act and a departure from FDA precedent and established scientific principles. By focusing on a limited and narrow subset of toxicological questions and data, the Agency did not even assess all these data let alone weigh them against more relevant biological, chemical, and clinical findings on health risk from actual use and exposure. Or it did not even consider them.

FDA, however, did consider and weigh such data for other applications. For IQOS, the Agency found that "some of the chemicals are genotoxic or cytotoxic" in the product but "these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in [combustible

[24] FDA Marketing Denial Order for JLI's PMTAs PM0000864, PM0000872, PM0000874, PM0000876, PM0000878, PM0000879; FDA. (2022, June 23). FDA Denies Authorization to Market JUUL Products. *FDA News Release*, retrieved from https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products.

cigarettes]."[25]. For Moonlight VLN Cigarettes (a combustible product), FDA found that the product's toxicological profile was "likely similar to" combustible cigarettes.[26] Not only were both products authorized through the PMTA process, but they also received authorizations as modified-risk tobacco products.[27]

It also remains unclear whether FDA assessed all substantive portions of the PMTAs and, if it did, to what extent those scientific findings on health risk and net-population impact were integrated.

In the technical project lead review (TPL Review) for the MDO, the Agency stated that "[i]n the clinical studies, significant reductions in blood and urinary BOEs indicate that exposure to carcinogens and other toxicants present in cigarette smoke were greatly reduced with exclusive use of [JUUL products] compared to [combustible-cigarette] smoking."[28] This follows and corroborates the TPL Review's assessment on HPHC yields in the aerosol and user exposure: "Toxicological evaluation of the mainstream aerosol yields of HPHCs included on the HPHC list, and other quantified chemical constituents found that levels of these compounds in [JUUL products] are not present at levels of concern."[29]

In its review of chemistry for the JUUL System, FDA found the following on HPHC exposure:

- "The aerosol HPHC yields from [JUUL products] are *much lower* than the mainstream smoke HPHC yields from the 3R4F reference cigarette, except for glycerol."[30]

[25] FDA TPL Review of Philip Morris Products S.A.'s PMTAs PM0000424–426, PM0000479, p. 42.

[26] FDA TPL Review of 22nd Century Group Inc.'s PMTAs PM0000491–PM0000492, p. 32.

[27] FDA Modified Risk Granted Order for Philip Morris Products S.A.'s MRTPAs MR0000192, MR0000133, MR0000059, MR0000060, MR0000061; FDA Modified Risk Granted Order for 22nd Century Group Inc.'s MRTPAs MR0000160, MR0000159

[28] FDA TPL Review of JLI's PMTAs (Toxicology) PM0000864, PM0000872, PM0000874, PM0000876, PM0000878, PM0000879, p. 13.

[29] *Id.* at 11.

[30] FDA 2nd Cycle Chemistry Review of JLI's PMTAs PM0000864, PM0000872, PM0000874, PM0000876, PM0000878, PM0000879, p. 15 (emphasis added). On glycerol, FDA stated that the "[h]igh level of glycerol aerosol yield in the new products is not a concern from a chemistry perspective since the level of formaldehyde and acrolein aerosol yields, common degradation products of glycerol upon heating, in the new products are much lower than those in the MSS yields of 3R4F reference cigarette." *Id.*

- "The aerosol HPHC yields from [JUUL products] are *much lower* than the aerosol HPHC yields from the IQOS heated tobacco system, except for glycerol, nicotine, 1,3-butadiene, isoprene, and nickel."[31]

- "The applicant provided 40 HPHC yields for [JUUL products] and ENDS comparison products. The aerosol HPHC yields from [JUUL products] are *mostly lower* than the ENDS comparison products . . . ."[32]

But how, if at all, were these chemical and clinical findings based on actual use and exposure assessed and balanced against the toxicological review?

How, if at all, were findings from JLI's behavioral-research program — which showed that over 50% of JUUL purchasers completely switched from combustible cigarettes within twelve months — assessed and balanced against the health risks and net-population impact associated with the use of the JUUL System and combustible cigarettes?

How, if at all, were all scientific findings beyond toxicology incorporated to do what the Tobacco Control Act requires — a complete, holistic, science- and evidence-based evaluation of the benefits and risks to the population as a whole?

These open substantive questions raise the broader question on the completeness and rigor of the Agency's review of JLI's PMTAs, particularly when viewed in comparison to other similarly-situated applicants.

The politics: Since JLI submitted its PMTAs, FDA has been under immense and unprecedented political pressure to reach a very specific decision — deny the applications and remove the products from the market. The record of statements and testimony from certain members of Congress speaks for itself:

- On March 23, 2021, a group of more than forty Members of Congress sent a letter to the Acting Commissioner specifically urging FDA to deny JLI's PMTAs.[33]

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[31] *Id.* (emphasis added). On glycerol, FDA stated that the "[h]igh level of glycerol aerosol yield in the new products is not a concern from a chemistry perspective since the level of formaldehyde and acrolein aerosol yields in the new products are lower than those of IQOS Heatsticks." *Id.* at 15. On the other constituents, the Agency similarly stated that they were "not of concern from a chemistry perspective." *Id.* at 16.

[32] *Id.* at 16 (emphasis added). FDA went on to compare differences in limited constituent yields between JUUL products and Vuse Alto, NJOY Ace, and blu PLUS+ products (i.e., the comparator ENDS products in JLI's PMTAs). *Id*. at 16–18. For these limited constituents, FDA stated that "they are much lower in comparison to those of combusted cigarettes. Therefore, they are not of concerns from a chemistry perspective." *Id.* at 18.

[33] Wasserman Schultz, D. DeGette, D. (March 23, 2021). Wasserman Schultz, DeGette Lead Congressional Call for Stronger Flavored E-cigarette Controls https://wassermanschultz.house.gov/news/documentsingle.aspx?DocumentID=2592.

- On June 23, 2021, the Oversight Subcommittee on Economic and Consumer Policy held a hearing titled "An Epidemic Continues: Youth Vaping in America." During the hearing, multiple Representatives and a Senator lobbied the Acting Commissioner to deny JLI's PMTAs:[34]

  - Representative Krishnamoorthi: "Now Juul's fate is, again, in your hands . . . Juul's marketing to children was simply unacceptable . . . Juul came in nicotine levels much higher than anything else on the market . . . Don't let any high-nicotine products on the market."[35]

  - Senator Durbin: "It is simple. Any product with a history of increasing youth use must be rejected by the Food and Drug Administration."[36]

  - Representative Bush: "[E]-cigarettes have hooked a generation of young people on nicotine. The FDA has an obligation to intervene and protect our children."[37]

  - Representative Wasserman Schultz: "To be clear, you should reject all of Juul's products, all of them, given what we know about how JUUL marketed and addicted kids to their product."[38]

- On June 29, 2021, Representative Krishnamoorthi and Senator Durbin sent a letter to the Acting Commissioner demanding that FDA review all documents that JLI had produced to the Office of the Attorney General of North Carolina "prior to ruling on a JUUL PMTA application."[39]

- On July 19, 2021, Senator Durbin tweeted that FDA "needs to finally do the right thing and take . . . JUUL off the market."[40]

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[34] An Epidemic Continues: Youth Vaping in America: Hearing Before the Subcomm. on Econ. and Consumer Pol'y of the H. Comm. on Oversight and Reform, 117th Cong. (2021).

[35] *Id.* (statement of Representative Krishnamoorthi).

[36] *Id.* (statement of Senator Durbin).

[37] *Id.* (statement of Representative Bush).

[38] *Id.* (statement of Representative Wasserman Schultz).

[39] Krishnamoorthi, R., Durbin, R. (2021, June 29). Chairman Krishnamoorthi & Senator Durbin Urge FDA To Review New and Disturbing Evidence From North Carolina That JUUL Deliberately Marketed High-Nicotine Products to American Youth. *Press Release*, retrieved from https://krishnamoorthi.house.gov/media/press-releases/chairman-krishnamoorthi-senator-durbin-urge-fda-review-new-and-disturbing.

[40] Senator Dick Durbin [@senatordurbin]. (2021, July 19). A big decision indeed. After dangerous delays, the @US_FDA needs to finally do the right thing and take addictive, kid-friendly products like JUUL off

- On March 9, 2022, a group of fifteen Senators wrote to the Commissioner describing the JUUL System as a "flavored" ENDS product and demanding that the Agency rescind its policy of enforcement discretion and remove JUUL products from the market.[41]

- On May 20, 2022, a group of eleven Senators wrote to the Commissioner again demanding that the Agency rescind its policy of enforcement discretion and remove JUUL products from the market.[42]

- On June 22, 2022, Senator Durbin issued a public statement asserting that the Commissioner should either deny JLI's PMTAs or "step aside."[43]

The next day, FDA issued the MDO for JLI's PMTAs.

On the same day, Representative Krishnamoorthi issued a celebratory press release lauding the MDO and his influence over the Agency: "[L]ast year I called on the FDA to deny Juul's PMTA applications for both kid-friendly flavored products and its especially addictive high-nicotine products because of the risk they pose to young people. Today, I applaud the FDA for following science and for clearing the market of the Juul products . . . ."[44]

The day after that, on June 24, Representative Krishnamoorthi and staffers working with Senator Durbin joined a private teleconference hosted by Parents Against Vaping e-cigarettes (PAVe). During that call, Representative Krishnamoorthi described "a long conversation with the FDA Commissioner" about JUUL products and suggested that this had motivated FDA to "finally . . . stop JUUL."[45]

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the market. [Tweet]. *Twitter*, retrieved from https://twitter.com/SenatorDurbin/status/1417233543936233476.

[41] Durbin, R. et al. (2022, Mar. 9). Senators to FDA Commissioner: Agency Is Six Months Past Court-Ordered Deadline to Regulate E-Cigarettes. https://www.durbin.senate.gov/imo/media/doc/Senate%20FDA%20Ltr_PMTA%206mo%20Court%20Deadline_Final.pdf.

[42] Durbin, R. et al. (2022, May 20). Senators To FDA Commissioner: Remove All Unauthorized E-Cigarettes From Market Immediately. Retrieved from https://www.durbin.senate.gov/imo/media/doc/Senate%20FDA%20Letter_E-Cig%20Delay_Enforcement%20Discretion.pdf.

[43] Durbin, R. (2022, June 22). Durbin Investigation Finds More Than 750,000 Kids Have Picked Up Vaping Since FDA's Missed Deadline to Regulate E-Cigarettes. *Press Release,* retrieved from https://www.durbin.senate.gov/newsroom/press-releases/durbin-investigation-finds-more-than-750000-kids-have-picked-up-vaping-since-fdas-missed-deadline-to-regulate-e-cigarettes.

[44] Krishnamoorthi, R. (2022, June 23). Chairman Krishnamoorthi Applauds FDA Decision to Ban All JUUL Products. *Press Release*, retrieved from https://oversight.house.gov/news/press-releases/chairman-krishnamoorthi-applauds-fda-decision-to-ban-all-juul-products.

[45] Redmond, H. (2022, July 11) The FDA's Unconscionable Campaign to Destroy Juul. *Filter Magazine,* retrieved from https://filtermag.org/fda-destroy-juul.

The decision-making process for a PMTA is, by law, required to be based on a fair and impartial assessment of the science and evidence. But these attempts of political influence and interference have the potential to undermine that process and, as a result, call into question the integrity of the administrative decision.

To mitigate these concerns, ensure transparency, and support an objective review on the science, JLI believes that referral to a scientific advisory panel is appropriate. Therefore, JLI requests, pursuant to 21 C.F.R. § 10.75(b)(2), that this matter, the underlying scientific controversy, and its PMTAs also be reviewed by the Tobacco Products Scientific Advisory Committee (TPSAC).

The appeal: There are two. First, as of July 5, 2022, the Agency initiated its own § 10.75 supervisory review of JLI's PMTAs. Citing to JLI's briefing materials in the Court of Appeals for the D.C. Circuit, the Agency "determined that there are scientific issues unique to this application that warrant additional review."[46] Presumably, based on those briefing materials, the fact that FDA failed to consider 6,000 pages of mainstream aerosol data despite finding that it needed such data to assess certain toxicological risks is one of the "scientific issues."[47] The Agency's own-initiated § 10.75 should warrant a rescission of the MDOs and re-review of JLI's PMTAs.

JLI also is requesting supervisory review of the Center for Tobacco Products Office of Science's (CTP-OS) MDO for the PMTAs.

In the sections that follow, JLI provides information and analysis based on its PMTAs to address the MDO and each deficiency that served as a basis for denial. Generally, the marketing decision:

- Failed to consider data provided in the PMTAs;
- Considered such data in the PMTAs inadequately;
- Misinterpreted data provided in the PMTAs;
- Applied data from the PMTAs incorrectly; and

[46] *See* FDA Correspondence to JLI Regarding "June 23, 2022 Marketing Denial Order Related to Certain Products Under Premarket Tobacco Product Application ('PMTA') PM0000864, PM0000872, PM0000874 PM0000876, PM0000878, PM0000879; *Juul Labs, Inc. v. FDA*, 22-1123 (D.C. Cir.)" (July 5, 2022).

[47] Petitioner Juul Labs, Inc.'s Corrected Redacted Emergency Motion for Stay Pending Review, Juul Labs, Inc. v. U.S. Food and Drug Administration, No. 22-1123 (D.C. Cir.) ("FDA instead rejected JLI's applications for deeply flawed reasons. In more than two dozen places, FDA claimed JLI did not provide aerosol data measuring the toxicological impact of four chemicals. But JLI provide that data — 6,000 pages of it. Had FDA done a more thorough review (like it did for other applicants), it would have seen data showing that those chemicals are not observable in the aerosol that JUUL users inhale.").

- Deviated from established policy, procedure, or process when reviewing the PMTAs.

Each deficiency in the MDO is subject to one or more of these errors that undercuts the MDO's conclusions and supporting findings. Based on the information in the administrative file, the deficiencies identified in the MDO, individually and collectively, should be set aside so that FDA can complete a full and fair substantive review of the PMTAs.

Accordingly, as supported by this § 10.75 request, JLI seeks the following:

- Supervisory review of the MDO and related deficiencies based on the complete administrative file;

- Consolidation of its § 10.75 request for supervisory review with FDA's own-initiated § 10.75 review;

- Referral of this matter, the underlying scientific controversy, and JLI's PMTAs to TPSAC;

- Rescission of the MDO and placement of JLI's PMTAs back into substantive review for FDA to complete its statutorily-required assessment and determine whether the JUUL System is APPH; and

- A full and fair opportunity to respond to any additional deficiencies, beyond those in the MDO, that FDA may identify or has identified in its review of JLI's PMTAs, as is customary in the review of product applications and necessary to assure that regulatory decision-making best protects public health.

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JLI also reserves the right to amend or supplement this § 10.75 request based on additional information it may obtain under the Freedom of Information Act (FOIA). On June 23, JLI requested certain CTP review documents relating to its PMTAs. These included "a copy of the technical project lead review (TPL) and any related documents for the mid-cycle review" and "[a] copy of the disciplinary review documents."[48] That is, documents that reflect CTP-OS's various findings, analyses, and conclusions relating to JLI's PMTAs which likely are relevant to CTP-OS's review of the PMTAs, the MDO, and this § 10.75 request.

[48] In email correspondence on July 1, JLI clarified that "related documents for the mid-cycle review" meant "all documents pertaining to both the first and second cycle scientific reviews, including all disciplinary review notes." FDA Correspondence to JLI Regarding "FOIA Requests 2022-4621 and 2022-4625 Partial Response" (July 8, 2022).

On July 8, CTP's FOIA Office provided a partial response which included the TPL Review and 1st and 2nd Cycle Toxicology Reviews. On July 21, CTP's FOIA Office provided a final response. It produced the 1st and 2nd Cycle Chemistry and Environmental Science Reviews but withheld the remaining documents (177 pages) under the "deliberative-process privilege."[49] In asserting the deliberative-process privilege, CTP's FOIA Office stated that "the scientific disciplinary reviews contain the thinking of CTP's scientists deliberating as part of the review of the PMTAs" and they would not be disclosed.[50] JLI believes that CTP-OS finished its deliberations on the PMTAs when it issued the MDO on June 23.[51]

JLI has appealed this decision through the administrative process. To the extent JLI receives additional CTP review documents relating to its PMTAs and such information is material to this § 10.75 request, JLI reserves the right to amend or supplement this submission.

II. EXECUTIVE SUMMARY

The MDO incorrectly and incompletely concluded that, based on a limited and narrow toxicology review, CTP-OS was precluded from determining that the marketing of the JUUL System is APPH. For each alleged deficiency, the MDO erred by overlooking key information, incorrectly analyzing the information it did consider, and inequitably holding the PMTAs to a new and different standard compared to similarly-situated applicants. The alleged deficiencies, if anything, were limitations that warranted additional engagement and review and could have been reconciled with information already provided in the PMTAs. Far from justifying a denial, the marketing decision reflected an analysis that failed to conduct a complete, holistic, and fair review of the body of science and evidence in JLI's PMTAs.

JUUL products are among the most studied ENDS products on the market. JLI's PMTAs included information, data, and analysis from more than 110 JLI-commissioned scientific studies and a wealth of relevant third-party scientific literature. The body of evidence runs the gamut from targeted and non-targeted chemical analyses to randomized,

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[49] *See* FDA Correspondence to JLI Regarding "FOIA Requests 2022-4621 and 2022-4625 Final Response (July 21, 2022).

[50] *Id.*

[51] In providing the 1st and 2nd Cycle Environmental Science Reviews and Chemistry Reviews, CTP's FOIA Office stated that they were "reviewed and considered for the TPL Review (Toxicology)" and "the Toxicology Reviews relied in part on analysis in the Chemistry Reviews." As for the other review documents, "[t]he TPL Review (Toxicology) did not reach other aspects of the applications beyond the potential toxicological health risks of the new products." *Id.*

The TPL Review said otherwise. As part of the toxicology review, CTP-OS at least reviewed information on "device functional parameters (i.e., coil temperature, power delivery and maximum puff duration)" and JLI's clinical studies. FDA TPL Review of JLI's PMTAs (Toxicology), p. 20, 27, 28, 33, 35, and 40 (for references to the device) and p. 12–13 (for analysis of the clinical studies).

controlled clinical studies. In line with JLI's comprehensive, stepwise approach to assess the health risk associated with the actual use of its products, all these data have a role to play in evaluating the products' toxicological profile.

The MDO nonetheless focused on limited issues within a narrow subset of toxicological data and minimized the fundamental premise underlying a comprehensive toxicological evaluation: An assessment of the data in the context of the overall health risk evaluation.

Health risk evaluations build off product information and integrate biological, chemical, and clinical findings that are relevant to the potential exposures and associated health risks. A stepwise approach, this evaluation:

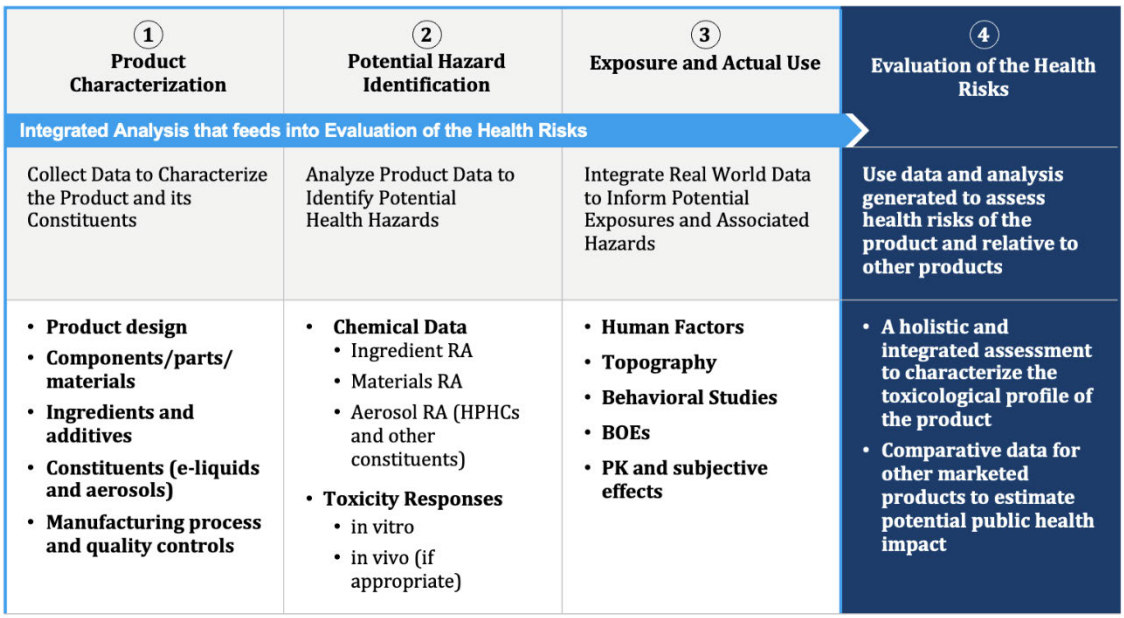
- Begins with a basic product characterization (e.g., evaluation of design, components, parts, materials, ingredients, additives, and constituents);

- Progresses to the identification of potential exposures and associated hazards based on information generated from the product (e.g., analysis of HPHCs and other chemical data and potential toxicity and other biological responses); and

- Integrates actual-use data and related findings to inform the risk profile (e.g., assessment of human factors, tobacco use behaviors, and in-human exposure studies).

Information generated from the study product is then compared against other relevant products to assess their relative risk. The assessment of health risks related to the use of other products — when combined with insights drawn from population-level tobacco use behavior data on initiation, switching, and cessation — enable an estimation of the potential public health impact of a product.

Figure 2 Framework for a Stepwise Approach to Evaluate the Health Risks of Tobacco Products: An Integrated Assessment of the Toxicological Profile



RA=risk assessment; HPHCs=harmful and potentially harmful constituents; BOEs=biomarkers of exposure; PK=pharmacokinetics

For the generation and evaluation of toxicological evidence, JLI also follows a stepwise approach:[52]

- First, a product-level assessment of the ingredients and materials;
- Second, a standard battery of in vitro, and when appropriate, in vivo studies to assess potential toxicological concerns and relevant endpoints;
- Third, a full characterization of the aerosol to identify toxicant exposure and evaluate constituent levels under the potential range of use conditions;
- Fourth, whole product quantitative and qualitative risk assessments informed by nonclinical findings and confirmed by clinical findings.

This approach taken by JLI in its PMTAs is in line with FDA's Guidance on Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (Guidance on PMTAs for ENDS) and ensures that the development of robust data is placed in the context

[52] PMTA Section H.1.1 Summary of Non-Clinical Studies (h-1-1-summary-of-nonclinical-studies.pdf) summarizing analytical data (Section H.1.1.1 Chemistry and Stability), toxicological data (Section H.1.1.2 Toxicology), a qualitative risk assessment (Section H.1.1.3 Qualitative Risk Assessment), and more in-depth quantitative risk assessment (Section H.1.1.4 Quantitative Risk Assessment), as well as other data relevant to the overall health risk evaluation of the JUUL System.

of their scientific relevance and specificity.[53] No one study or set of studies is dispositive. All data must be reviewed in its entirety to assess the potential health risks of the JUUL System and in relation to relevant comparator products to determine the potential public-health impact.

Looking at the data, CTP-OS found that "[t]he variety of *in vitro*, *in vivo*, and clinical data provided by the applicant were generally supportive of each other."[54] Specifically, the chemistry data show that "[t]he aerosol HPHC yields from [JUUL products] are much lower than the mainstream smoke HPHC yields from the 3R4F reference cigarette, except for glycerol"[55] and that HPHCs "are not present [in the product aerosol] at levels of concern" which translates to "significant reductions in blood and urinary BOEs" in clinical studies.[56] These critical data points support likely substantial reductions in HPHC exposures and associated health hazards from JUUL System use compared to cigarette smoking.

Indeed, CTP-OS has relied on similar data in its toxicological assessments for other ENDS products that it has authorized.[57] So, too, for IQOS (PMTA- and MRTPA-authorized

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[53] FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (2019). The Guidance on PMTAs for ENDS reflects this weight of evidence approach: "Although nonclinical studies alone are generally not sufficient to support a determination that permitting the marketing of the product would be APPH (PMTAs would generally need clinical data), information from these nonclinical studies provides insight into the mechanisms of disease incidence caused by a tobacco product and, more generally, provides context for the data obtained from human studies regarding health risks." *Id.* at 34.

[54] FDA 1st Cycle Toxicology Review of JLI's PMTAs PM0000864, PM0000872, PM0000874, PM0000876, PM0000878, PM0000879, p. 21.

[55] FDA 2nd Cycle Chemistry Review of JLI's PMTAs, p. 15 (emphasis added). On glycerol, FDA stated that the "[h]igh level of glycerol aerosol yield in the new products is not a concern from a chemistry perspective since the level of formaldehyde and acrolein aerosol yields, common degradation products of glycerol upon heating, in the new products are much lower than those in the MSS yields of 3R4F reference cigarette." *Id.*

[56] FDA TPL Review of JLI's PMTAs (Toxicology), p. 11, 13.

[57] FDA TPL Review of NJOY LLC's PMTAs PM0000630–PM0000631, p. 6 ("The overall toxicological risk to the users of the new product sis lower compared to combusted cigarette smoke due to significant reductions in aerosol harmful and potentially harmful constituents (HPHCs) of the new products compared to cigarettes, as evidenced by results of nonclinical and aerosol studies. The biomarker data provided by the applicant demonstrated that participants who had used only the new products had lower levels of measured biomarkers of exposure compared to the dual users of the new tobacco products and combusted cigarettes.").

FDA TPL Review of R.J. Reynolds Vapor Company's PMTAs PM0000635, PM0000636, PM0000646, PM0000712, PM0004287, PM0000429, p. 6 ("The overall toxicological risk to the users of the new products is lower compared to cigarettes due to significant reductions in aerosol harmful and potentially harmful constituents (HPHCs) of the new products compared to cigarettes, as evidenced by results of nonclinical studies.").

FDA TPL Review of PMTAs for NJOY, LLC.'s PMTAs PM0000613–PM0000615 and PM0000622, p. 6 ("Chemical testing submitted in the PMTAs was sufficient to determine that overall harmful and potentially harmful constituent (HPHC) levels in the aerosol of these products are lower than in combusted cigarette smoke. The overall toxicological risk to the users of the new products is lower compared to cigarettes.").

heated tobacco product): FDA found that "some of the chemicals are genotoxic or cytotoxic" in the product but "these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in [combustible cigarettes]."[58]

But here CTP-OS did not complete a full evaluation of the health risks for the JUUL System. The MDO made the unjustified determination that JLI did not provide a complete product characterization, bypassed the product risk assessments, and then jumped to conclusions on toxicological risk based on potential hazards without placing these data in context.[59] In doing so, CTP-OS also overlooked follow-up assessments and data on the products that fully inform and contextualize the results for which it was concerned. Of the 75 nonclinical studies that JLI provided in its PMTAs, the MDO focused on data from just three assessments — extractables and leachables studies, an in vitro micronucleus assay with follow-up in vivo testing, and an in vitro Ames assay.

In other words, the marketing decision avoided looking at the entire forest and instead honed in on just a few leaves on a single tree.

The four deficiencies identified in the MDO relate to toxicological signals and potential hazards that, while relevant, have been effectively ruled out or further characterized in a scientific manner beyond what is described in the MDO. The deficiencies themselves can be resolved through clarification and explanation based on the information already provided in the PMTAs.

Scientific and technical errors in each of the deficiencies include:

- **Deficiency 1 is premised on a finding that overlooked critical and dispositive data.** The MDO asserted that JLI identified certain leachable constituents of potential toxicological concern in simulated e-liquid studies but did not evaluate the mainstream aerosol yields of those constituents to determine whether and at what level users could be exposed. As a result, the MDO claimed that CTP-OS was precluded from making a determination of APPH.

  But JLI did provide these data in its PMTAs. Through non-targeted analysis of the JUUL System aerosol, the PMTAs showed that the leachables in question were not detected in the aerosol and thus do not pose a health risk to the user.

[58] FDA TPL Review of Philip Morris Products S.A.'s PMTAs PM0000424–426, PM0000479, p. 42.

[59] FDA Marketing Denial Order for JLI's PMTAs, p. 3 ("Because we do not have adequate information to fully evaluate the products' toxicological profile, and the evidence you did submit raises substantial toxicity concerns, we cannot determine that these products have met the statutory standard. Therefore you have not met your burden of 'showing' that permitting the marketing of the new products would be APPH as required by Section 910(c)(2)(A).").

- **Deficiencies 2 and 3 are premised on an incomplete and inadequate assessment.** The MDO asserted that JLI did not provide reliable and valid data to assess the genotoxic potential of JUUL products and as compared to combustible cigarettes and other ENDS products. As a result, the MDO claimed that CTP-OS was precluded from making a determination of APPH.

  But the MDO focused on limited methodological differences in select in vitro and in vivo studies, from which JLI did provide sufficient and reliable information to inform on the genotoxic potential of JUUL products. More importantly, the MDO did not account for the additional science and evidence in which a signal of potential genotoxicity from an in vitro study was further assessed by subsequent studies and incorporated into whole product risk assessments to characterize potential exposures and associated health risk from the use of the JUUL System.

  CTP-OS did just that for another authorized product. For IQOS, CTP-OS found that "some of the chemicals are genotoxic or cytotoxic" in the product but "these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in [combustible cigarettes]."[60] It should have done the same here but chose otherwise.[61]

- **Deficiency 4 is premised on an arbitrary deviation from the study protocol and OECD guideline and an incorrect application of testing criteria.** The MDO asserted that JLI provided data showing its Menthol 5.0% product is potentially mutagenic. As a result, the MDO claimed that CTP-OS was precluded from making a determination of APPH.

  But the in vitro Ames study showed that the product was not mutagenic, according to the study protocol, OECD guideline, and testing criteria for determining a positive or negative response. Under the study protocol, the testing criteria compared the test article (here, Menthol 5.0%) to the concurrent vehicle controls. CTP-OS, however, used a comparison to historical controls, presumably confusing the difference between assay acceptance criteria (where historical control data are relevant) and testing criteria for a positive or negative mutagenic response (where historical control data are not relevant). According

[60] FDA TPL Review of Philip Morris Product's S.A.'s PMTAs PM0000424–426, PM0000479, p. 42.

[61] In the 1st Cycle Chemistry Review for JLI's PMTAs PM0000864, PM0000872, PM0000874, PM0000876, PM0000878, PM0000879, CTP-OS found that "[a]mongst the 22 HPHC yields that are comparable between [JUUL products] and IQOS Heatsticks, 17 HPHC yields are 57–99% lower in [JUUL products] compared to IQOS Heatsticks." at 36.

to the study report, applying the correct criteria and analysis, Menthol 5.0% was "considered to be negative for inducing mutagenicity in this assay."[62]

In short, the MDO denied JLI's PMTAs based on alleged deficiencies that failed to consider the data, considered the data inadequately, misinterpreted the data, and applied the data incorrectly. All the while, the MDO continued to neglect the whole product risk assessments and other relevant data that inform the health risks of the JUUL System and relative to other products including combustible cigarettes.

The marketing decision also applied a new and different standard to the data, which appears to have been created for, and applied only to, JLI's PMTAs. For example, CTP-OS has previously authorized new products that lacked toxicological data (VERVE), had genotoxic and mutagenic concerns (IQOS), presented toxicological risks from unknown leachable compounds (Logic), or showed a toxicological profile that was similar to a traditional cigarette (Moonlight VLN Cigarettes). Yet the outcome for JLI's PMTAs and the JUUL System was quite different.

Table 1 Summary of CTP-OS's Toxicological Evaluations for Certain Authorized Products

PMTA	Toxicological Concerns	Resolution
Verve[63]	"No original toxicology studies were submitted by the applicant for any of the VERVE® products. The applicant provided toxicological assessments, which included hazard and exposure assessments of the ingredients associated with VERVE® Discs and Chews. The exposure assessments relied on toxicity values intended for foods as derived by regulatory and industrial trade associations; as such, these values are not intended for tobacco products."	"Nonetheless, based on the data from oral exposure studies and the estimated exposures to ingredients made by the applicant from the use of VERVE®, the information supported the determination that the added ingredients were not of toxicological concern given the margins of exposure in relation to oral toxicity studies derived from published reference values."
IQOS[64]	"Eleven chemicals were identified with genotoxic potential. Based on the available toxicological data and predictive toxicology modeling analysis submitted by the applicant, 20 of the 30 chemicals exhibit concerns for potential health effects." "Many of the chemicals do not have sufficient inhalation toxicity or genotoxicity/carcinogenicity	"[H]owever, although there is potential for genotoxicity with some of these compounds, the exposure levels appear low and the available data does not preclude a conclusion the products are appropriate for the protection of public health."

[62] PMTA Section N.3.1.1 Report 03408REVA (Menthol 5%), p. 16 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf).

[63] FDA TPL Review of U.S. Smokeless Tobacco Company LLC.'s PMTAs PM0000470–PM0000473, p. 25.

[64] FDA TPL Review of Philip Morris Product S.A.'s PMTAs PM0000424–426, PM0000479, p. 32, 39, 42.

PMTA	Toxicological Concerns	Resolution
	data to inform the toxicological evaluation of heated tobacco products. The data provided by the applicant is not sufficient to support their conclusion that these compounds pose no risk to IQOS users . . . ." "Similar to the in vitro studies, it is difficult to determine the carcinogenic potential of long-term exposure to Heatstick aerosols from these evaluations. The data suggest there is potential for carcinogenic effects from Heatstick aerosols, but at much higher exposure levels than required for CC smoke."	"Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHcs found in CC."
Logic[65]	"The applicant submitted a risk assessment for the identified, partially identified, and unknown simulated leachable compounds in the new products. The applicant concluded that the potential risks to consumers from identified and partially identified leachable compounds are acceptable but risk for the unknown leachable compound was above the benchmark value of 1.0 which indicates potential risks of concern."	"Although simulated leachable compounds for all new products can be hazardous, at the low levels present, if there is any contribution towards cancer hazard, these risks are outweighed by decreases in HPHCs by 83–99% in all new products."
Moonlight VLN Cigarettes[66]	"HPHC data for both VLN™ cigarettes indicates that noncancer hazards and cancer risks are likely similar to or slightly lower than NNC cigarettes, based on HPHC comparisons to top market-share cigarettes." "The toxicology review determined that overall, based on ISO regimen HPHC data, the noncancer hazards due to use of the VLN™ cigarettes are likely similar to those with use of the commercially marketed NNC cigarette comparators. In addition, based on the ISO regimen HPHC data, cancer risks due to use of the VLN™ cigarettes are likely similar and may be less than those associated with use of the commercially marketed NNC cigarette comparators." "The toxicology review noted that increases in acetaldehyde and acrylonitrile via the CI regimen likely do not raise cancer-risk-related concerns for the VLN™ cigarettes. Overall based on these CI regimen HPHC data, cancer risks are likely similar with use of VLN™ cigarettes and use of commercially marketed NNC cigarette comparators."	"As TPL, I agree with the toxicology review conclusion. After consideration of all the toxicological data presented, the overall toxicological risks of VLN™ cigarettes are likely similar to those associated with use of the six comparator products that represent a significant portion of the cigarette market. However, the potential for a relative benefit compared to NNC cigarettes exists for smokers who switch completely to VLN™ cigarettes, then reduce cigarette use, and eventually totally quit."

All perceived limitations identified by the MDO could have been resolved by clarifications through the usual, iterative process that defines a full review of product

[65] FDA TPL Review of Logic Technology Development LLC's PMTAs PM0000529.PD1–PM0000531.PD1, PM0000535.PD1–PM0000537.PD1, PM0000540.PD1–PM0000541.PD1, p. 37.

[66] FDA TPL Review of 22nd Century Group Inc.'s PMTAs PM0000491–PM0000492, p. 15, 27, 28, 34.

applications. Or even a mere phone call. JLI's PMTAs were under review for nearly two years. In the year between June 2021 (when JLI submitted the Deficiency Response) and June 2022 (when CTP-OS issued the MDO), CTP-OS had no further substantive engagement with JLI.

Moreover, the MDO is inconsistent with FDA's statutorily-mandated objectives to protect and promote public health. By statute, FDA has been provided comprehensive authority and jurisdiction over tobacco products to reduce tobacco-related death and disease, including through "efforts to develop, introduce, and promote less harmful tobacco products."[67]

The MDO for JLI's PMTAs prompts the question (and risk) on whether the Agency will fail to authorize products that have the most potential to serve this public-health goal. FDA's own review affirmed that JLI's PMTAs provided evidence that "exposure to carcinogens and other toxicants present in cigarette smoke were greatly reduced with exclusive use of [JUUL products] compared to [combustible cigarette] smoking."[68] CTP-OS's reluctance to consider the overall characterization of the relative health risks and net-population impact of the JUUL System — and instead base its decision on four discrete toxicological considerations — does not promote public health.

These and other issues described below make the MDO inconsistent with the data provided in JLI's PMTAs, inconsistent with the principles of sound scientific assessment, inconsistent with established FDA policies, procedures, and processes, and inconsistent with statutory authorities which required CTP-OS to give JLI's PMTAs a complete and fair review. To say that there were procedural and program irregularities in the review of JLI's PMTAs would be an understatement.

III. FACTUAL BACKGROUND

A. The JUUL System

The JUUL System is designed to be an alternative to combustible cigarettes for adult smokers — products they can and will switch to completely. The JUUL System is a closed, cartridge-based ENDS product. ENDS operate on the principle that products that deliver nicotine without burning tobacco can pose much lower levels of health risk than cigarettes. This is because the toxicants in the smoke from burning tobacco cause the vast majority of cigarette-related diseases. Nicotine, while addictive and not without risk, is not the primary source of harm.[69]

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[67] Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, § 3(4), 123 Stat. 1782 (2009).

[68] FDA TPL Review of JLI's PMTAs (Toxicology), p. 13.

[69] Gottlieb, S., & Zeller, M. (2017). A nicotine-focused framework for public health. *New England Journal of Medicine*, *377*(12), 1111–1114.

The JUUL System neither contains nor burns tobacco, instead heating a nicotine-containing liquid within a controlled temperature range to produce an aerosol that the user inhales. As a result, the JUUL System aerosol is less complex than cigarette smoke and contains significantly fewer and lower levels of HPHCs.[70] Reductions in HPHCs in the JUUL System aerosol translate to reductions in human exposures to these toxicants, as shown by the reductions in relevant BOEs measured in clinical studies.[71] In fact, smokers who switched completely to the JUUL System in short-term clinical studies saw reductions in exposure to HPHCs comparable to those who did not use tobacco at all.[72]

B. JLI's PMTAs

On July 29, 2020, JLI submitted six PMTAs — five for currently marketed JUUL products and one for a new device with age-verification technology (the JUUL Locked Device) to better restrict underage access. CTP-OS assigned the following STNs for the products subject to the PMTAs:

- PM0000864 – JUULpods Menthol (3.0%)
- PM0000872 – JUULpods Menthol (5.0%)
- PM0000874 – JUULpods Virginia Tobacco (3.0%)
- PM0000876 – JUULpods Virginia Tobacco (5.0%)
- PM0000878 – JUUL Device
- PM0000879 – JUUL Locked Device

CTP-OS issued an acceptance letter on August 5, 2020, a filing letter on August 17, 2020, and deficiency letters on March 26, 2021, and March 30, 2021. The deficiency letters covered JLI's PMTAs and its Tobacco Product Master Files (TPMPFs), respectively.[73]

JLI responded to the PMTA-specific deficiency letter on June 22, 2021. Between JLI's June 2021 response and the June 2022 MDO, CTP-OS did not have any additional, substantive engagements with or requests for additional information from JLI.

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[70] PMTA Section H.1.1.1 Chemistry and Stability (h-1-1-1-chemistry-and-stability.pdf).

[71] PMTA Section H.1.2 Clinical Studies (h-1-2-clinical-studies.pdf).

[72] *Id.*

[73] In addition, in November 2020, CTP-OCE asked JLI to verify information and data contained in the PMTAs to facilitate inspections of certain manufacturing and research sites. JLI discussed the request with OCE via a teleconference and provided a written response with additional information to facilitate the inspections of its contract manufacturers and research sites.

1. Summary of the Health-Risk Profile of the JUUL System

JLI's PMTAs included the results of more than 75 nonclinical studies, including targeted and non-targeted chemistry analyses and in vitro and in vivo toxicology studies, as well as 13 clinical studies and a computational modeling study to assess environmental exposure from JUUL product use. These multidisciplinary studies, alongside analyses of information and data from published literature, formed the basis of both quantitative and qualitative risk assessments of the JUUL System. As summarized in PMTA Section H.1 Summary of the Health Risks of the Tobacco Product, the lines of evidence are consistent and converge on the conclusion that use of the JUUL System presents significantly less health risk than smoking combustible cigarettes.[74]

2. Nonclinical Studies

JLI's nonclinical program included chemistry and toxicology studies, as well as a complete risk assessment of the e-liquid, the aerosol, and component parts of the JUUL System. As referenced in the Executive Summary of the PMTAs, the following are some of the key findings on the JUUL System:[75]

- The majority (40 of 53) HPHCs and other constituents assessed in the targeted aerosol analyses were not detected in the JUUL System aerosols;
- JUUL System aerosols contain between 99 and 114 compounds (depending on e-liquid variant), compared to more than 5,000 compounds identified in cigarette smoke;
    - Among these compounds, 59–68 (depending on flavor and nicotine concentration) were exclusive to the aerosols of the JUUL System, while 36–46 were also found in cigarette smoke;
    - Excluding nicotine, propylene glycol (PG), vegetable glycerin (glycerol or VG), and other constituents measured in the targeted analysis, the remaining compounds in the JUUL System aerosols account for approximately 0.2% of the total aerosol collected mass; and
    - A toxicological review of these compounds revealed that, to the extent they were identified as potential toxicants, they were present at concentrations below the level of toxicological concern;

[74] PMTA Section H.1 Summary of the Health Risks of the Tobacco Product (h-1-health-risks-introduction.pdf).

[75] PMTA Section B.1 Executive Summary, p. 17–18 (b-1-executive-summary.pdf).

- On average, HPHCs and other chemicals are reduced by 98% or more in the JUUL System aerosols compared to cigarette smoke (excluding nicotine, glycerol, and water);

- On average, HPHCs and other chemicals are reduced by 82% or more in the JUUL System aerosols compared to aerosols from IQOS (excluding nicotine, glycerol, and water); and

- JUUL System aerosols contain similar or lower levels of HPHCs and chemicals in comparison to other marketed ENDS.

Taken together, the nonclinical information, data, and analysis demonstrate the potential for significant reductions in exposure to HPHCs and subsequent cancer risk and non-cancer hazards with the use of the JUUL System compared to smoking cigarettes.

3. Clinical Studies

JLI's clinical program included randomized, controlled clinical studies to assess the effects of the JUUL System on humans who use it, including nicotine pharmacokinetics, puffing topography, and exposure to HPHCs found in cigarette smoke for both users and nonusers. As referenced in the Executive Summary of the PMTAs, the following are some of the key findings on the JUUL System:[76]

- Switching from combustible cigarettes to JUUL products leads to substantial reductions in BOEs to a degree similar to that seen with abstinence from smoking;

- Dual users who reduced their cigarette consumption by 50% or more and used JUUL products also saw substantial reductions in BOEs compared to those who continued smoking during confinement;

- There is minimal environmental exposure to HPHCs and other toxicants present in tobacco smoke through secondhand exposure to JUUL product aerosols.

Taken together, the clinical information, data, and analysis demonstrate that exclusive use of the JUUL System has the potential to reduce health risks compared to smoking cigarettes, both to users and nonusers exposed to secondhand JUUL aerosols. The available evidence further shows that adult smokers who switch completely to the JUUL System have reduced toxicant exposures, which, in turn, is likely to result in less risk of long-term tobacco-related diseases.

[76] *Id.* at 18.

C. The MDO

On June 23, 2022, FDA issued an MDO for all of JLI's PMTAs. The MDO provided four deficiencies as the bases for the decision, which precluded a determination of APPH for all JUUL products. Each of the deficiencies related to a toxicological assessment of JUUL products and purportedly prevented CTP-OS from completing a full toxicological evaluation.

Additional information and analysis on each of the deficiencies and JLI's bases for reconsideration are in Section IV.A below.

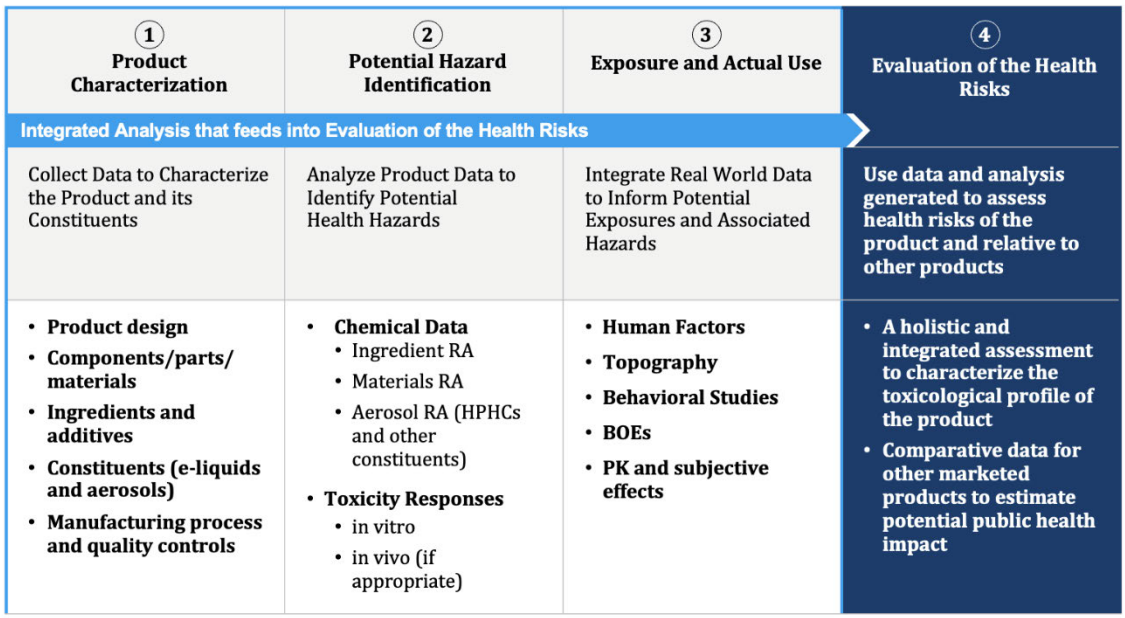
IV. BASES FOR RECONSIDERATION

A. Scientific and Technical Considerations

In its PMTAs, JLI provided a comprehensive assessment of the health risks associated with the use of the JUUL System and relative to combustible cigarettes and other comparator products including marketed ENDS.[77] This stepwise health-risk evaluation begins with a basic characterization of the product, progresses to the evaluation of information generated from the product and identification of potential hazards, and then integrates actual-use data into whole product quantitative and qualitative risk assessments. The risk assessments build off product evaluations and incorporate biological and chemical findings that are increasingly more relevant and informative to the potential health risks and confirmed by clinical findings from actual use and exposure.

[77] PMTA Section H.1. Summary of the Health Risks of the Tobacco Product (h-1-health-risks-introduction.pdf).

Figure 3 Framework for a Stepwise Approach to Evaluate the Health Risks of Tobacco Products



RA=risk assessment; HPHCs=harmful and potentially harmful constituents; BOEs=biomarkers of exposure; PK=pharmacokinetics

Based on JLI's PMTAs, these lines of evidence converge on the conclusion that use of the JUUL System presents substantially less risk than combustible cigarettes for adult smokers.

CTP-OS found as much: "Among the 25 HPHC yields that are comparable between [JUUL products] and the 3R4F reference cigarette, 23 HPHC yields were 98–99% lower in [JUUL products] compared to the 3R4F reference cigarette."[78] And according to CTP-OS: "In the clinical studies, significant reductions in blood and urinary BOEs indicate that exposure to carcinogens and other toxicants present in cigarette smoke were greatly reduced with exclusive use of the new products compared to [combustible-cigarette] smoking."[79]

But CTP-OS also found that "[w]hile it is theoretically possible for the decreased HPHC yields and reduced BOE levels to offset risk posed by the genotoxic leachables, the applicant provided no data indicating if, and how much of, these leachables are transferred into mainstream aerosol."[80]

[78] FDA 1st Cycle Chemistry Review of JLI's, p. 35.

[79] FDA TPL Review of JLI's PMTAs (Toxicology), p. 13.

[80] *Id.*

It was not theoretical. JLI provided these data (over 6,000 pages of it) that fully characterize the JUUL System aerosol and confirm that the leachables in question are not detected in the aerosol.[81] This is but one example where the MDO erred.

In the sections below, JLI addresses each MDO deficiency in turn and shows, based on information, data, and analysis from its PMTAs, how the MDO is flawed. Generally, the marketing decision:

- Failed to consider data provided in the PMTAs;
- Considered such data in the PMTAs inadequately;
- Misinterpreted data provided in the PMTAs;
- Applied data from the PMTAs incorrectly; and
- Deviated from established policy, procedure, or process when reviewing the PMTAs.

Here, JLI summarizes key points of analysis:

Deficiency 1: The MDO found that JLI did not provide a proper identification of two potential leachables in the JUUL System and did not provide mainstream aerosol yield data for these constituents. As a result, CTP-OS could not perform an accurate and complete risk assessment of the products.

- CTP-OS misinterpreted the data provided in JLI's PMTAs that correctly identify the leachables in question.
- CTP-OS failed to consider the comprehensive mainstream aerosol yield data provided in JLI's PMTAs that confirm the leachables in question are not detected in the aerosol.
- CTP-OS can conduct an accurate and complete risk assessment of JUUL products when the data provided in JLI's PMTAs are reviewed and interpreted correctly.
- CTP-OS deviated from established process and decision-making principles by failing to complete a full toxicological evaluation because of "unknown" leachables.
- CTP-OS did not provide a full and fair opportunity to address its new requirement for specific testing data on the leachables in question.

[81] PMTA Section H.1.1.1 Chemistry and Stability (h-1-1-1-chemistry-and-stability.pdf); *see also* PMTA Section N.3.4 Chemistry and Stability (including full reports).

Deficiencies 2 and 3: The MDO found that the methods used for and data from an in vitro MN assay raised uncertainty about the genotoxic potential of JUUL products.

- CTP-OS did not adequately consider scientifically valid data that are relevant to assess the genotoxic potential of JUUL products.

- CTP-OS incorrectly concluded that, based on the available in vitro MN assay data and in vivo genotoxicity data, JUUL products presented genotoxic potential which precluded an accurate and complete toxicological evaluation.

- CTP-OS was not precluded from conducting a full toxicological evaluation based on the alleged methodological issues and failed to consider other relevant biological and chemical data adequately.

- CTP-OS deviated from established process and decision-making principles by failing to conduct a complete scientific review.

Deficiency 4: The MDO found that Menthol 5.0% was mutagenic based on data from an in vitro Ames assay.

- CTP-OS failed to apply the study protocol, OECD guideline, and testing criteria correctly to assess the mutagenic potential of Menthol 5.0%.

- Applied correctly, the results from the in vitro Ames assay confirm that Menthol 5.0% is not mutagenic.

Based on these scientific and technical considerations, the MDO should be rescinded and JLI's PMTAs should be placed back into substantive review. Under that review, CTP-OS not only can undertake a full toxicological evaluation of the JUUL System but also must complete a holistic review of the entirety of science and evidence presented in the PMTAs to determine whether the marketing of the JUUL System is APPH.

1. Information in the PMTAs Identifies the Leachables in Question, Shows They Are Not Detected in the Aerosol, and Enables an Accurate and Complete Risk Assessment of the JUUL System (Deficiency 1)

a. Basis for the Deficiency

The MDO found that JLI did "not provide[] proper identification of leachable constituents (leachables) in the new products nor [did JLI] provide[] mainstream aerosol yield data for these leachables generated by the new products . . . ."[82] The MDO further stated that, as a result, CTP-OS "cannot perform an accurate and complete risk assessment

[82] FDA Marketing Denial Order for JLI's PMTAs, p. 3.

of the new products."[83] Specifically, CTP-OS identified two potentially genotoxic leachables that were "improperly identified" such that there "is insufficient information to characterize their risks" and that "the application lacks mainstream aerosol data, and an appropriate toxicological risk assessment for these constituents."[84]

As discussed below, the MDO's conclusion and supporting findings are flawed because JLI did identify the leachables in question correctly and, more critically, conducted a non-targeted analysis of the JUUL System aerosol that confirms these leachables are not detected in the aerosol and thus do not present a health risk to the user.

- On the identity of leachable constituents, CTP-OS misinterpreted chemical data and mass spectra data provided across the initial PMTAs and the Deficiency Response. When interpreted correctly, the data properly identify the leachable constituents.

- On mainstream aerosol yields, CTP-OS overlooked JLI's comprehensive aerosol characterization and evaluation, including the non-targeted analysis, which demonstrates the leachables in question are not detected in the aerosol of JUUL products.

Therefore, CTP-OS can conduct an accurate and complete risk assessment of the JUUL System.

b. Summary of Facts and Background

JLI's PMTAs included a series of extractables and leachable (E&L) studies that were conducted to screen for any potential chemicals that could be transferred into the e-liquid from the container-closure system (JUULpod) and components within the aerosol path.

JLI performed a health risk assessment on each of the leachables derived from the leachables studies (i.e., leachables risk assessment) to identify whether any toxicological concerns are introduced by the materials.[85] Based on the leachables risk assessment, JLI flagged compounds of potential toxicological concern for monitoring and evaluation in real-time stability testing, which began before the initial PMTAs were submitted but was ongoing at the time of submission.[86] In the initial PMTAs, JLI identified two leachables of potential concern as Ethyl-4-hydroxyquinoline-3-carboxylate, aminobutyric acid related

[83] *Id.*

[84] FDA TPL Review of JLI's PMTAs (Toxicology), p. 5.

[85] PMTA Section H.1.1.4 Quantitative Risk Assessment, Section 4.3 (h-1-1-4-quantitative-risk-assessment.pdf).

[86] *Id.*

compound (EHQC) and Propylpyridine,1H-pyrrole-1-hexanoic acid,2,5-dihydro-2,5-dioxo-related compound (PHDC).[87]

The Deficiency Letter stated that the PMTAs did not provide mainstream aerosol yields for these leachables of potential concern and requested such information.[88] Following further scientific assessment, the identity of the constituents EHQC and PHDC was updated to 1,8,9-trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone (TCEQ) and Nornicotine, N-carboxyglycerol-5'-(methoxy-1-(p-hydroxybenzene-O4-yl-acetic acid)) (NNMA), respectively. JLI provided the refined identifications and updated testing reports and supporting analyses in its Deficiency Response.[89] JLI also provided a new risk assessment that concluded that the leachable constituents, if transferred from the pod to the e-liquid and then to the aerosol, were not present at levels of toxicological concern.[90]

In the leachables risk assessment, JLI explained that aerosol data enable a more accurate assessment of the potential leachables risk to users of JUUL products because they are exposed to the aerosol.[91] JLI's leachables risk assessment was highly health precautionary and relied on the assumption that 100% of the potential leachables detected in the simulated e-liquid studies could be transferred from the e-liquid into the aerosol.[92] This risk may be superseded with aerosol data, given that it is the constituents in the aerosol and not the e-liquids that are ultimately inhaled by the consumer.

Accordingly, as part of its stepwise, scientific approach, JLI reported any identified leachable compounds for follow-up in the non-targeted analysis of the JUUL System aerosols. If any leachables of potential toxicological concern were identified in the non-targeted analysis, then targeted approaches would be considered to confirm identification and quantification.[93]

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[87] PMTA Section N.3.3 Whole Pod Leachables Technical Risk Assessment Report, p. 6-7 (n-3-3-whole-pod-leach-tra-report.pdf).

[88] FDA Deficiency Letter to JLI for PMTAs, Question 17.

[89] JLI Deficiency Response to Question 17; Appendix 17.01 Whole Pod Leachables Report 238873 Version 2 (app-17-02-n-3-4-[redacted]-whole-pod-leachable-report-2.pdf); Appendix 17.02 Whole Pod Leachables Report 238874 Version 2 (app-17-01-n-3-4-[redacted]-whole-pod-leachable-report-1.pdf).

[90] JLI Deficiency Response to Question 17, p. 132–144.

[91] PMTA Section H.1.1.4 Quantitative Risk Assessment, p. 38 (h-1-1-4-quantitative-risk-assessment.pdf).

[92] *Id.* at 39.

[93] PMTA Section H.1.1.4 Quantitative Risk Assessment (h-1-1-4-quantatitative-risk-assessment.pdf); PMTA Section H.1.1.4 Whole Pod Leachables Technical Risk Assessment Report p. 8. (n-3-3-whole-pod-leach-tra-report.pdf).

Additional information on the facts and background relating to Deficiency 1, including data and analysis from JLI's PMTAs and Deficiency Response, are included in Appendix 1.

c. Analysis

i. CTP-OS Misinterpreted the Data Provided in JLI's PMTAs That Correctly Identify the Leachables in Question

CTP-OS stated that "you have not provided proper identification of leachables constituents (leachables) in the new products."[94] CTP-OS specifically noted that JLI provided information in the Deficiency Response that is "incompatible with chemical analysis and mass spectral data you previously submitted" and pointed to "conflicting data" that it believes undermines the true identities of the leachables.[95]

There seems to be confusion about the source of truth for information used to identify the leachables — namely, the mass spectral data collected by [redacted] (the contract laboratory for the leachables analysis). Although CTP-OS stated that the information provided in the Deficiency Response is "incompatible with chemical analysis and mass spectral data you previously submitted,"[96] this is based on a flawed premise because JLI did not provide chemical analysis or mass spectral data until the Deficiency Response. The leachables reports provided in the initial PMTAs only contained chemical information based on library matching and not the actual mass spectral data.[97]

Specifically, the leachables reports provided in the initial PMTAs reported assigned chemical structure and compound molecular mass for the compounds (or class of compounds) based on automated spectral library matches.[98] After the initial leachables reports were finalized, follow-up analysis was performed using the commonly accepted method of manual mass spectrum interpretation of the acquired mass spectral data to confirm the identity of the compounds.[99] Updated structural information (e.g., ions) identified during the manual evaluation was added to the spectral library, and the mass

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[94] FDA Marketing Denial Order for JLI's PMTAs, p. 3.

[95] *Id*. at 4.

[96] *Id.*

[97] PMTA Section N.3.4 Whole Pod Leachables Report 238873 (n-3-4[redacted]-whole-pod-leachable-report-2.pdf); PMTA Section N.3.4 Whole Pod Leachables Report 238874 (n-3-4-[redacted]-whole-pod-leachable-report-1.pdf).

[98] *Id.*

[99] Sussman, E. M., Oktem, B., Isayeva, I. S., Liu, J., Wickramasekara, S., Chandrasekar, V., & . . . Zheng, J. (2022). Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices. *ACS Biomaterials Science & Engineering*, 8(3), 939–963.

spectral data was then reprocessed, resulting in more precise matches. Specifically, EHQC was updated to TCEQ and PHDC was updated to NNMA.

In the Deficiency Response, JLI provided updated leachables reports as well as chemical analyses of the leachables study data — with the underlying mass spectra from [redacted] — to support the updated identifications.[100] While there are some inconsistencies in assigned compound information provided in the leachables reports, the Deficiency Response included the underlying mass spectra from [redacted] and actual chemical analysis based on those data to demonstrate any updates are better aligned with the source data and product composition.

Overall, the initial chemical identifications of EHQC and PHDC for the leachables in question were automated partial tentative identifications, which JLI had good reason to further investigate. JLI and its vendor followed commonly accepted analytical practices to address the tentative findings and confirm the identifications. The updated identifications of TCEQ and NNMA better match the mass spectral data and, unlike the partial tentative identifications, are consistent with the known product attributes.

The leachable compounds also were evaluated in the whole pod leachables risk assessment reports.[101] In these risk assessments, synonym chemical names of leachable compounds and classes of compounds may be referred to or used interchangeably with surrogate compounds.[102] One source of "conflicting" data that CTP-OS pointed to is a mismatch in chemical names between the updated leachables reports and updated risk assessment provided in the Deficiency Response. [103] As CTP-OS itself acknowledged, however, the leachable chemical in question has the same structure, regardless of the chemical naming convention used to describe it.[104] The compounds are structurally identical. Differences in chemical nomenclature are not relevant to assessing the potential risk of the compounds and are not a sound basis for a deficiency.

For further clarity, JLI addresses the respective compound identifications, data sources within the PMTAs, and naming conventions used in each of the relevant documents for the leachables in question in more detail in Appendix 1.

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[100] JLI Deficiency Response to Question 17.

[101] PMTA Section N.3.3 Whole Pod Leachables Technical Risk Assessment Report (n-3-3-whole-pod-leach-tra-report.pdf); JLI Deficiency Response Appendix 17: Appendix C Whole Pod Leachables Risk Assessment (Bibra Update) (app-17-03-n-3-3-whole-pod-leach-tra-report.pdf).

[102] *Id.*

[103] FDA Marketing Denial Order for JLI's PMTAs, p. 4.

[104] FDA 2nd Cycle Toxicology Review of JLI's PMTAs PM0000864, PM0000872, PM0000874, PM0000876, PM0000878, PM0000879, p. 7.

Based on information in the PMTAs, as amended by the Deficiency Response, the correct identification of the leachables is TCEQ and NNMA.

ii. CTP-OS Failed to Consider the Comprehensive Mainstream Aerosol Yield Data Provided in JLI's PMTAs That Confirm the Leachables in Question Are Not Detected in the Aerosol

The MDO contended that JLI has not "provided mainstream aerosol yield data for these leachables generated by the new products." Specifically, the MDO asserted that JLI "declined to provide testing results of these leachables in mainstream aerosol . . . ."[105]

In reaching this conclusion, the MDO overlooked the comprehensive characterization of the JUUL System aerosols using both quantitative targeted analysis and semi-quantitative non-targeted analysis over the product shelf life, which was provided by JLI in its initial PMTAs and as amended by the Deficiency Response.[106] The leachables in question, as initially identified and/or updated, were not detected in the JUUL product aerosols.[107] Thus, CTP-OS was not precluded from assessing the presence (or lack thereof) of these leachables in the aerosol, let alone precluded from completing an accurate and complete risk assessment and toxicological evaluation of the JUUL System.

As defined by CTP-OS, "leachables here are chemicals that migrate from the pod or device components into the e-liquid and *may* subsequently be inhaled by the consumer."[108] As part of a stepwise risk assessment, the simulated e-liquid leachables assessment represents an initial step to characterize health risk from constituents that *may* be introduced from the JUULpod materials and lead to potential consumer exposure.

The potential risks estimated using simulated e-liquid data are superseded by actual aerosol data, as it becomes available, and the whole product risk assessment forms the basis for the final evaluation of toxicological risks. This is because not all constituents from the e-liquid transfer to the aerosol and it is the aerosol that is exposed to users.

The transfer from e-liquid to the aerosol during product use depends on several factors, including the size and volatility of the compound and its chemical structure. For the leachables in question, the molecular mass and estimated boiling points suggests that the compounds would not transfer to aerosol: TCEQ has an estimated boiling point of approximately 993^{o}K and NNMA has an estimated boiling point of approximately 1266^{o}K, which are significantly greater than the 550^{o}K boiling point of glycerin. As a result, it not

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[105] FDA Marketing Denial Order for JLI's PMTAs p. 3.

[106] PMTA Section H.1.1.1 Chemistry and Stability (h-1-1-1-chemistry-and-stability.pdf); JLI Deficiency Response.

[107] PMTA Section H.1.1.1 Chemistry and Stability (h-1-1-1-chemistry-and-stability.pdf) (detailing complete aerosol characterization).

[108] FDA TPL Review of JLI's PMTAs (Toxicology) p. 10, footnote 4 (emphasis added).

surprising that these leachables were not detected in the aerosol data that CTP-OS already have.

As detailed in Section H.1.1.1 Chemistry and Stability of the PMTAs, chemistry and stability studies were conducted to evaluate the chemical and physical properties of the JUUL System. JLI provided a comprehensive characterization and evaluation of the JUUL System aerosols using both quantitative targeted analysis and semi-quantitative non-targeted analysis methods. For both targeted and non-targeted approaches, aerosol samples were generated under intense and non-intense puffing conditions.[109]

Using targeted and non-targeted analyses, HPHCs and other chemicals were identified and measured to evaluate potential user exposures. The aerosol results also were evaluated against comparator products, including combustible cigarettes, IQOS, and marketed ENDS products. For each aerosol constituent identified, JLI determined the potential human health risks based on the risk assessment framework described in Section H.1.1.4 Quantitative Risk Assessment.[110] Details regarding the aerosol risk assessments are provided in Appendix 1.

Quantitative targeted analysis performed on the JUUL System included multiple studies analyzing HPHCs as specified in the Draft Guidance on PMTAs for ENDS, as well as additional analytes that were added to the Guidance on PMTAs for ENDS.[111] Additional chemicals were measured in the stability studies to monitor their presence and potential changes over time. These chemicals included metals, nicotine-related compounds, water, and benzoic acid. In total, the targeted analysis focused on 40 HPHCs and other chemicals, along with pH, particle size distribution, device mass loss (DML), and aerosol collected mass (ACM).[112]

Moreover, stability data for additional timepoints to substantiate a minimum twelve-month shelf life were provided in the Deficiency Response for Question 12. JLI explained in the Deficiency Response that the stability data were provided from "a full characterization" based on twelve months of long-term stability storage, which demonstrated that "minimal chemical and physical changes occur over the twelve-month long-term stability studies for the e-liquid and the aerosol, under both puffing regimes."[113]

While the targeted analysis covers the vast majority of the aerosol mass, in addition to HPHC and target constituent testing, non-targeted analysis was conducted to completely

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[109] PMTA Section H.1.1.1 Chemistry and Stability (h-1-1-1-chemistry-and-stability.pdf).

[110] PMTA Section H.1.1.4 Quantitative Risk Assessment (h-1-1-4-quantatitative-risk-assessment.pdf).

[111] FDA, Guidance for Industry (Draft): Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems 26–27 (2016); FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems 28–29 (2019).

[112] PMTA Section H.1.1.1 Chemistry and Stability (h-1-1-1-chemistry-and-stability.pdf).

[113] JLI Deficiency Response to Question 12, p. 108–109.

characterize the remaining aerosol constituents. Non-targeted analysis is a semi-quantitative screening approach[114] to assess additional compounds not directly measured in the targeted methods.[115] JLI developed two complementary non-targeted screening methods to characterize the compounds present in the aerosol from all JUUL products (GC-MS and LC-HRMS).[116] Estimated concentrations in comparison to an internal standard that were above 0.7 μ g/g were reported for GC analyses and above 0.5 μg/g-with a p-value less than 0.05 were reported for LC-HRMS analyses.[117]

The non-targeted analysis is capable of detecting and semi-quantifying a wide range of chemicals — including nitrogen-containing compounds (e.g., amides, pyrroline, nicotine degradants, nicotine related compounds), PG/VG degradants, benzoic acid reaction products, and extractables and leachable compounds (like the potential leachables subject to this deficiency). Outside of the compounds already measured in the targeted analysis, the non-targeted analysis identified between 92 and 107 compounds in the JUUL System aerosols (the range represents the different SKUs), which accounted for approximately 0.2% of the total aerosol mass.[118]

All aerosol compounds from the non-targeted analysis were categorized into five groups for a thorough understanding of product composition. The five groups were ingredients, HPHCs, E&L, reaction products, and not rationalized:

- Group 1 consisted of any compound that matched an ingredient or a likely ingredient impurity;
- Group 2 included any HPHCs listed in the "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List";[119]
- Group 3 included compounds detected in the E&L analysis report;

[114] Semi-quantitative techniques are based on the comparison of a compound response to the response of a known amount of an internal standard to determine the estimation concentration.

[115] PMTA Section H.1.1.1 Chemistry and Stability, Section 2.1.5 (h-1-1-1-chemistry-and-stability.pdf).

[116] PMTA Section H.1.1.1 Chemistry and Stability, Section 2.1.5 (h-1-1-1-chemistry-and-stability.pdf). The two non-targeted analysis techniques are complementary to each other, with only a few of the same compounds identified in both GC-MS and LC-HRMS. Because the GC-MS NTA method is less susceptible to analyte-specific ionization efficiency in comparison to LC-HRMS, the GC-MS estimated concentrations prevailed to avoid duplication.

[117] PMTA Section H.1.1.1 Chemistry and Stability, p. 31 (h-1-1-1-chemistry-and-stability.pdf).

[118] *Id.* at 111.

[119] FDA (2012) Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List in: U.S. Department of Health and Human Services, Center for Tobacco Products, eds. Vol 77. Rockville, MD: U.S. Food and Drug Administration; 20034-20037.

- Group 4 included any reaction product compounds resulting from known one- or two-step reaction pathways from ingredients; and

- Group 5 encompassed any unknown compounds or compounds not rationalized into Groups 1–4.

Across JUUL products, less than 0.0081% of the total aerosol was not rationalized based on the tentative chemical identifications. Between the targeted analysis and the non-targeted analysis, JLI has provided full characterization of the JUUL System aerosols.[120]

For additional information on the non-targeted analysis methods and results, as provided in the PMTAs, Table 2 below provides an overview of the technical summaries and reports for each product.

Table 2 Overview and PMTA References for Non-Targeted Analysis Aerosol Data

SKU	Time Point (months)	Report Description	File Name
Virginia Tobacco 5.0%	0	T0 NTA Technical Summary	n-3-4-vt-5-nta-tech-summary-t0.pdf
	0	GC NTA Vendor Report	n-3-4-[redacted]-nta-report-vt-5-t0.pdf
	0	LC NTA JLI Report	n-3-4-vt-5-nta-lcms-t0-tech-summary.pdf
	12 (aged pods)	T12 NTA Technical Summary	n-3-4-vt-5-nta-tech-summary-t12.pdf
	12 (aged pods)	GC NTA Vendor Report	n-3-4-[redacted]-vt-5-aged-pod-report-t12.pdf
Virginia Tobacco 3.0%	0	T0 NTA Technical Summary	n-3-4-vt-3-nta-tech-summary-t0.pdf
	0	GC NTA Vendor Report	n-3-4-[redacted]-nta-report-vt-3-t0.pdf
	0	LC NTA JLI Report	n-3-4-vt-3-nta-lcms-t0-tech-summary.pdf
Menthol 5.0%	0	T0 NTA Technical Summary	n-3-4-me-5-nta-tech-summary-t0.pdf

[120] For a complete list of compounds detected in the aerosol by non-targeted analysis, see PMTA Section H.1.1.1 Chemistry and Stability (h-1-1-1-chemistry-and-stability.pdf) (Table 10 [Virginia Tobacco 5%, Non-Intense, p. 51-54], Table 11 [Virginia Tobacco 5%, Intense, p. 55-59], Table 16 [Virginia Tobacco 3%, Non-Intense, p. 69-72], Table 17 [Virginia Tobacco 3%, Intense, p. 72-76], Table 22 [Menthol 5%, Non-Intense, p. 85-88], Table 23 [Menthol 5%, Intense, p. 89-93], Table 28 [Menthol 3%, Non-Intense, p. 102-105], and Table 29 [Menthol 3%, Intense, p. 106-109]).

SKU	Time Point (months)	Report Description	File Name
	0	GC NTA Vendor Report	n-3-4-[redacted]-nta-report-menthol-5-t0.pdf
	0	LC NTA JLI Report	n-3-4-me-5-nta-lcms-t0-tech-summary.pdf
	6 (aged pods)	T6 NTA Technical Summary	n-3-4-me-5-nta-tech-summary-t6.pdf
	6 (aged pods)	GC NTA Vendor Report	n-3-4-[redacted]-me-5-aged-pod-report-t6.pdf
Menthol 3.0%	0	T0 NTA Technical Summary	n-3-4-me-3-nta-tech-summary-t0.pdf
	0	GC NTA Vendor Report	n-3-4-[redacted]-nta-report-menthol-3-t0.pdf
	0	LC NTA JLI Report	n-3-4-me-3-nta-lcms-t0-tech-summary.pdf

NTA=non-targeted analysis; GC=gas chromatography mass spectrometry; LC=liquid chromatography high resolution mass spectrometry

Relevant to leachables, JLI provided non-targeted analysis data that are representative of real-time stability across all JUUL products. As shown in the table above, JLI provided non-targeted analysis data at the initial time point for all JUUL products, six months for Menthol 5.0%, and twelve months for Virginia Tobacco 5.0%.[121]

Overall, the non-targeted analysis data provided in the PMTAs are representative of low potential for user exposure to pod leachables. Further, all these data show that none of the leachables in question were detected in JUUL product aerosols under intense and non-intense puffing conditions over the product shelf life. That is, for the chemicals identified as a theoretical concern in the simulated leachables studies, the non-targeted analysis data show they are not an actual concern because they are not detected in the aerosol.

CTP-OS stated that "the risk assessment determined these compounds should be quantified during real-time stability assays and in the aerosol generated from the new tobacco products" and that "the applicant did not provide data demonstrating these measurements were performed."[122] CTP-OS failed to recognize that the absence of these

[121] Due to the identical nature of the pod components and the similarity of the base formulations used in the JUUL System, potential leachables are not expected to differ between formulations. This hypothesis is confirmed by the data: the majority of detected extractable and leachable compounds identified in Virginia Tobacco 5.0% at T=12 months (thirteen total compounds) and in Menthol 5.0% at T=6 months (twelve total compounds) have identical tentative identifications (eight compounds). PMTA Section N. 3. 4. Virginia Tobacco 5% NTA Technical Summary T12 (n-3-4-vt-5-nta-tech-summary-t12.pdf); PMTA Section N. 3. 4. Menthol 5% NTA Technical Summary T6 (n-3-4-me-5-nta-tech-summary-t6.pdf).

[122] FDA 1st Cycle Toxicology Review of JLI's PMTAs, p 27.

compounds in the aerosol data already provided confirms that they are not detected in the aerosol and thus do not present a health risk to the user.

In its initial PMTAs and as amended by the Deficiency Response, JLI did not "decline" to provide aerosol data on the leachable compounds. Rather, in keeping with the risk assessment framework and approach as discussed in Section H.1.1.4 Quantitative Risk Assessment of the PMTAs, JLI did not provide *targeted* "aerosol measurements" for the compounds because they were not detected in the aerosol non-targeted analysis.

Targeted testing for these compounds is unnecessary and unduly burdensome because:

- The non-targeted analysis indicates the compounds are not detected in the aerosol; and

- Relevant analytical methods for the compounds are not currently available and would need to be developed with the idea of quantifying something that JLI has no reason to believe is present, let alone present at levels that would be of toxicological concern.

If any of the leachables in question — either the two as identified correctly or the four as misinterpreted — were present in the JUUL System aerosol at measurable levels, JLI's non-targeted analysis of the aerosols were capable of detecting those compounds.

JLI's assessment and resolution of phenol as a leachable and of potential toxicological concern is illustrative. Unlike the other compounds discussed above, JLI detected phenol in its non-targeted analysis and followed its risk-assessment framework by conducting a follow-up targeted analysis of phenol to quantify exposure. Quantification was warranted because: (i) phenol was detected in the non-targeted analysis, meaning it is present at some detectable level in the aerosol; and (ii) phenol is a proposed HPHC and known mutagenic compound, raising a potential toxicological concern.

With the aerosol yields for phenol, CTP-OS went on to do an "offsetting" evaluation, in which it considered the risks posed by this constituent as well as other mutagenic and carcinogenic constituents in relation to combustible cigarettes. It concluded that:

> [W]hile it may be assumed that inhaled phenol might possess mutagenicity and carcinogenic potential, when evaluating the totality of reductions in HPHC yield for the new products, compared to the combustible cigarette comparator product, the potential toxicity of phenol is offset by the totality of HPHC yield reduction in the new products, including the 99% reduction in phenol yields.[123]

[123] FDA 2nd Cycle Toxicology Review of JLI's PMTAs, p. 10.

CTP-OS could have done a parallel offsetting evaluation of the leachables in question here. For example, when CTP-OS considered that 3R4F smoke contains between 5.58 mcg to 9.96 mcg of phenol per mg of nicotine depending on the puffing condition, it should have also considered that the levels of the leachables in question were originally reported at levels of 0.219 mcg per mg nicotine and 0.178 mcg per mg nicotine respectively in the 18-month whole pod leachables studies. [124] Based on these comparator values, CTP-OS could have conducted an offsetting analysis that would have concluded that the levels of phenol, a known mutagenetic compound, in cigarette smoke greatly exceed the low levels of the leachables in question that were reported in the original whole pod leachables studies.

More to the point, based on the non-targeted analysis aerosol data provided by JLI in its PMTAs, CTP-OS should have concluded that there was no risk posed by these leachables in question to offset because they were not detected in the aerosol.

All leachables detected in the aerosol produced by the JUUL System are known and quantified under intense and non-intense use of the products in the aerosol data already provided to CTP-OS. The leachables of interest to CTP-OS, however, were not detected in the aerosol and thus do not present a health risk to the user.

iii. CTP-OS Can Conduct an Accurate and Complete Risk Assessment of JUUL Products When the Data Provided in JLI's PMTAs Are Reviewed and Interpreted Correctly

CTP-OS stated that JLI's Deficiency Response "provided a new risk assessment" of the updated compounds.[125] CTP-OS took issue with the risk assessment because it "uses a less conservative approach (Carthew et al., 2009) than what was used in the original risk assessment (Escher et al., 2010)"[126] in the initial PMTAs. CTP-OS also noted that, while JLI's risk assessment determined that the leachables "are not present at levels of toxicological concern[,]" use of the original approach does suggest the products are of toxicological concern.[127] CTP-OS concluded that the "risk assessment has not adequately addressed the toxicology concerns regarding these leachables constituents . . . ."[128]

In the Deficiency Response, JLI claimed to use the same approach applied in the initial PMTAs leachables risk assessments. CTP-OS, however, is right that JLI applied the

[124] JLI Deficiency Response to Question 17.

[125] FDA Marketing Denial Order for JLI's PMTAs, p. 4.

[126] *Id.* at 4; Carthew P., Clapp C., Gutsell S. (2009) Exposure based waiving: the application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. *Food and Chem Toxicology,* 47(6):1287-95; Escher S.E., Tluczkiewicz I., Batke M., Bitsch A., Melber C., Kroese E.D., Buist H.E., Mangelsdorf I. (2010) Evaluation of inhalation TTC values with the database RepDose. *Regulatory Toxicology and Pharmacology,* 58(2):259-74; *See also* PMTA Section N.12 Escher et al 2010 (n-12-escher-et-al-2010.pdf).

[127] FDA Marketing Denial Order for JLI's PMTAs, p. 4.

[128] *Id.* at 5.

Carthew, et al., 2009 approach instead of the Escher et al., 2010 approach when deriving certain values used in the risk assessment for these leachables. JLI initially used the Carthew, et al. 2009 approach for its risk assessment of aerosol, but not leachable constituents. JLI mistakenly applied Carthew, et al. 2009 for the leachables risk assessment in the Deficiency Response.[129]

But the use of more or less conservative values for the leachables risk assessment is inconsequential here, given the overriding aerosol data which demonstrates these leachables are not detected in the aerosol and thus do not pose a health risk to the user. The correct or incorrect approach for a predictive leachables risk assessment is not singularly determinative; nor can it preclude a determination of APPH for the JUUL System.

Based on the information, data, and analysis provided in JLI's PMTAs — including the leachables study data and comprehensive aerosol data — CTP-OS had sufficient information to both complete its own leachables risk assessment and consider and draw meaningful conclusions from JLI's comprehensive whole product risk assessment. In fact, CTP-OS indicated that it did complete its own Escher-based leachables risk assessment for the leachables in question based on the levels detected in the simulated e-liquid,[130] but chose not to go on to consider the whole product risk assessment. Had it done so, it may have realized that the aerosol data provided in the PMTAs show an absence of actual exposure and risk to the user.

All JLI's leachables risk assessments were conducted under a conservative approach. The risk assessment of the leachables identified in the simulated e-liquid studies assumed complete transfer to the aerosol and predicts inhalation risks based on the best available, but sometimes limited, toxicity data to ensure vigilant monitoring. Where JLI could not reach firm conclusions based on the limited nature of the available toxicity data, as was the case for the leachables in question, JLI flagged those compounds for future monitoring.[131] This is a highly health precautionary methodology for screening purposes to support product stewardship; however, it is the whole product risk assessment that forms the basis for the more complete and final determination of the toxicological risks.

Following the stepwise risk assessment approach, the simulated e-liquid leachables assessment represents an initial step to characterize potential health risk from constituents that may be introduced from the JUULpod materials and lead to potential consumer exposure. The potential risks estimated using simulated e-liquid data are superseded by actual aerosol data, and the whole product risk assessment forms the basis for the final evaluation of toxicological risks.

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[129] JLI Deficiency Response to Question 17, p. 137–138.

[130] FDA TPL Review of JLI's PMTAs (Toxicology), p. 19.

[131] PMTA Section H.1.1.4 Quantitative Risk Assessment, p. 38–39 (h-1-1-4-quantatitative-risk-assessment.pdf).

As CTP-OS observed, JLI's data show overall decreased HPHC yields and reduced BOE levels:

> HPHC Yields: Toxicological evaluation of the mainstream aerosol yields of HPHCs included on the HPHC list, and other quantified chemical constituents found that levels of these compounds in the new products are not present at levels of concern. This toxicological evaluation was made by comparing the mainstream aerosol HPHC yields of the new products to the mainstream smoke HPHC yields of the 3R4F combustible cigarette comparator. A limitation of this toxicological evaluation for remaining non-HPHC chemical constituents measured in the mainstream aerosol of the new products is that the levels of propylene glycol (PG), menthol and several other constituents were not provided for the CC comparison product, therefore no comparisons to the new products can be made for these constituents. This limitation is outweighed by the total reduction in mainstream aerosol yields of the measured HPHCs in the new products versus the 3R4F CC comparison product, and by taking into account the available scientific literature suggesting reduced inhalation toxicity of PG relative to other listed HPHCs.[132]
>
> BOEs: Clinical studies measuring biomarkers of exposure (BOE) levels showed that after 6 days of exclusive use of the new products, CC users who switched to exclusive use of the new products had BOE levels similar to those in the tobacco product cessation group.[133]

CTP-OS stated that such results could be used to offset the risk posed by genotoxic leachables, if only JLI had provided data indicating if and how much of the leachables in question are transferred into aerosol.[134]

As discussed in detail above, JLI provided those data in its PMTAs. The data show that: (i) the leachables in question as correctly identified are not genotoxic and (ii) they are not detected in the aerosol.[135] Additionally, JLI conducted a risk assessment for all aerosol constituents to further characterize the potential health risk from exposure to HPHCs and constituents detected in the non-targeted analysis (as shown in Table 3 below). This comprehensive approach accounts for all leachables classified in the aerosol of the JUUL System.

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[132] FDA TPL Review of JLI's PMTAs (Toxicology), p. 11–12.

[133] *Id. at* 12.

[134] FDA Marketing Denial Order for JLI's PMTAs, p. 3.

[135] Section IV.A.1.c.ii *supra*.

Table 3 Classification and Number of Constituents Detected in the Non-Targeted Analysis of the JUUL System Aerosols

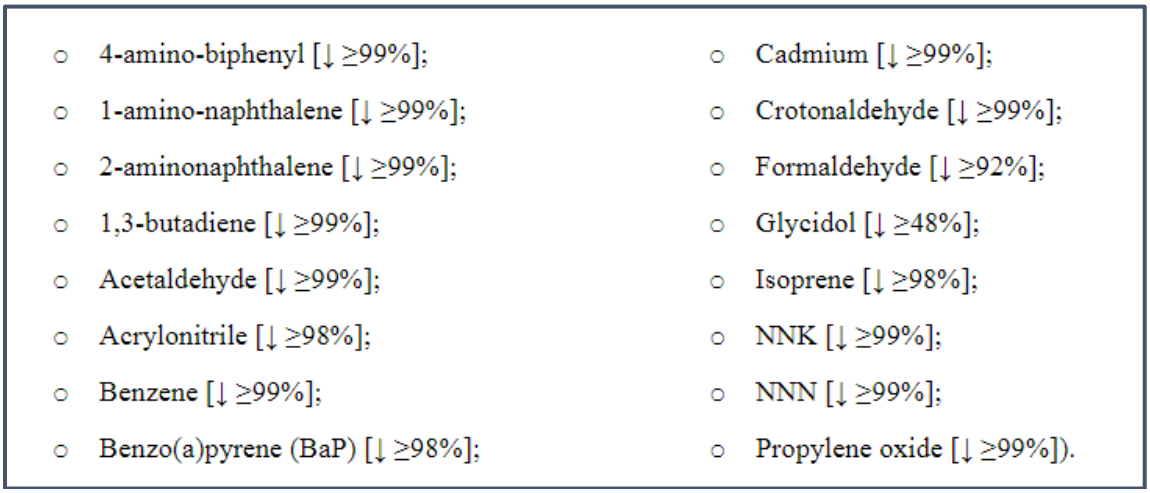
Group Name	Virginia Tobacco 5.0% (# compounds)		Virginia Tobacco 3.0% (# compounds)		Menthol 5.0% (# compounds)		Menthol 3.0% (# compounds)	
Puffing Regimen	Intense	Non-Intense	Intense	Non-Intense	Intense	Non-Intense	Intense	Non-Intense
Ingredients	13	12	13	11	20	21	21	19
HPHCs	1	1	1	0	2	2	3	2
E&L	3	3	5	5	8	3	8	6
Reaction Products	64	58	57	54	58	56	51	48
Not Rationalized	11	8	8	2	5	2	2	2
Total	**91**	**81**	**83**	**72**	**93**	**84**	**84**	**77**
# Nicotine Degradants	35	31	29	29	29	30	24	22
Common to Cigarette and JUUL[a]	33		29		39		39	
Exclusive to JUUL[a] (# nicotine degradants)[b]	68 (30)		63 (29)		68 (29)		59 (23)	

Source: PMTA Section H.1.1.4 Quantitative Risk Assessment, p. 56 Table 8 (h-1-1-4-quantatitative-risk-assessment.pdf)
E&L=extractable and leachable; HPHC=harmful and potentially harmful constituents; NI=non-intense; No.=number; NTAs=Non-targeted analytes
[a] Comparison to compounds detected in cigarette smoke and compounds detected in the GC and LC non-targeted analysis; compounds exclusive to the JUUL System aerosols (intense and non-intense combined) (PMTA Section H.1.1.1 Chemistry and Stability, h-1-1-1-chemistry-and-stability.pdf)
[b] Of the NTAs exclusive to JUUL, the largest group was nicotine degradants

On genotoxicity, which appears to be a primary cause for CTP-OS's concern, it should be noted that the leachable compounds as updated no longer have genotoxic structural alerts.[136] Further, all JLI measured carcinogenic constituents (fifteen HPHCs and one proposed HPHC [glycidol]) are significantly lower in the JUUL System aerosols compared to cigarette smoke:

[136] JLI Deficiency Response to Question 17; Appendix 17.01 Whole Pod Leachables Report 238873 Version 2 (app-17-02-n-3-4-[redacted]whole-pod-leachable-report-2.pdf); Appendix 17.02 Whole Pod Leachables Report 238874 Version 2 (app-17-01-n-3-4-[redacted]-whole-pod-leachable-report-1.pdf).

Figure 4 Reductions in Measured Carcinogenic Constituents Compared to Cigarette Smoke*



* BLOQ analytes include: 4-amino-biphenyl, 1-amino-naphthalene, 2-aminonaphthalene, 1,3-butadiene, acrylonitrile, benzene, benzo(a)pyrene (BaP), cadmium, crotonaldehyde, isoprene, NNK, NNN, propylene oxide.

As CTP-OS found in the 2nd Cycle Chemistry Review for JLI's PMTAs: "The aerosol HPHC yields from [JUUL products] are *much lower* than the mainstream smoke HPHC yields from the 3R4F reference cigarette, except for glycerol."[137] And according to CTP-OS: "In the clinical studies, significant reductions in blood and urinary BOEs indicate that exposure to carcinogens and other toxicants present in cigarette smoke were greatly reduced with exclusive use of the new products compared to [combustible-cigarette] smoking."[138]

Of these carcinogenic HPHCs, seven (NNK, NNN, BaP, 1,3-butadiene, benzene, acetaldehyde, and formaldehyde) were identified by the World Health Organization (WHO) and other published studies among the "most hazardous" in cigarette smoke.[139] These

[137] FDA 2nd Cycle Chemistry Review of JLI's PMTAs, p. 15 (emphasis added). On glycerol, FDA stated that the "[h]igh level of glycerol aerosol yield in the new products is not a concern from a chemistry perspective since the level of formaldehyde and acrolein aerosol yields, common degradation products of glycerol upon heating, in the new products are much lower than those in the MSS yields of 3R4F reference cigarette." *Id.*

[138] FDA TPL Review of JLI's PMTAs (Toxicology), p. 13.

[139] PMTA Section H.1.1.4 Quantitative Risk Assessment, p. 40 (h-1-1-4-quantatitative-risk-assessment.pdf); The World Health Organization identified nine compounds as the "most hazardous" which should be considered for mandatory reductions in cigarette smoke (World Health Organization. (2007). WHO Technical Report Series Vol. 945: The scientific basis of tobacco product regulation; World Health Organization. (2008). WHO Technical report series Vol. 951: The scientific basis of tobacco product regulation: second report of a WHO study group; World Health Organization. (2019). WHO study group on tobacco product regulation: report on the scientific basis of tobacco product regulation: seventh report of a WHO study group). The nine compounds are acetaldehyde, acrolein, benzene, benzo[a]pyrene, 1,3-butadiene, carbon monoxide, formaldehyde, NNK, and NNN.

lower levels of carcinogenic HPHCs in JUUL System aerosols compared to cigarette smoke support substantial reductions in potential exposures and associated cancer risk.[140]

CTP-OS has data on the levels of and potential health risk posed by all aerosol constituents produced by JUUL products, which enable CTP-OS to conduct an accurate and complete risk assessment of the JUUL System. In fact, JLI provided such a risk assessment, incorporating targeted and non-targeted analysis aerosol values. A quantitative evaluation of potential exposures to aerosol constituents generated by the JUUL System is detailed in Section H.1.1.4 Quantitative Risk Assessment of the PMTAs.[141] Moreover, the whole product risk assessments provide a foundation for comparison of potential health risks from JUUL products to other tobacco products, including combustible cigarettes, IQOS, and marketed ENDS products.[142]

If CTP-OS had reviewed these data completely and correctly, it would have seen that the significant decreases in toxicant levels indicate a potential for substantial reductions in exposures and associated cancer risks and non-cancer hazards from the use of the JUUL System compared to smoking cigarettes.

iv. CTP-OS Deviated from Established Process and Decision-Making Principles by Failing to Complete a Full Toxicological Evaluation Because of "Unknown" Leachables

JLI notes that CTP-OS has previously authorized PMTAs in which applicants were unable to identify and quantify the levels of certain leachables of toxicological concern. In these prior reviews, unlike here, CTP-OS went on to conduct a full toxicological evaluation and determine that the products were APPH.

In the review of PMTAs for Logic ENDS products, CTP-OS noted that:

> The applicant submitted a risk assessment for the identified, partially identified, and unknown simulated leachable compounds in the new products. The applicant concluded that the potential risks to consumers from identified and partially identified leachable compounds are acceptable but *risk for the unknown leachable compound was above the benchmark value of 1.0 which indicates potential risks of concern.* Although the simulated leachable compounds for all new products can be hazardous, at the low levels present, *if*

[140] PMTA Section H.1.1.3 Qualitative Risk Assessment (h-1-1-3-qualitative-risk-assessment.pdf).

[141] PMTA Section H.1.1.4 Quantitative Risk Assessment, section 3.2 (h-1-1-4-quantatitative-risk-assessment.pdf).

[142] PMTA Section H.1.1.3 Qualitative Risk Assessment (h-1-1-3-qualitative-risk-assessment.pdf); PMTA Section H.1.1.4 Quantitative Risk Assessment (h-1-1-4-quantitative-risk-assessment.pdf).

there is any contribution towards cancer hazard, these risks are outweighed by decreases in HPHCs by 83-99% in all new products.[143]

But for JLI's PMTAs, CTP-OS claimed that "with unknown aerosol yields of these leachables and their disputed chemical identities, resulting in an unknown cancer potency and genotoxicity risk, it is not possible to do an offsetting evaluation for carcinogens (where decreased levels of one carcinogen mitigate increased levels of another)."[144]

JLI not only provided the known aerosol yields in its PMTAs, which reflect that these leachables in question are not detected in the aerosols, but also conducted a comprehensive and quantified risk assessment for the product as a whole in its PMTAs.[145] Like its approach and analysis for the Logic PMTAs, CTP-OS could and should have concluded that, if there were any contribution towards cancer hazard posed by the leachables in question, which were detected at very low levels in the simulated e-liquid studies, these risks are outweighed by substantial decreases in HPHCs from the JUUL System compared to combustible cigarettes.

Additionally, the chemistry, stability, and other nonclinical data are supportive of the risk assessment's conclusion that the JUUL System is substantially less toxic than combustible cigarettes and IQOS and comparable to other marketed ENDS products.[146] A complete review of these converging lines of evidence overcomes any apparent or actual uncertainties in the presence of low levels of leachables of potential toxicological concern and supports the determination that the marketing of the JUUL System is APPH.

v. CTP-OS Did Not Provide a Full and Fair Opportunity to Address Its New Requirement for Specific Testing Data on the Leachables in Question

In the administrative process, an applicant should have a full and fair opportunity to respond to deficiencies that are material to an agency decision. This ensures that clear rules are established, decision-making processes are followed, and standards are applied equitably among applicants.

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[143] FDA TPL Review of PMTAs for Logic Technology Development LLC.'s PMTAs PM0000529.PD1–PM0000531.PD1, PM0000535.PD1–PM0000537.PD1, PM0000540.PD1–PM0000541.PD1, p. 37 (emphasis added).

[144] FDA TPL Review of JLI's PMTAs (Toxicology), p. 20–21.

[145] PMTA Section H.1.1.4 Quantitative Risk Assessment (h-1-1-4-quantitative-risk-assessment.pdf).

[146] PMTA Section H.1.1 Summary of Non-Clinical Studies (h-1-1-summary-of-nonclinical-studies.pdf) summarizing analytical data (Section H.1.1.1 Chemistry and Stability), toxicological data (Section H.1.1.2 Toxicology), a qualitative risk assessment (Section H.1.1.3 Qualitative Risk Assessment), and more in-depth quantitative risk assessment (Section H.1.1.4 Quantitative Risk Assessment), as well as other data relevant to the overall health risk evaluation of the JUUL System.

Here, however, CTP-OS imposed a new testing requirement to address the deficiency during the decision-making process. CTP-OS said it needed one thing in the Deficiency Letter; then turned around and asked for something else in the MDO.

In the MDO, CTP-OS stated that JLI needed to provide targeted aerosol data for the leachables in question from JUUL products subject to accelerated aging conditions under intense and non-intense use conditions (i.e., not subject to real-time stability). [147] In the Deficiency Letter, however, CTP-OS emphasized the "need for evaluation of [the leachables in question] during real-time stability testing" under intense and non-intense use conditions (i.e., not subject to accelerated aging conditions)." [148] Such data, according to CTP-OS, would enable it to "perform a full toxicological evaluation of these leachable constituents."[149]

The mainstream aerosol data generated from JUUL products during real-time stability, which JLI already provided in its initial PMTAs, are more relevant because they are the most indicative of which leachables (including those in question) could transfer to the aerosol and be exposed to the user. First, CTP-OS overlooked the comprehensive aerosol data it already had; now it changed its mind on what data it wants.

This moving target, appearing for the first time in the MDO, denied JLI a full and fair opportunity to address CTP-OS's concerns.

2. Information in the PMTAs Provides Reliable and Valid Data to Assess the Genotoxic Potential of JUUL Products and Relative to Comparator Products Including Combustible Cigarettes (Deficiencies 2 and 3)

a. Basis for the Deficiencies

JLI's PMTAs included a stepwise series of in vitro and in vivo genotoxicity studies. Genotoxicity was first assessed in JUUL product and ENDS comparator product e-liquids and aerosol condensates, as well as reference cigarette smoke, using the in vitro micronucleus (MN) assay with the human lymphoblastoid cell line TK6 in accordance with OECD TG 487. Based on potential hazard identifications for some JUUL products, JLI followed established scientific principles and FDA's own guidance to further investigate the potential risks with in vivo inhalation genotoxicity studies.[150]

While Deficiency 2 focuses on methodological limitations associated with the conduct of the in vitro MN assay, Deficiency 3 focuses on the potential genotoxicity of

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[147] FDA Marketing Denial Order for JLI's PMTAs, p. 5.

[148] FDA Deficiency Letter to JLI for PMTAs, p. 8.

[149] *Id.*

[150] FDA Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, (2019)

certain JUUL products based on the results of the in vitro MN assay and in vivo studies. Because of the nexus between the studies and how they collectively inform an assessment of the genotoxic potential of JUUL products, JLI addresses both deficiencies together.

For Deficiency 2, the MDO found that "the methodology [JLI] used in the assays to evaluate in vitro genotoxicity (i.e., the in vitro micronucleus assay) raises concerns regarding the scientific validity of the assay results," due to "uneven application of acceptance criteria (including inconsistent cell counting) for the scoring and evaluation of positive and negative genotoxic responses" and "use of different methodologies to evaluate the new products and the comparison products." The MDO also stated that the methodological choices are "not supported by TG 487 or by [the] submitted study protocol" and "prevent[] accurate and meaningful toxicological conclusions on the genotoxic potential of the new products from being made."[151]

For Deficiency 3, the MDO found that the in vitro MN results "indicate that PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) with PM0000878 [JUUL Device] and PM0000879 [JUUL Locked Device] may be relatively more genotoxic than the combustible cigarette comparison product." The MDO noted that JLI provided data from an in vivo genotoxicity study for Menthol 5.0% and Virginia Tobacco 3.0%, which indicated negative responses for both induction of DNA damage and genotoxicity in vivo. The MDO, however, stated that "the results were highly variable and may not reliably indicate the occurrence of DNA damage" and "the inclusion of a combustible cigarette comparison product within the in vivo genotoxicity study is needed to perform a complete toxicological evaluation[.]" Further, the MDO took issue with the interpretation of the negative in vivo study results, stating "[i]t is not scientifically sufficient or adequate to accept the negative genotoxicity results from the in vivo genotoxicity study without an explanation or justification for why the positive in vitro genotoxicity results should be considered biologically insignificant or irrelevant."[152]

As discussed below, rather than conducting a complete science-based review of the data provided in JLI's PMTAs, the MDO both dismissed data on methodological grounds and then turned around to use the same data to draw incorrect conclusions on the potential toxicity of certain JUUL products. JLI maintains that it conducted scientifically valid in vitro and in vivo studies that inform the evaluation of the genotoxic potential of JUUL products. The in vitro and in vivo studies should have been interpreted on a case-by-case basis, considering methodological limitations and all available biological and chemical data, and placed in the context of the overall health risk evaluation.

Assessed adequately, a rigorous review of the body of scientific evidence — and in light of the consistent supporting biological and chemical data — addresses CTP-OS's concerns about the genotoxic potential of JUUL products compared to combustible

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[151] FDA Marketing Denial Order for JLI's PMTAs, p. 6–7.

[152] *Id. at* 9–10.

cigarettes. An adequate assessment, in turn, enables CTP-OS to conduct an accurate and complete toxicological evaluation.

b. Summary of Facts and Background

As described in PMTA Section H.1.1.2 Toxicology, JLI conducted a series of in vitro and in vivo toxicity studies to support an assessment of the health risks associated with the use of the JUUL System and relative to combustible cigarettes and other comparator products. Because of the variety of potential toxic responses produced by conventional tobacco products (i.e., combustible cigarettes), there is currently no single validated in vitro assay that can provide comprehensive information on product toxicity. JLI selected an in vitro test battery consistent with the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) standard battery that is commonly used for tobacco products. This covers three major toxicity endpoints: cytotoxicity (Neutral Red Uptake [NRU] cytotoxicity assay), genotoxicity (MN assay), and genotoxicity via a mutagenic mode of action (Ames assay).[153]

Genotoxicity tests are designed to detect compounds that can induce genetic damage by various mechanisms. Different in vitro genotoxicity studies provide different insights based on several factors — including the mechanisms underlying the measured responses, metabolic activation system, experimental conditions, and cell type used — and each study comes with its own benefits and limitations. Accordingly, the assessment of genotoxic hazards to humans follows a stepwise approach, beginning with a basic battery of in vitro tests covering multiple modes of action followed by, in some cases, in vivo testing.

While there are no specific requirements for in vitro genotoxicity studies in support of a PMTA, JLI followed FDA's Guidance on PMTAs for ENDS, which suggests using the ICH S2(R1) guidance and Organization for Economic Cooperation and Development (OECD) protocols as a guide to assess genotoxic potential.[154] For genotoxicity, the recommended core test battery includes two or three validated tests with at least one in vitro test in a bacterial cell line (e.g., Ames) and one in mammalian cell line (e.g., MN).

The MN assay specifically screens for potential genotoxic concerns by detecting chromosomal damage by quantifying micronuclei in the cytoplasm during interphase. Cell cultures are exposed to the test chemical under certain conditions, then grown for a period that is sufficient to allow chromosome damage or other effects on cell cycle/cell division that would lead to the formation of micronuclei in interphase cells. The relevant OECD testing guideline outlines the assay acceptance criteria as well as the data evaluation and

[153] CORESTA In Vitro Toxicology Testing Sub-Group, Technical Report, Rationale and Strategy for In Vitro Toxicology Testing of Combustible Tobacco Products (2019).

[154] See FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, at 36 (2019).

scoring methodologies.[155] The in vitro MN assay provides binary yes/no outcomes — scored positive, negative, or equivocal (not allowing a conclusion of positive or negative) — based on an evaluation and interpretation of results against the set criteria.[156]

For its PMTAs, JLI conducted in vitro MN assays using the human lymphoblastoid cell line TK6. JLI tested the JUUL System and ENDS comparator e-liquids and aerosol condensates. JUUL aerosol condensates were collected under two puffing regimens (ISO 20768 puffing regimen and a JUUL-specific intense puffing regimen), comparator ENDS aerosol condensates were collected under the ISO 20768 puffing regimen, and 3R4F and 1R6F cigarette smoke condensates were collected under the Health Canada Intense puffing regimen.[157] In accordance with OECD TG 487, the samples were evaluated across three treatment conditions (4-hour [short treatment] in the presence or absence of S9 metabolic activation, followed by recovery, and 27-hour [log-term treatment] in the absence of S9). At least three sample concentrations were selected for MN evaluation based on level of cytotoxicity, which was based on OECD TG 487. JLI provided technical summaries and study reports for the in vitro genotoxicity studies in PMTA Section N.3.1.2 Micronucleus Testing.

The in vitro MN response for JUUL products was first evaluated counting 2,000 cells per concentration for each treatment condition. For responses that were unequivocally positive or equivocal, JLI counted an additional 2,000 cells and the results of the combined 4,000 cells were evaluated. For the evaluation of comparator products, which was initiated after the in vitro MN assays on JUUL products were completed, all cultures were evaluated counting 4,000 cells per concentration. As the 4,000-cell count was used from the start, no additional cells were counted for the comparator products regardless of outcome.

In Question 19 of the Deficiency Letter, CTP-OS asked JLI to "[p]rovide and discuss the rationale for using separate criteria for evaluation and scoring of your new tobacco products versus their comparators."[158] In its Deficiency Response, JLI explained the rationale for the cell counting approach and why it believed that the criteria used and data generated were nonetheless valid and in keeping with OECD TG 487.[159]

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[155] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 487: In Vitro Mammalian Cell Micronucleus Test (2016).

[156] The full set of study criteria are provided in Appendix 2.

[157] JLI evaluated 1R6F reference cigarette smoke, using the same assay and test conditions, after the initial set of studies was completed. The 1R6F results were included in JLI's Deficiency Response.

[158] FDA Deficiency Letter to JLI for PMTAs, p. 9.

[159] Additional information on this approach is provided in Appendix 2.

Figure 5 (aerosol condensate and smoke condensate) and Figure 6 (e-liquid) below summarize the in vitro MN results across all products tested. The groupings indicate the puffing regimen, and the columns indicate the test condition.[160]

[Figures on the next pages]

[160] All results are taken directly from the study reports submitted as part of JLI's PMTAs. *See* N.3.1.2 Technical Summary Condensate (n-3-1-2-mn-testing-technical-summary-condensate.pdf); N.3.1.2. Technical Summary Liquid (n-3-1-2-mn-testing-technical-summary-liquid.pdf).

Figure 5 In Vitro MN Results for JUUL Aerosol, Comparator ENDS Aerosol, and Cigarette Smoke Condensate

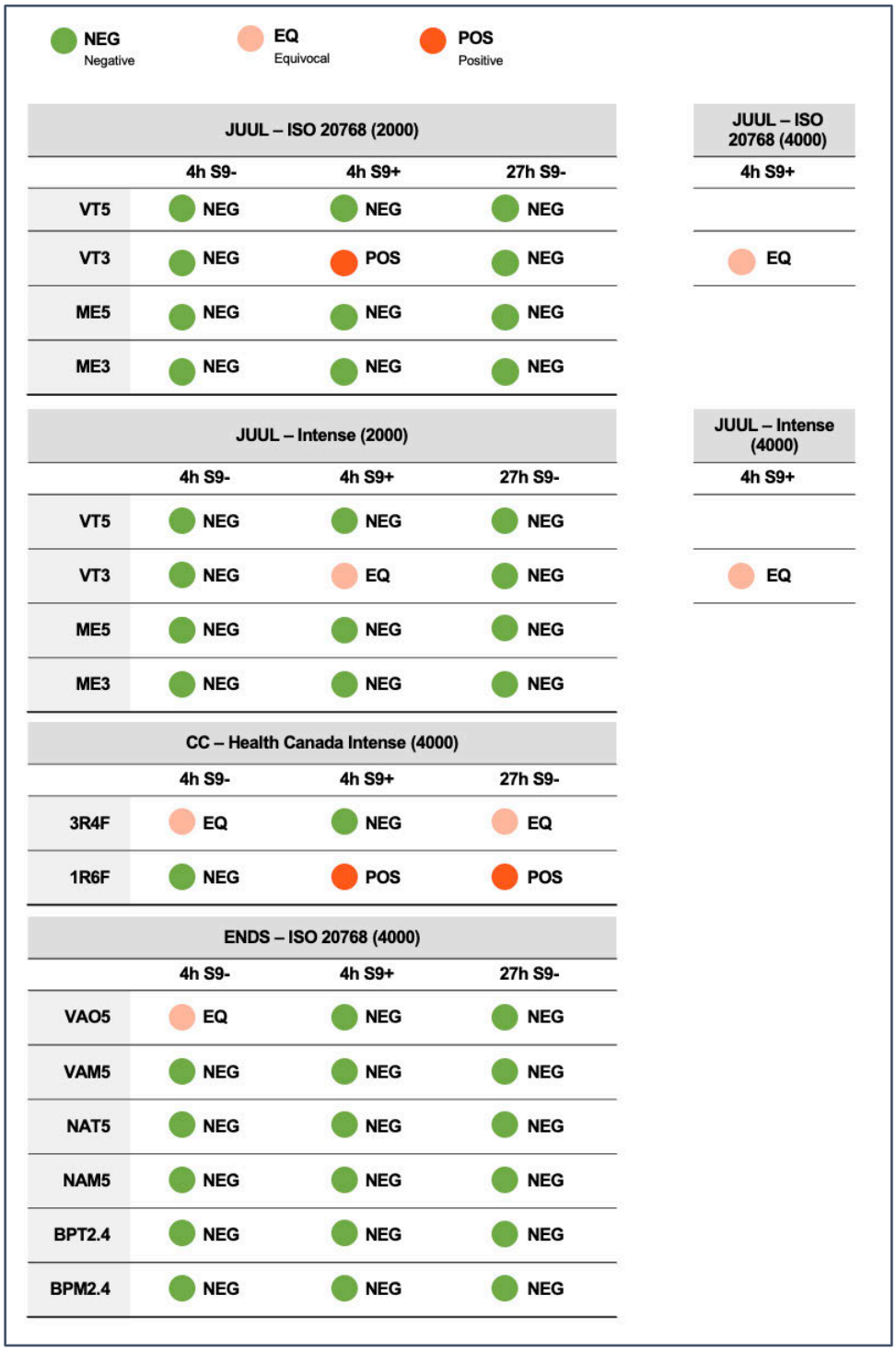

Figure 6 In Vitro MN Results for JUUL E-liquids and Comparator ENDS E-liquids

JUUL (2000)	4h S9-	4h S9+	27h S9-
VT5	POS	EQ	EQ
VT3	NEG	NEG	NEG
ME5	POS	POS	NEG
ME3	NEG	NEG	NEG

JUUL (4000)	4h S9-	4h S9+
VT5	NEG	NEG
VT3		
ME5	POS	POS
ME3		

ENDS (4000)	4h S9-	4h S9+	27h S9-
VAO5	EQ	EQ	EQ
VAM5	EQ	NEG	NEG
NAT5	NEG	EQ	NEG
NAM5	POS	EQ	EQ
BPT2.4	NEG	NEG	POS
BPM2.4	NEG	NEG	EQ

Based on results from the initial cell counts (2,000 for JUUL products and 4,000 for comparator products) for tested aerosol condensate and smoke condensate, the in vitro MN assay found that:

- Aerosol condensates for Virginia Tobacco 5.0%, Menthol 5.0%, and Menthol 3.0% were negative in all test conditions.
- Aerosol condensates for Virginia Tobacco 3.0% were negative in four out of the six test conditions, equivocal in one, and positive in one.
- Smoke condensate for the 3R4F reference cigarette was equivocal in two test conditions and negative in one.
- Smoke condensate for 1R6F reference cigarette was positive in two test conditions and negative in one.
- Comparator ENDS aerosol condensates were negative in all test conditions except for one equivocal result.[161]

[161] PMTA Section N.3.1.2. Technical Summary Condensate (n-3-1-2-mn-testing-technical-summary-condensate.pdf).

Overall, aerosols for Virginia Tobacco 5.0%, Menthol 5.0%, and Menthol 3.0% and five of the six comparator ENDS were not genotoxic under any test condition. Comparator Vuse Alto Original Tobacco 5% aerosol had an equivocal result, and Virginia Tobacco 3.0% aerosol had a positive result and equivocal result. 3R4F smoke had two equivocal results and 1R6F smoke had two positive results.

For the e-liquids, based on results from the initial cell counts (2,000 for JUUL products and 4,000 for comparator products), they produced a mixture of negative, equivocal, and positive responses across JUUL products and comparator ENDS products. For JUUL products, Menthol 5.0% was positive under two test conditions and Virginia Tobacco 5.0% was positive in one condition and equivocal in another.

Based on the ICH Guidance S2(R1), the in vivo significance of the in vitro MN results was further investigated with Menthol 5.0% and Virginia Tobacco 3.0% aerosol condensates in an in vivo genotoxicity study using two endpoints (MN and Comet assays).[162] The in vivo genotoxicity study was performed according to OECD guidelines (MN, TG 474;[163] Comet, TG 489[164]). Sprague-Dawley rats were exposed to aerosols from the JUUL System with Menthol 5.0% or Virginia Tobacco 3.0% groups. The studies were conducted as nose-only, four-day inhalation studies at the maximum tolerable nicotine dose. The in vivo genotoxicity responses were negative (no significant increases compared to the negative control; with the negative and positive control within the historical range) in terms of %MN in the bone marrow or the DNA breakage in liver, lung, and nasal tissues. Therefore, under the test conditions, the JUUL System aerosols for Menthol 5.0% and Virginia Tobacco 3.0% were not genotoxic the in vivo study.[165]

Additional information on the facts and background relating to Deficiencies 2 and 3, including data and analysis from JLI's PMTAs and Deficiency Response, are included in Appendix 2.

c. Analysis

i. CTP-OS Did Not Adequately Consider Scientifically Valid Data That Are Relevant to Assess the Genotoxic Potential of JUUL Products

First, the MDO stated that "[t]he inconsistent use of assay acceptance criteria resulted in unequal treatment of test articles within the genotoxicity assay, which adversely affects the scientific validity of the assay, thereby preventing accurate and

[162] FDA, Guidance for Industry: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (2012).

[163] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 474: Mammalian Erythrocyte Micronucleus Test (2016).

[164] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 489: *In Vivo* Mammalian Alkaline Comet Assay (2016).

[165] *See* PMTA Section N.3.2 Technical Summary (n-3-2-in-vivo-technical-summary.pdf).

meaningful toxicological conclusions on the genotoxic potential of the new products from being made."[166]

As explained in JLI's Deficiency Response to Question 19, JLI's in vitro MN assays were conducted in accordance with OECD TG 487, including a "minimum" count of 2,000 cells to assess the genotoxic potential of the products. JLI undertook further product-specific evaluation by counting and assessing additional cells for certain JUUL products based on outcomes that warranted further investigation. JLI also evaluated all comparator products by counting 4,000 cells from the outset; the in vitro MN studies for comparator products were conducted after completion of the studies for JUUL products.[167]

Although this approach led to some differences in cell counting, JLI nonetheless believes that the results from each in vitro MN study are valid and relevant to assess the genotoxic potential of JUUL products and relative to comparator products as appropriately contextualized.

JLI agrees with CTP-OS's assessment that the in vitro MN assay results from counting the initial 2,000 cells for all JUUL products "met all assay acceptance criteria"[168] and can be considered "valid assay results."[169] Contrary to what the MDO asserted, JLI did not "reject[]" the results from the counting of 2,000 cells.[170] Rather, JLI went on to further investigate them.

The collection and investigation of additional information for positive results — in line with JLI's stepwise approach to investigate indications of potential hazards — does not constitute an explicit or implicit rejection of the data. JLI fully reported these results in the study reports included in its PMTAs. The three in vitro MN study reports that included cases of the additional counting of 2,000 cells (4,000 in total) all included an evaluation of the assay results for the initial 2,000 cell counts. For example, the report for Virginia Tobacco 3.0% states:[171]

[166] FDA Marketing Denial Order for JLI's PMTAs, p. 7.

[167] JLI Deficiency Response to Question 19, p. 155–156.

[168] FDA Marketing Denial Order for JLI's PMTAs, p. 7.

[169] FDA TPL Review of JLI's PMTAs (Toxicology), p. 6.

[170] FDA Marketing Denial Order for JLI's PMTAs, p. 6.

[171] PMTA Section N.3.1.2 Report 00819REVA (Virginia Tobacco 3%), p. 19-20 (n-3-1-2-micronuc-vt-3-rpt-03425reva-report.pdf).

> In the 4-hour treatment with metabolic activation, concentrations selected for micronucleus analysis were as follows (with percent cytotoxicity): 0.490% (0%), 0.700% (0%), and 1.00% (1%). Percent micronucleated cells were first analyzed in 1000 cells/culture (2000 cells/concentration). A statistically significant increase in the percent micronucleated cells was observed at ≥0.490% (Appendix 4, Table 4.12). The increase at 1.00% was outside of the historical control range (0.28% -1.46 %) of the vehicle control and it was significant for trend using the Cochran-Armitage Test. The response was considered positive but lacked a clear dose response. Upon scoring an additional 1000 cells/culture to confirm the response, there were statistically significant increases in the percent of micronucleated cells observed at ≥ 0.490% in the 4-hour treatment with metabolic activation (Appendix 4, Table 4.13). The increases were within the historical control range of the vehicle control but the treatment was positive for dose-response trend using the Cochran-Armitage Test. Therefore, this response was considered equivocal for inducing micronuclei.

JLI acknowledges that the counting of an additional 2,000 cells for some results could have been more clearly articulated in the summary sections of the initial PMTAs.[172] Nonetheless, JLI provided the complete dataset for evaluation and explained its rationale and resulting interpretation in its initial PMTAs and Deficiency Response.[173]

Other than the "enhanced scrutiny" applied beyond the initial scoring of 2,000 cells, as referenced in the TPL Review,[174] neither the MDO nor Deficiency Letter raised any other concerns about the ability to identify potentially genotoxic articles for JUUL products when evaluated with the 2,000-cell count.[175] While the MDO took issue with additional cell counting, and the conclusions JLI drew from it, the TPL Review stated that the data provided in Deficiency Response to Question 19 "suggests that sufficient sampling and statistical power were present at 2000 cells per concentration to accurately assess the genotoxic potential of the new and comparison products."[176]

Even if CTP-OS disagreed with JLI's rationale for additional cell counting, it could have discounted those additional data and considered the results produced from the initial

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[172] Section H.1.1.2 Toxicology (h-1-1-2-toxicology.pdf); H.1.1 Summary of Non-Clinical Studies (h-1-1-summary-of-nonclinical-studies.pdf).

[173] JLI Deficiency Response to Question 19, p. 155–161.

[174] FDA TPL Review of JLI's PMTAs (Toxicology), p. 22.

[175] Indeed, increased sample size for this particular assay has been the subject of much scientific discourse, given that the in vitro MN assay is prone to high rates of irrelevant positive results because it has high sensitivity, but suffers from low specificity. *See, e.g.*, EFSA Scientific Committee. (2011 Sept. 30) Scientific Opinion on Genotoxicity Testing Strategies Applicable to Food and Feed Safety Assessment. *EFSA Journal*,9(9):2379 (data table).

[176] FDA TPL Review of JLI's PMTAs (Toxicology), p. 23.

2,000 cell count (and, in fact, it did so in reaching conclusions stated on genotoxic potential for certain JUUL products in Deficiency 3).[177]

Therefore, the limited methodological differences related to additional cell counting for certain in vitro MN assays did not preclude CTP-OS from considering the data from the initial 2,000-cell count. In doing so, CTP-OS could have assessed the genotoxic potential of JUUL products based on these results that it already had deemed valid. This assessment then should progress into a full health risk evaluation that integrates biological, chemical, and clinical findings to reach meaningful conclusions on the toxicological profile of the products.

Second, the MDO raised certain methodical concerns about the comparability of in vitro MN data between JUUL and comparator products based on inconsistent counting. Specifically, the MDO stated that "[f]or scientific validity, it is necessary that the new and comparison products are evaluated for genotoxic potential using a consistent methodology to ensure that accurate comparisons are made between the products."[178]

In its Guidance on PMTAs for ENDS, FDA recommends including comparator products in in vitro assays "for appropriate hazard identification comparison . . . ."[179] Consistent with the stepwise approach to toxicological evaluations and the role played by in vitro studies within that framework, the comparison of products in this context is not intended to be a one-to-one assessment of the relative magnitude of genotoxicity between products. Rather, it is an initial indication of genotoxic potential. It is not "necessary" for two studies to be conducted identically to make "accurate" comparisons.[180]

Here, JLI conducted the comparator product testing after the JUUL product testing. Because some JUUL products results had been evaluated with the 4,000-cell count, the decision was made to evaluate all comparator products at the increased 4,000 cell-count. As stated in the Deficiency Response, JLI recognizes it would have been preferable to conduct each of the in vitro MN studies under the same cell-counting approach (i.e., either all at 2,000 or all at 4,000). JLI maintains, however, that the increased sample size of 4,000

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[177] Specifically, for Deficiency 3, the MDO stated "your data demonstrate that PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) induced clearly positive genotoxic responses under the initial conditions of analyzing 2000 cells per concentration used in this assay" and goes on to find that "these results indicate that [the products] may be relatively more genotoxic than the combustible cigarette comparison product." As a result, the MDO concluded that JLI needed to have provided scientific data and rationale to address the positive in vitro genotoxicity scores using 2,000 cells. FDA Marketing Denial Order for JLI's PMTAs, p. 9-10.

[178] FDA TPL Review of JLI's PMTAs (Toxicology), p. 37.

[179] FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems 26 (2019).

[180] FDA Marketing Denial Order for JLI's PMTAs, p. 8.

cells across all comparator products did not jeopardize the reliability of the test results for these comparator products.[181]

Despite differences in statistical power between some of the JUUL product studies and the comparator product studies, both cell-counting measures were adequate and appropriate for the test conditions. JLI's study protocols and OECD TG 487 establish a floor and not a ceiling for cell counting. Indeed, OECD TG 487 specifically contemplates situations in which further investigations can be undertaken based on outcomes and identifies scoring additional cells as one method that "could be useful."[182] It follows that some variation in cell counting is not unexpected.

Further, the acceptance criteria and criteria for determining positive, negative, and equivocal results remained the same (i.e., the acceptance criteria were not "uneven" as claimed by CTP-OS), and the counting and scoring for all comparator products was consistent. In any case, per the study protocol and OECD TG 487, further investigations of outcomes for biological relevance are a matter of discretion.

Thus, the comparator product results established a reliable comparative dataset. The methodological differences may give rise to greater scrutiny when interpreting and directly comparing the results from the tests performed on the JUUL products and comparator products, but do not impact the overall scientific validity of the studies and indications of genotoxic potential for the respective products.

The results indicate that there is some, limited genotoxic potential for JUUL products and comparator ENDS products and combustible cigarettes under the test conditions; this provides a basis for further assessment and contextualization. As with any in vitro study, the interpretation of the results "can only be done on a case-by-case basis, considering all available chemical and biological data . . . and placing the data in the context of the overall product risk assessment."[183]

ii. CTP-OS Incorrectly Concluded That, Based on the Available In Vitro MN and In Vivo Genotoxicity Data, JUUL Products Presented Genotoxic Potential Which Precluded an Accurate and Complete Toxicological Evaluation

The MDO found that results from the in vitro and in vivo genotoxicity tests suggest that Menthol 5.0%, Virginia Tobacco 3.0%, and Virginia Tobacco 5.0% may be relatively

[181] JLI Deficiency Response to Question 19, p. 161.

[182] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 487: In Vitro Mammalian Cell Micronucleus Test (2016).

[183] CORESTA In Vitro Toxicology Task Force (2019). The Rationale and Strategy for Conducting In Vitro Toxicology Testing of Combustible Tobacco Products, p. 3.

more genotoxic than the combustible cigarette.[184] As a result, the MDO stated that JLI needed to have:

> [P]rovided data from a repeated in vivo genotoxicity study using a relevant and justifiable exposure concentration of aerosol from PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) with PM0000878 and/or PM0000879 and smoke from the 3R4F combustible cigarette comparison product" or "[p]rovided scientific data and a rationale to address conflicting genotoxicity results for PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) from the in vitro and in vivo genotoxicity study data you provided.[185]

For Virginia Tobacco 5.0%, on which an in vivo study was not conducted, the MDO stated that JLI needed to have "[p]rovided scientific data and a rationale to address the positive in vitro genotoxicity score [for e-liquid] from the initial genotoxicity assay . . . using 2000 cells."[186]

The MDO, however, misconstrued these in vitro and vivo results for JUUL products in three critical ways: (i) by comparing apples to oranges with ENDS e-liquid and cigarette smoke condensates under different test conditions; (ii) imputing relative risk from studies designed only for hazard identification; and (iii) isolating the data from the broader, more holistic, and increasingly relevant scientific context provided by JLI. When placed in the appropriate context, it becomes clear that JLI has in fact provided the data and scientific rationale to demonstrate the JUUL products as actually used by consumers have lower substantially lower exposures to carcinogenic constituents and associated cancer risk that is in line with the ENDS category and less than combustible cigarettes.

First, in suggesting that the in vitro studies indicate Virginia Tobacco 5.0% and Menthol 5.0% may be more genotoxic than combustible cigarettes, CTP-OS's assessment was based upon the flawed premise that Virginia Tobacco 5.0% and Menthol 5.0% e-liquid assay results can be directly compared to the results from cigarette-smoke condensate. As noted by JLI in its PMTAs, and previously recognized by CTP-OS itself, ENDS e-liquids and cigarette smoke are not directly comparable for purposes of assessing genotoxic potential.

Per CTP-OS's Decision-Making Principles for Review of Premarket Tobacco Applications for Electronic Nicotine Delivery Systems, comparison of an e-liquid to a cigarette includes:

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[184] FDA Marketing Denial Order for JLI's PMTAs, p. 9–10.

[185] *Id.* at 10.

[186] *Id.*

- Imputation of the delivery mechanism and subsequent exposure generated by the e-liquid;

- Assurance that the imputed delivery mechanism is representative of typical use; and

- Assurance that different or atypical use of the e-liquid does not raise separate health concerns.[187]

As stated in the MDO, the devices "are responsible for aerosolizing and delivering the e-liquid to the user."[188] The device functional parameters mediate and control the delivery of these [] constituents to the user and are a critical factor in evaluating the genotoxicity of the new products."[189] Human factors and other behavioral testing demonstrate that users are able to use the device with the JUULpods to deliver aerosol as designed and intended.[190] Additionally, JLI has implemented controls, coupled with the inherent design of the JUUL System, to limit the potential for unintended e-liquid ingestion including hazard exposure to children and infants. As explained in PMTA Section G.1 Product Design and Properties, JUULpods are not intended to be opened or refilled and are tamper-resistant.[191] Therefore, while e-liquids are a component of JUUL products and it is appropriate to assess for potential hazards as a part of the stepwise approach to toxicological evaluation, any risk of unintended e-liquid exposures has been mitigated. Aerosol data is most relevant for evaluating for potential health risk from inhalation exposures associated with product use.

The appropriate comparator for assessing risk relative to smoke condensate is the aerosol condensate, because it is the smoke (for cigarettes) and aerosol (for JUUL products) that is exposed to the user during product use. Although the in vitro MN assay results on the e-liquids for Virginia Tobacco 5.0% and Menthol 5.0% showed some potential for genotoxicity, aerosol condensate results for Virginia Tobacco 5.0% and Menthol 5.0% were negative in the in vitro MN assay under all test conditions, while smoke condensate from the 3R4F reference cigarette had equivocal (inconclusive) results and 1R6F reference cigarette had positive results. Therefore, the negative in vitro MN assays results for the aerosol condensates coupled with other relevant biological (e.g., inhalation in vivo) and chemical (e.g., targeted and non-targeted aerosol analyses) data are most relevant to

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[187] Center for Tobacco Products Office of Science, Decision-Making Principles for Review of Premarket Tobacco Applications for Electronic Nicotine Delivery Systems, p. 7 (June 12, 2020).

[188] FDA Marketing Denial Order for JLI's PMTAs, p. 10.

[189] *Id.* at 10–11.

[190] PMTA Section H.2.1 Summary of Behavioral Studies and Analyses (h-2-2-adult-behavioral-studies-and-analyses.pdf).

[191] PMTA Section G.1 Product Design and Properties, p. 55 (g-1-product-design-and-properties.pdf).

evaluate the genotoxic potential of the products as actually used by consumers — and support the conclusion that these products are less genotoxic relative to cigarette smoke.

Second, the in vitro MN assays are qualitative, binary yes/no screening tests, with inherently limited comparability. As stated by FDA in its Guidance on PMTAs for ENDS, comparator products are included in in vitro assays for "hazard identification comparison" only. [192] While the in vitro MN assays inform the hazard-identification step in the whole product health risk evaluation process (Figure 7 below), these studies do not provide information on the magnitude or relative health risks from potential user exposures to the JUUL System aerosols compared to cigarette smoke. As with any in vitro study, the interpretation of the results must be placed in the context of the overall product risk assessment, and the differences in the methods used in the in vitro MN studies does not preclude CTP-OS from conducting an accurate and complete toxicological evaluation of JUUL products.

Figure 7 Framework for the Evaluation of Health Risks: Step 2 – Potential Hazard Identification

Here, CTP-OS skipped several steps in the health risk evaluation process by attempting to make a relative risk assessment between JUUL products and combustible cigarettes based solely on a comparison between inconclusive smoke condensate results and mixed JUUL product e-liquid and aerosol results from this binary assay. The in vitro MN results reflect some genotoxic potential for certain JUUL product e-liquids. For aerosol condensates, positive results were observed only in the Virginia Tobacco 3.0% aerosol condensates under some conditions. For smoke condensates, the in vitro MN results were predominantly equivocal (inconclusive) for the 3R4F reference cigarette. [193] These potential hazard identifications do not form the basis for a one-to-one comparison of

[192] FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems 26 (2019).

[193] JLI's tests utilized the 3R4F and 1R6F reference cigarettes, which are representative of commercially marketed combustible cigarettes and have previously been accepted by FDA for comparative evaluations with new tobacco products. It has been scientifically established that the newer 1R6F, which was designed by CTP, is a suitable comparator replacement for 3R4F, including for toxicology. For example, Jaccard 2019, which was referenced in JLI's PMTAs, found: "On the basis of the results obtained from aerosol chemistry and *in vitro* assays, we consider that the 1R6F reference cigarette is a suitable replacement for the 3R4F reference cigarette as a comparator/monitor cigarette. Its specific use as a comparator for novel tobacco products was checked on the basis of a comparative test with the Tobacco Heating System 2.2 as an example." Jaccard G., Djoko D.T., Korneliou A., Stabbert R., Belushkin M., Esposito M. (2019). Mainstream smoke constituents and *in vitro* toxicity comparative analysis of 3R4F and 1R6F reference cigarettes. *Toxicology Reports*, *6*, 222–231.

relative risk and instead form a basis for further assessment and require additional contextualization.

Third, in reaching the conclusion that these results may indicate increased genotoxic potential of the JUUL products relative to combustible cigarettes, CTP-OS not only conflated comparisons between the products, but also failed to consider the well-established and key next steps for completing a toxicological evaluation.

CTP-OS gave undue weight to the in vitro MN results, which are a narrow subset of data provided to evaluate potential genotoxicity, while ignoring the rest of the body of evidence. JLI evaluated genotoxicity using a battery of assays to assess different modes of action. In addition to the in vitro MN assays, other assessments included in vitro Ames assays and in vivo testing. Notably, the in vitro Ames assays showed all JLI products were negative while cigarette-smoke condensate was positive under the test conditions[194]. The Ames assay data provide additional information relevant to genotoxicity, and more specifically mutagenicity which is a key toxicological endpoint relevant to cancer adverse effects from tobacco product use. Additionally, the in vivo testing evaluated two distinct toxicological endpoints for genotoxicity (chromosome damage using MN assay and DNA damage using the Comet assays). Consistent with the ICH S2(R1) guidance, the data from these studies is relevant to, and further informs, the hazard characterization of the JUUL System aerosols.

While in vitro studies (i.e., outside of a living organism) are time and cost effective with added ethical benefits, they often cannot capture the full range of biological effects such as absorption, distribution, metabolism, and excretion (ADME) that impact the toxicology of substances in vivo (i.e., inside a living organism). The ICH S2(R1) guidance describes internationally agreed upon standards for follow-up testing and interpretation of positive results in vitro and in vivo.[195] In line with this guidance, JLI went on to develop additional insights to support the toxicological characterization of JUUL products, through the recommended in vivo inhalation genotoxicity study for MN and for DNA damage. The in vivo tests were negative under the test conditions.[196]

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[194] PMTA Section N.3.1.1. Technical Summary Condensate (n-3-1-1-ames-testing-technical-summary-condensate.pdf).

[195] *See* FDA, Guidance for Industry: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (2012).

[196] No in vivo study was conducted for Virginia Tobacco 5.0%. However, because acute nicotine toxicity is the limiting factor for the in vivo inhalation studies conducted at the maximum tolerated dose, a higher exposure concentration can be achieved using the Virginia Tobacco 3.0% (because of the lower nicotine dose). Virginia Tobacco 3.0% and Virginia Tobacco 5.0% contain the same flavor ingredients and at such levels that all exposures would be lower with a Virginia Tobacco 5.0% test product due to the difference in nicotine levels — i.e., the in vivo study using Virginia Tobacco 3.0% exposed animals to a higher chemical load for each ingredient than a Virginia Tobacco 5.0% would and thus provides a "worst case" baseline.

The MDO asserted that JLI failed to provide a rationale to address the conflicting genotoxicity results for in vitro versus in vivo data. As pointed out in JLI's PMTAs and Deficiency Response, however, JLI followed the precise framework recommended by FDA for doing so.[197] According to the ICH S2(R1) guidance cited in the Guidance on PMTAs for ENDS, there are several additional in vivo studies that can be used in the battery of tests or as follow-up tests to further assess and contextualize the results of in vitro or other in vivo assays. Specifically, per the ICH S2(R1) guidance, "[n]egative results in appropriate in vivo assays (usually two), with adequate justification for the endpoints measured, and demonstration of exposure . . . are generally considered sufficient to demonstrate absence of significant genotoxic risk."[198]

JLI explained that the in vivo studies evaluated two distinct genotoxic endpoints (chromosome damage via MN and DNA damage via Comet assays) at exposure concentrations approaching the maximum tolerated dose based on nicotine toxicity.[199] The exposure was verified by measuring plasma nicotine levels, which was determined to be approximately 100-fold above the typical peak plasma nicotine levels reported for human smokers (demonstration of exposure). The MN assay was conducted in the rat bone marrow. The Comet assay was conducted using three different tissues for specific evaluation: nasal tissue (portal of entry tissues where the exposure dose is the highest), lung (potential target tissue), and liver (site of metabolism). The selection of target tissues is consistent with standard toxicological practice and addresses concerns raised in the TPL Review regarding metabolism of aerosol constituents.[200]

Overall, these selections are well correlated to establish in vivo relevance for JUUL product aerosols, with distinct advantages over the in vitro assay. Therefore, under the ICH S2(R1) guidelines, to which the FDA recommends, the negative results under these test conditions demonstrate an "absence of significant genotoxic risk" when taken together with the full battery of in vitro tests.

Of course, JLI recognizes that these in vivo studies conducted in Sprague-Dawley rats are short-term exposure studies that are not necessarily conclusive on the genotoxic potential of the products in long-term use by humans. However, it is the next best step in the stepwise approach, and JLI supported this approach and drew conclusions in line with the general framework for assessing such results. Additionally, JLI appropriately placed these data in the context of the whole product risk assessment, together with other

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[197] FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (2019).

[198] FDA, Guidance for Industry: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use, at 3 (2012).

[199] Per ICH S2(R1), the MN and Comet assays are the typical and recommended standard battery of tests for a comprehensive assessment of genotoxic potential in vivo. *Id*. at 9–10.

[200] FDA TPL Review of JLI's PMTAs (Toxicology).

product-specific chemical, biologic, and clinical data relevant to genotoxic potential, which CTP-OS has failed to consider.

On relative risk, the MDO took issue with the lack of a comparator cigarette in the in vivo genotoxicity studies. Generally, FDA supports reducing, replacing and/or refining the use of animal testing in research where adequate and scientifically valid non-animal alternatives can be substituted. The Guidance on PMTAs for ENDS states that in vivo toxicology studies should be used "to address unique toxicology issues that cannot be addressed by alternative approaches."[201] As previously explained by JLI, the genotoxicity issues posed by combustible cigarettes are well-researched and not unique.[202] A direct in vivo comparison under these test conditions is not necessary where, as here, there are readily available comparator data that inform a more complete and relevant relative risk profile.

To support a full toxicological evaluation of JUUL products, including in comparison to cigarettes, JLI provided a full battery of in vitro tests, including Ames assays that also are informative for evaluating toxicological endpoints relevant to cancer outcomes (e.g., DNA damage from mutagens that directly interact with DNA).[203] The in vitro and in vivo study results are consistent with the aerosol chemistry data, which show significantly lower levels of carcinogenic HPHCs in aerosol generated from JUUL products compared to smoke from the comparator cigarette, thus supporting substantial reductions in potential exposures and associated health risks from the JUUL product aerosols relative to cigarette smoke.[204] These data and analyses provide context for the MN study results and support the conclusion that, although use of the JUUL System is not safe and presents some risk, that risk is far lower than smoking combustible cigarettes.

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[201] FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, at 35 (2019).

[202] PMTA Section H.1.1.2 Toxicology: "3R4F smoke has been demonstrated to be genotoxic in vivo." (citing Dalyrymple et al 2016 [n-12-dalrymple-et-al2016.pdf]).

JLI Deficiency Response, Question 18, p. 146–150: "The genotoxic potential of the particulate fraction of cigarette smoke, cigarette smoke condensate in vitro, has also been previously reported in published literature. (DeMarini et al 2008 [n-12-demarini-et-al-20008.pdf]; Doshi et al 2018 [n-12-doshi-et-al-2018.pdf]); "As stated in the 2010 Surgeon General's Report condensate from cigarette smoke is mutagenic in a variety of systems." (citing Center for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US) (2010). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta (GA). *Centers for Disease Control and Prevention (US)*, retrieved from http://www.ncbi.nlm.nih.gov/books/NBK53017/).

[203] PMTA Section H.1.1 Summary of Non-Clinical Studies (h-1-1-summary-of-nonclinical-studies.pdf) summarizing analytical data (Section H.1.1.1 Chemistry and Stability), toxicological data (Section H.1.1.2 Toxicology), a qualitative risk assessment (Section H.1.1.3 Qualitative Risk Assessment), and more in-depth quantitative risk assessment (Section H.1.1.4 Quantitative Risk Assessment), as well as other data relevant to the overall health risk evaluation of the JUUL System.

[204] *Id.*

Isolating the in vitro and in vivo MN data from other biological, chemical, and clinical findings for JUUL products and well-established risks and hazards of combustible cigarettes led the MDO to the wrong conclusion. Had CTP-OS adequately considered the results — alongside the body of information, data, and analysis in JLI's PMTAs for JUUL products and combustible cigarettes on health risks — it would not have found reasons to be concerned about the genotoxic potential of these JUUL products relative to cigarettes. And it should not have precluded CTP-OS from conducting an accurate and complete toxicological evaluation.

iii. CTP-OS Was Not Precluded from Conducting a Full Toxicological Evaluation Based on the Alleged Methodological Issues and Failed to Consider Other Relevant Biological and Chemical Data Adequately

The in vitro MN assay is a screening assay that is informative on the genotoxic potential of different products, but it cannot give a definitive conclusion on their absolute or relative genotoxicity and overall toxicological risk. This requires a holistic review integrating all the available biological, chemical, and clinical findings into an overall whole product risk assessment, such as those presented by JLI in its PMTAs.[205] It is scientifically unsound to stop the toxicological evaluation at such an early stage because of limited methodological questions in a narrow subset of toxicological data when the entire risk assessment is built upon the successive identification and evaluation of potential hazards and risks.

JLI's PMTAs included the results of more than 75 nonclinical studies, including targeted and non-targeted chemistry analyses and in vivo and in vitro toxicology studies, as well as 13 clinical studies and a computational modeling study to assess environmental exposure from JUUL products use. These multidisciplinary studies formed the basis for both quantitative and qualitative risk assessments of the JUUL System. The data, information, and analysis also enable a comparative assessment relative to combustible cigarettes and other marketed ENDS products.

CTP-OS, however, found that it could not conduct a full toxicological evaluation of JUUL products.[206] It is not clear whether and to what extent this conclusion considered the body of evidence and interrelated scientific findings of increasing relevance in JLI's PMTAs that bear on genotoxic potential or go well beyond genotoxicity to assess health risk from actual use and exposure. Similarly, it is not clear whether CTP-OS considered the inherent limitations of in vitro genotoxicity testing to assess health risks from actual use and exposure and weighed the evidence accordingly. Instead, CTP-OS should have conducted a complete and holistic review of the scientific evidence in JLI's PMTAs as a whole and

[205] H.1.1.3 Qualitative Risk Assessment (h-1-1-3-qualitative-risk-assessment.pdf); Quantitative Risk Assessment (h-1-1-4-quantatitative-risk-assessment.pdf).

[206] FDA Marketing Denial Order for JLI's PMTAs, p. 5–11.

balanced that evidence against its concerns of genotoxic potential limited to the in vitro MN assay results.

As explained in detail above, the evaluation of genotoxic hazards to humans follows a stepwise approach, beginning with a basic battery of in vitro tests followed in some cases by in vivo testing. Because in vitro testing looks at specific cells and not the whole organism, these experiments are more suited for initial product testing. Findings typically need to be extrapolated to in vivo use or further explored and confirmed in in vivo studies. To support a full toxicological evaluation of JUUL products, JLI provided the in vitro MN results with a full battery of in vitro tests, including Ames assays that also are informative for evaluating aspects of cancer outcomes (e.g., DNA damage from mutagens that directly interact with DNA), and follow-on in vivo testing as appropriate and recommended by FDA's Guidance on PMTAs for ENDS.[207,208]

CTP-OS stated that JLI should have provided data comparing the genotoxic potential of JUUL products and comparator products using a consistent methodology.[209] The in vitro data provided by JLI indicates that combustible cigarettes and ENDS products (including the JUUL System) have some genotoxic potential. These findings should have been assessed within the overall health-risk profile of the products, of which a genotoxicity evaluation is a piece and genotoxic potential as evaluated in the in vitro MN assay a smaller piece of that.[210] JLI provided such a holistic and comparative assessment of the JUUL System, combustible cigarettes, and other marketed ENDS in its PMTAs.[211] This included a range of biological, chemical, and clinical studies and risk-assessment methodologies, which CTP-OS seemingly paid scant attention to justify not completing a full toxicological evaluation of JUUL products and precluding a determination of APPH.

These studies included a comprehensive assessment of the aerosol via target and non-targeted analysis — which characterized more than 99.99% of the total aerosol mass — as well as non-clinical and clinical measurements showing dramatic reductions in HPHCs and BOEs when compared to combustible cigarettes as well as some comparator ENDS products.

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[207] PMTA Section H.1.1 Summary of Non-Clinical Studies, p. 26-28 (h-1-1-summary-of-nonclinical-studies.pdf).

[208] FDA, Guidance for Industry: Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems 36 (2019) ("We suggest using the ICH S2(R1) guidance[] and Organization for Economic Cooperation and Development protocols as a guide for genotoxicity assessments.").

[209] *Id.* at 5–8.

[210] *Id.*

[211] PMTA Section H.1.1 Summary of Non-Clinical Studies (h-1-1-summary-of-nonclinical-studies.pdf).

iv. CTP-OS Deviated from Established Process and Decision-Making Principles by Failing to Conduct a Complete Scientific Review

As discussed in above, CTP-OS was not precluded from drawing meaningful inferences about the genotoxic potential of the JUUL products, including as compared to combustible cigarettes and comparator ENDS products based on limited methodological questions. In fact, CTP-OS has frequently accepted some methodological limitations and even genotoxicity concerns in prior PMTAs that have been authorized, including in MN assays.

For example, in the TPL review for IQOS, the toxicological assessment found: "The method the applicant used to score micronuclei frequency is unclear (e.g., blinded judge or automated system) and there are unexplained inconsistencies in the number of nuclei scored in some cases (e.g., exceeded protocol by 150%)."[212]

CTP-OS also previously found negative in vitro MN aerosol data to be sufficient to complete a full toxicological evaluation and support a finding that the new products are APPH. In the TPL review for Vuse Solo ENDS products, CTP-OS found that:

> Results from the in vitro toxicology studies demonstrated that combusted cigarette smoke fractions (total particulate matter (TPM), gas vapor phase (GVP), or both) were mutagenic, cytotoxic, and genotoxic. By contrast, even at the maximum dose levels tested, neither the TPM nor GVP from any of the aerosols of all the new products or ENDS market comparisons was mutagenic, cytotoxic, or genotoxic under the test conditions.[213]

Then in the TPL review for Logic ENDS products:

> The genotoxicity study indicates that total aerosol collected matter (ACM) and gas vapor phase (GVP) from all new products, under the conditions of the study, had no mutagenic potential in vitro in a bacterial reverse mutation assay (Ames test) at any concentration tested, either with or without metabolic activation. In contrast, total particulate matter (TPM) from 3R4F reference cigarette and CC Pall Mall Red Kings smoke produced a positive result in five strains of bacteria used in the Ames test after metabolic activation. In addition, for all new products, no evidence of mutagenic toxicity was observed in in vitro and in vivo micronucleus assays; and there was no evidence of cytotoxicity in neutral red uptake (NRU) assay under the conditions of these studies.

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[212] FDA PMTA Toxicology Review of Philip Morris Products S.A.'s PMTAs PM0000424, PM0000425, PM0000436, PM0000479, p. 53.

[213] FDA TPL Review of PMTAs for R.J. Reynolds Vapor Company's PMTAs PM0000551, PM0000553, PM0000560, p. 22 (included Virginia Tobacco 5.0% as comparator product).

> In general, exposure of CC mainstream smoke tested at all the concentrations (low, mid, and high) produced toxic effects that were more severe than those produced by the new products.[214]

The same findings about in vitro aerosol results should apply to Virginia Tobacco 5.0%, Menthol 5.0%, and Menthol 3.0% products. Even at the maximum tested dose, aerosols from Virginia Tobacco 5.0%, Menthol 5.0%, and Menthol 3.0% were not cytotoxic, genotoxic, or mutagenic under the test conditions when evaluated with NRU, MN, and Ames assays, respectively.

It is unclear whether in vitro MN assays for e-liquids were included in the PMTAs for ENDS products referenced above, but no such data were referenced in the TPL reviews for the authorized applications. Thus, either no such data were included, or they were not material enough to be raised and analyzed. Consistent with a stepwise risk-assessment approach, CTP-OS's approach to evaluating PMTAs for ENDS products, at least for those that received marketing authorizations, makes it clear that in vitro aerosol data is more relevant to the toxicological risk assessment than in vitro e-liquid data.

Moreover, CTP-OS has authorized the marketing of new products with positive genotoxic results, such as IQOS and Moonlight VLN Cigarettes.[215] At least in these evaluations, even where actual toxicological issues persisted, such as genotoxicity or mutagenicity, CTP-OS weighed the body of evidence, considered the relative risk, and emphasized the role of more scientifically relevant findings. In these PMTA reviews, positive genotoxic signals from in vitro studies did not preclude CTP-OS from completing a full toxicological evaluation. Nor did they preclude a determination of APPH based on a complete and holistic review of the science and evidence in support of those applications.

Table 4 Examples of Authorized Products That Presented Toxicological Concerns

PMTA	Toxicological Concerns	Resolution
IQOS[216]	"Eleven chemicals were identified with genotoxic potential. Based on the available toxicological data and predictive toxicology modeling analysis submitted by the applicant, 20 of the 30 chemicals exhibit concerns for potential health effects." "Many of the chemicals do not have sufficient inhalation toxicity or	"[H]owever, although there is potential for genotoxicity with some of these compounds, the exposure levels appear low and the available data does not preclude a conclusion the products are appropriate for the protection of public health."

[214] FDA TPL Review of PMTAs for Logic Technology Development LLC's PMTAs PM0000529.PD1-PM0000531.PD1, PM0000535.PD1-PM0000537.PD1, PM0000540.PD1-PM0000541.PD1, p. 37.

[215] *See* FDA TPL Review of Philip Morris Products S.A.'s PMTAs PM0000424–426, PM0000479; FDA TPL Review 22nd Century Group Inc.'s PMTAs PM0000491–PM0000492.

[216] FDA TPL Review of Philip Morris Products S.A.'s PMTAs PM0000424–426, p. 32, 38, 42.

PMTA	Toxicological Concerns	Resolution
	genotoxicity/carcinogenicity data to inform the toxicological evaluation of heated tobacco products. The data provided by the applicant is not sufficient to support their conclusion that these compounds pose no risk to IQOS users . . . ." "Similar to the in vitro studies, it is difficult to determine the carcinogenic potential of long-term exposure to Heatstick aerosols from these evaluations. The data suggest there is potential for carcinogenic effects from Heatstick aerosols, but at much higher exposure levels than required for CC smoke."	"Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHcs found in CC."
Moonlight VLN Cigarettes[217]	"HPHC data for both VLN™ cigarettes indicates that noncancer hazards and cancer risks are likely similar to or slightly lower than NNC cigarettes, based on HPHC comparisons to top market-share cigarettes." "The toxicology review determined that overall, based on ISO regimen HPHC data, the noncancer hazards due to use of the VLN™ cigarettes are likely similar to those with use of the commercially marketed NNC cigarette comparators. In addition, based on the ISO regimen HPHC data, cancer risks due to use of the VLN™ cigarettes are likely similar and may be less than those associated with use of the commercially marketed NNC cigarette comparators." "The toxicology review noted that increases in acetaldehyde and acrylonitrile via the CI regiment likely do not raise cancer-risk-related concerns for the VLN™ cigarettes. Overall based on these CI regimen HPHC data, cancer risks are likely similar with use of VLN™ cigarettes and use of commercially marketed NNC cigarette comparators."	"As TPL, I agree with the toxicology review conclusion. After consideration of all the toxicological data presented, the overall toxicological risks of VLN™ cigarettes are likely similar to those associated with use of the six comparator products that represent a significant portion of the cigarette market. However, the potential for a relative benefit compared to NNC cigarettes exists for smokers who switch completely to VLN™ cigarettes, then reduce cigarette use, and eventually totally quit."

But for JLI's PMTAs, CTP-OS simply stopped at the potential hazard signal and decided it could not conduct a full toxicological evaluation of JUUL products.

[217] FDA TPL Review of PMTAs for 22nd Century Group Inc.'s PMTAs PM0000491–PM0000492, p. 15, 27, 28, 34 (emphasis omitted).

3. Information in the PMTAs Shows That the Menthol 5.0% Product Is Not Mutagenic (Deficiency 4)

a. Basis for the Deficiency

The MDO found that "the aerosol condensate produced from PM0000872 (Menthol 5%) using devices PM0000878 and PM0000879, using standard puffing parameters, induced a significant mutagenic response when compared to the historical vehicle control group."[218] The MDO also stated that "[a]ccording to your study guidelines, the criteria for a positive mutagenic response include a three-fold increase in TA98 revertants seen in two or more successive concentrations, or a repeatable response at a single concentration."[219] Specifically, in the TPL Review, CTP-OS noted that:

> The mean (± Standard Deviation) revertant colonies per plate were reported as 50 (12) and 48 (6) at the test article concentrations of 3.13 µL/plate and 6.25 µL/plate, respectively. The corresponding historical vehicle control data for the bacterial reverse mutation assay reports the mean revertant colonies per plate as 15 (6). According to your study guidelines, the criteria for a positive mutagenic response include a threefold increase in TA98 revertants seen in two or more successive concentrations, or a repeatable response at a single concentration. The submitted data met these criteria for a positive response.[220]

As discussed below, the MDO's conclusion and supporting findings were reached by deviating from the study protocol and OECD guideline, applying the incorrect testing criteria to determine a positive or negative mutagenic response for Menthol 5.0%, and disregarding generally accepted methods for conducting and evaluating the results of an in vitro Ames assay.[221]

b. Summary of Facts and Background

As part of its nonclinical program to assess toxicological risk, JLI conducted in vitro Ames testing, an assay that is a "bacterial short-term test for identification of carcinogens using mutagenicity in bacteria as an end point."[222] JLI's contract laboratory, [redacted]

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[218] FDA Marketing Denial Order for JLI's PMTAs, p. 11.

[219] *Id.*

[220] FDA TPL Review of JLI's PMTAs (Toxicology), p. 28.

[221] In the MDO, TPL Review, 2nd Cycle Toxicology Review, Deficiency Letter, and 1st Cycle Toxicology Review, CTP-OS vaguely referred to JLI's "study guidelines" when evaluating the in vitro Ames assay. JLI is not clear whether CTP-OS means the study protocol and/or OECD TG 471 with which the study was conducted in general accordance. For clarity, in its analysis for Deficiency 4, JLI refers specifically to the study protocol and OECD TG 471 where appropriate.

[222] Föllmann W., Degen, G., Oesch, F., Hengstler, J.G. (2013) Ames Test. *Brenner's Encyclopedia of Genetics* (2d ed.) 104-107. https://doi.org/10.1016/B978-0-12-374984-0.00048-6.

[redacted] tested the e-liquid and aerosol condensate of the JUUL System and comparator ENDS products and 3R4F cigarette smoke condensate to evaluate the mutagenic potential of e-liquids or condensates in five strains of *S. typhimurium* with and without S9 metabolic activation. The testing was conducted in general accordance with OECD Guidelines for the Testing of Chemicals, Section 4 Health Effects, Test Guideline No. 471: Bacterial Reverse Mutation Test (1997) (OECD TG 471).[223]

The Ames assay identifies chemicals or chemical mixtures that can induce mutations in bacteria, called revertants, in the test articles (i.e., JUUL products and comparator products). These data are compared to a concurrent vehicle control (a solvent-based control conducted concurrently with the test assay) to determine whether a response is positive or negative for mutagenicity. The concurrent vehicle control is compared to relevant historical control data ([redacted] pooled control group data from prior assays) to assess whether the assay meets acceptance criteria; that is, whether the assay is valid and provides reliable results.

Relevant here, the study protocol provides specific criteria and references for assessing: (i) the testing criteria for a positive or negative mutagenic response; and (ii) the assay acceptance criteria to determine whether the assay is valid and the results are reliable.[224]

On assay acceptance criteria, the study protocol states the following:

> The vehicle control and positive control plates from each tester strain (with or without S9) must exhibit a characteristic number of revertant colonies when compared against relevant *historical control data* generated at the Testing Facility (Ames_2019_01 or newer). In addition, vehicle control plates should display normal growth (i.e., normal background lawn) in the presence and absence of S9.[225]

On testing criteria, the study protocol states the following to assess a positive response:

> The test article is considered positive for mutagenicity if it induces an increase of revertants per plate with increasing concentration. The increases should be at least 2 times the *vehicle control background frequency* for strains with high spontaneous levels (i.e., TA100 and TA102) and 3 times for those with low spontaneous levels (TA1537, TA98, and TA1535). These increases should be

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[223] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 471: Bacterial Reverse Mutation Test (1997).

[224] PMTA Section N.3.1.1 Report 03408REVA (Menthol 5%), sec. 10 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf) (emphasis added).

[225] *Id.* at sec. 10.1 (emphasis added).

> seen in at least 2 or more successive concentrations or the response should be repeatable at a single concentration.[226]
>
> OECD TG 471, in relevant part, states the following:
>
> Concurrent strain-specific positive and negative (solvent or vehicle) controls, both with and without metabolic activation, should be included in each assay. Positive control concentrations that demonstrate the effective performance of each assay should be selected.[227]
>
> . . .
>
> Negative controls, consisting of solvent or vehicle alone, without test substance, and otherwise treated in the same way as the treatment groups, should be included. In addition, untreated controls should also be used unless there are historical control data demonstrating that no deleterious our mutagenic effects are induced by the chosen solvent.[228]
>
> . . .
>
> ***Treatment of results***
>
> []Data should be presented as the number of revertant colonies per plate. The number of revertant colonies on both negative (solvent control, and untreated control if used) and positive control plates should also be given.
>
> []Individual plate counts, the mean number of revertant colonies per plate and the standard deviation should be presented for the test substance and positive and negative (untreated and/or solvent) controls.[229]

Based on the study protocol and informed by the OECD guideline, two-steps generally are required to assess the mutagenic potential of a test article (here, Menthol 5.0%): First, determine whether the assay meets acceptance criteria and is valid by comparing the vehicle control and positive control plates against "relevant *historical control data*."[230] Second, determine whether the test article induces a mutagenic response

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[226] *Id.* at sec. 10.3 (emphasis added).

[227] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 471: Bacterial Reverse Mutation Test (1997), p. 4.

[228] *Id.* at 5.

[229] *Id.* at 6.

[230] PMTA Section N.3.1.1 Report 03408REVA (Menthol 5%), sec. 10.1 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf) (emphasis added).

by comparing the increase of revertants per plate against the "*vehicle control background frequency*."[231]

In its PMTAs, JLI provided the results from the Ames assay on the JUUL System e-liquids and aerosol condensates, comparator ENDS e-liquids and aerosol condensates, and 3R4F cigarette smoke condensate.[232] Following OECD TG 471, the Ames assay evaluated the ENDS e-liquids and aerosols and smoke condensate in five *S. typhimurium* tester strains (TA1537, TA98, TA100, TA1535, and TA102) across increasing concentrations with and without S9 metabolic activation. ENDS aerosols were evaluated under intense and non-intense puffing parameters while smoke condensate was evaluated under the Health Canada Intense puffing regimen (ISO 20778).[233]

All JUUL products and comparator ENDS products (e-liquids and aerosols) were negative for mutagenicity for all tester strains with and without metabolic activation. Specifically for Menthol 5.0%, the study report included in the PMTAs concluded that:

> Mean increases in the number of revertant colonies indicative of a positive response were not observed with Menthol 5% formulation in the *S. typhimurium* strains TA1537, TA98, TA100, TA1535, and TA102, with and without metabolic activation, under the conditions of this assay. Therefore, all preparation types (e-Liquid, Condensate – Standard Regime, Condensate – Intense Regime) of Menthol 5% are considered to be negative for inducing mutagenicity in this assay.[234]

The 3R4F smoke condensate was mutagenic. When the 3R4F smoke condensate was evaluated with S9, the number of revertants increased in a dose dependent manner and met the criteria for a clear positive response in TA1537, TA98, and TA100 tester strains.[235]

The MDO, however, found that Menthol 5.0% induced a mutagenic response for the TA98 tester strain under the non-intense puffing condition.[236] In reaching this conclusion, CTP-OS did not correctly follow the study protocol and OECD guideline and did not correctly apply the testing criteria. Rather, CTP-OS appears to have relied on the historical

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[231] *Id.* at sec. 10.3 (emphasis added).

[232] PMTA Section N.3.1.1. Technical Summary Condensate (n-3-1-1-ames-testing-technical-summary-condensate.pdf).

[233] ISO (2018) ISO 20778:2018 Cigarettes — Routine analytical cigarette smoking machine — Definitions and standard conditions with an intense smoking regime. Retrieved from https://www.iso.org/standard/69065.html.

[234] PMTA Section N.3.1.1 Report 03408REVA (Menthol 5%), sec. 6 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf).

[235] PMTA Section N.3.1.1 Ames Testing Technical Summary Condensate, p. 12 (n-3-1-1-ames-testing-technical-summary-condensate.pdf).

[236] FDA Marketing Denial Order for JLI's PMTAs, p. 11.

control data — as opposed to the concurrent vehicle control data per the study protocol — to score the assay and determine a positive response.

Additional information on the facts and background relating to Deficiency 4, including data and analysis from JLI's PMTAs and Deficiency Response, are included in Appendix 3.

c. Analysis

i. CTP-OS Failed to Apply the Study Protocol, OECD Guideline, and Testing Criteria Correctly to Assess the Mutagenic Potential of Menthol 5.0%

The MDO concluded that Menthol 5.0% was mutagenic by misinterpreting the criteria in the study protocol and incorrectly applying the historical control to determine a positive response. By applying the historical control — rather than the concurrent vehicle control as required by the study protocol and OECD guideline — the MDO found that Menthol 5.0% showed a positive mutagenic response in TA98 under two concentrations using standard puffing parameters and without metabolic activation.

Interpreted and applied correctly, the data show that Menthol 5.0% was not mutagenic under any tester strain, concentration, or puffing parameter regardless of metabolic activation. When compared to the concurrent vehicle control — as required by the criteria in the study protocol and OECD guideline — the values for Menthol 5.0% show no mutagenic response across all testing criteria and conditions:

> The highest observed mean (+/- SD) revertant counts/plate in the treated cultures was 50 (+/- 12) observed at a concentration of 3.13 μL/plate. This represents only a 2-fold increase in the number of mean revertant counts/plate while the positive criteria for TA98 strain is an increase of at least 3-fold over the vehicle control background frequency. Therefore, the Menthol 5.0% aerosol condensate was not found positive for mutagenicity in strain TA98 in these treatment conditions, at any of the tested concentrations.[237]

Substantively, the MDO is flawed on two fronts, which independently and collectively undermine its conclusion that Menthol 5.0% was mutagenic. First, the MDO misinterpreted the study protocol and OECD guideline on acceptance criteria and testing criteria. Second, as a result, the MDO applied the incorrect control group (historical control group versus concurrent vehicle control group) to assess a positive or negative mutagenic response.

The study protocol establishes clear and explicit references for assessing acceptance criteria of the assay and testing criteria to determine a positive or negative mutagenic

[237] JLI Deficiency Response to Question 18, p. 147.

response for the test article. Similarly, the study protocol clearly and explicitly delineates the relevance of the historical control data (assay acceptance criteria) and vehicle control data (testing criteria). As stated in the study protocol:

> **10.1 Assay Acceptance Criteria**
>
> The vehicle control and positive control plates from each tester strain (with or without S9) must exhibit a characteristic number of revertant colonies when compared against relevant *historical control data* generated at the Testing Facility (Ames_2019_01 or newer). In addition, vehicle control plates should display normal growth (i.e., normal background lawn) in the presence and absence of S9.[238]
>
> **10.3 Criteria for Positive Response**
>
> The test article is considered positive for mutagenicity if it induces an increase of revertants per plate with increasing concentration. The increases should be at least 2 times the *vehicle control background frequency* for strains with high spontaneous levels (i.e., TA100 and TA102) and 3 times for those with low spontaneous levels (TA1537, TA98, and TA1535). These increases should be seen in at least 2 or more successive concentrations or the response should be repeatable at a single concentration.[239]
>
> **10.4 Criteria for Negative Response**
>
> The test article is considered negative for mutagenicity if it does not induce a response which fulfills the above criteria.[240]
>
> **10.5 Criteria for Equivocal Response**
>
> Cases which do not clearly fit into the positive or negative criteria may be judged equivocal. In these cases the Study Director, based on sound scientific judgment, may take additional factors into consideration in evaluating the test results.[241]

As indicated by the study protocol, the historical control data are relevant for determining whether the assay is acceptable and the concurrent vehicle control data are relevant for determining whether the test article is mutagenic.

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[238] PMTA Section N.3.1.1. Report 03408REVA (Menthol 5%), sec. 10.1 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf) (emphasis added).

[239] *Id.* at sec. 10.3.

[240] *Id.* at sec. 10.4.

[241] *Id.* at sec. 10.5.

In addition to the study protocol, OECD TG 471 and other guidelines and scientific literature are clear that the concurrent vehicle control is the relevant comparator when scoring an Ames assay to assess mutagenic potential — not the historical control.

Table 5 References on the Application of Concurrent Vehicle Controls to Assess a Mutagenic Response in Ames Assays

Reference	Relevant Text
OECD Test Guideline No. 471: Bacterial Reverse Mutation Test (1997)[242]	Treatment of results []Data should be presented as the number of revertant colonies per plate. The number of revertant colonies on both negative (solvent control, and untreated control if used) and positive control plates should also be given. []Individual plate counts, the mean number of revertant colonies per plate and the standard deviation should be presented for the test substance and positive and negative (untreated and/or solvent) controls.
OECD Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines (2015)[243]	4.2.5.1 Concurrent negative controls Negative control groups are important for providing a contemporaneous control group for use in comparisons with the treated groups. This group can also be used to assess, whether the experiment is of acceptable quality by comparison with a set of historical control groups.
CORESTA Technical Report: Rationale and Strategy for In Vitro Toxicity Testing of Combustible Tobacco Products[244]	The positive controls induce a statistically significant increase in the number of revertants relative to the vehicle control; and the strain-specific fold-increase is acceptable.
Kluxen, et al. (2021)[245]	While it is widely acknowledged that the concurrent control is the most relevant control, it is obvious that control groups are subject to random sampling. . . . The most relevant control group in toxicological bioassays is the concurrent control as long as animals, cells or tissues were randomly allocated from the same population into concurrent control and treatment groups.

[242] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 471: Bacterial Reverse Mutation Test (1997), p. 6.

[243] Organisation for Economic Co-operation and Development, Guidance Document on Revisions to OECD Genetic Toxicology Test Guidelines (2015), p. 31.

[244] CORESTA In Vitro Toxicology Testing Sub-Group, Technical Report, Rationale and Strategy for *In Vitro* Toxicology Testing of Combustible Tobacco Products (2019), p. 13.

[245] Kluxen F.M., Weber K., Strupp C., Jensen S.M., Hothorn L.A., Garcin J.C., Hofmann T. (2021) Using historical control data in bioassays for regulatory toxicology. *Regulatory Toxicology and Pharmacology*, *125* (105024), 1-16.

Reference	Relevant Text
FDA Redbook: Toxicological Principles for the Safety Assessment of Food Ingredients (2000)[246]	Data should be presented as the number of revertant colonies per plate. The number of revertant colonies on both negative (solvent control, and untreated control if used) and positive control plates should also be given.

OECD TG 471 specifically, with which the study protocol aligned, does not provide for the use of historical controls to assess mutagenicity of the test article:

> Concurrent strain-specific positive and negative (solvent or vehicle) controls, both with and without metabolic activation, should be included in each assay. Positive control concentrations that demonstrate the effective performance of each assay should be selected.[247]

Yet here for the Ames assay, CTP-OS compared the historical control data against the results for the test article (Menthol 5.0%) to find mutagenicity. This finding was consistent throughout the review of JLI's PMTAs:

- 1st Cycle Toxicology Review: "Based on the applicant-provided data, the *historical control data* for strain TA98 in the bacterial reverse mutation assay is a mean of 15 revertants. The data from PM0000872 at 3.13 µL/plate and 6.25 µL/plate indicate 3.3-fold and 3.2-fold increase in revertants, respectively. While this is an unexpected result, it meets the criteria for a positive mutagenic response, as specified by the applicant."[248]

- 2nd Cycle Toxicology Review: "When evaluating the applicant-provided data for PM0000872 (Menthol 5%) from the *in vitro* bacterial reverse mutation (Ames assay), the aerosol condensate generated from the new product was found to induce a three-fold increase in TA98 revertants at two successive test article concentrations when compared to the *historical vehicle control group*."[249]

- TPL: "The mean (± Standard Deviation) revertant colonies per plate were reported as 50 (12) and 48 (6) at the test article concentrations of 3.13 µL/plate and 6.25 µL/plate, respectively. The corresponding *historical vehicle control data* for the bacterial reverse mutation assay reports the mean revertant colonies per plate as 15 (6)."[250]

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[246] FDA, Guidance Document, Redbook 2000: IV.C.1.a. Bacterial Reverse Mutation Test, (July 2018).

[247] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 471: Bacterial Reverse Mutation Test (1997), p. 4.

[248] FDA 1st Cycle Toxicology Review of JLI's PMTAs, p. 14 (emphasis added).

[249] FDA 2nd Cycle Toxicology Review of JLI's PMTAs, p. 11 (emphasis added).

[250] FDA TPL Review of JLI's PMTAs (Toxicology), p. 28 (emphasis added).

- MDO: "Your submitted data show that the aerosol condensate produced from PM0000872 (Menthol 5%) using the devices PM0000878 and PM0000879, using standard puffing parameters, induced a significant mutagenic response when compared to the *historical vehicle control group*."[251]

But these findings and the ultimate conclusion in the MDO were inconsistent with the study protocol and OECD guideline, and as a result, CTP-OS applied the incorrect control group to determine that Menthol 5.0% was mutagenic.

ii. Applied Correctly, the Results from the In Vitro Ames Assay Confirm that Menthol 5.0% Is Not Mutagenic

Contrary to the MDO, and following the study protocol and OECD guideline, results from the in vitro Ames assay for Menthol 5.0% did not show a mutagenic response when assessed against the correct control group — the concurrent vehicle control data. Moreover, the assay met acceptance criteria when assessed against the historical control data.

As noted throughout this discussion, per the study protocol and in accord with the OECD guideline, the criteria for a positive response are:

> The test article is considered positive for mutagenicity if it induces an increase of revertants per plate with increasing concentration. The increases should be at least 2 times the *vehicle control background frequency* for strains with high spontaneous levels (i.e., TA100 and TA102) and 3 times for those with low spontaneous levels (TA1537, TA98, and TA1535). These increases should be seen in at least 2 or more successive concentrations or the response should be repeatable at a single concentration.[252]

The test article is negative "if it does not induce a response which fulfills the above criteria."[253]

The MDO, albeit incorrectly applying the historical data as the control, found that Menthol 5.0% induced a mutagenic response against the TA98 tester strain in two or more successive concentrations under the standard puffing parameter.[254] As shown in Table 6 below from the study report included in JLI's PMTAs, when correctly applying the concurrent vehicle data as the control, Menthol 5.0% does not induce a mutagenic response

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[251] FDA Marketing Denial Order for JLI's PMTAs, p. 11 (emphasis added). Notably, the Deficiency Letter did not provide a basis or notice on how CTP-OS reached this conclusion other than citing JLI's "study guidelines," which, as explained here, were not followed.

[252] PMTA Section N.3.1.1. Report 03408REVA (Menthol 5%), sec. 10.3 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf) (emphasis added).

[253] *Id*. at sec. 10.4.

[254] FDA Marketing Denial Order for JLI's PMTAs, p. 11.

in any concentration against the TA98 tester strain with or without metabolic activation.[255] For TA98, the study protocol required a three-fold increase of revertants per plate with increasing concentration.[256]

Table 6 Results from the In Virto Ames Assay on Menthol 5.0% Aerosol Under the Standard Puffing Parameter[257]

Table 4.2
Mutagenicity Assay: Individual Data of the Preincubation Experiment for Menthol 5% Condensate – Standard Regime in the Bacterial Reverse Mutation Assay

REVERTANT COLONIES PER PLATE

Treatment Group	µL/plate	TA1537			TA98			TA100			TA1535			TA102		
WITHOUT ACTIVATION																
Replicates		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
200 Proof Ethanol	100 µL	6	6	4	24	28	23	62	76	77	17	16	17	270	279	289
ICR-191 Acridine	0.5 µg/plate	401	309	410												
2-Nitrofluorene	2.5 µg/plate				799	909	840									
Sodium Azide	1.0 µg/plate							312	361	408	427	436	426			
4-Nitroquinoline-N-oxide	2.0 µg/plate													1394	1472	1477
	0.781	5	4	6	29	20	28	69	75	71	7	4	13	172	216	370
Menthol 5% Condensate –	1.56	3	5	3	33	42	56	101	102	83	7	5	6	233	265	261
Standard Regime	3.13	4	3	8	62	50	38	72	88	72	5	7	9	253	282	166
	6.25	2	4	8	41	51	52	82	79	73	7	10	9	234	291	--[a]
	12.5	4	0	2	48	27	29	62	59	82	9	4	13	295	--[a]	--[a]
	25	7	5	2	38	30	21	70	72	58	9	9	11	--[a]	--[a]	--[a]
	50	1	3	2	16	12	30	76	63	62	4	11	4	--[a]	--[a]	--[a]
	100	5	7	4	23	29	21	67	65	63	--[a]	--[a]	--[a]	--[a]	--[a]	--[a]
WITH ACTIVATION																
Replicates		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
200 Proof Ethanol	100 µL	2	2	4	19	28	29	39	60	42	9	7	6	312	296	204
2-Aminoanthracene	2.5 µg/plate	169	104	118	1506	1247	1462	802	1097	680	168	185	177			
2-Aminoanthracene	10.0 µg/plate													1716	1735	2374
	0.781	2	6	5	25	21	25	48	51	48	6	10	7	299	301	166
Menthol 5% Condensate –	1.56	0	8	4	23	24	30	42	30	38	10	8	8	332	132	81
Standard Regime	3.13	3	3	3	35	31	28	61	62	42	11	3	7	275	272	236
	6.25	7	3	4	28	32	26	49	52	71	9	10	9	363	248	286
	12.5	4	3	3	18	21	32	47	51	59	11	9	17	213	182	127
	25	4	6	5	26	28	33	64	53	61	9	11	10	138	271	149
	50	0	5	5	26	25	33	53	61	47	11	10	17	74	254	261
	100	3	5	5	18	18	34	72	51	60	17	12	9	130	145	90

Note: All plates had confluent background lawn, unless otherwise noted.
[a] Reduced background lawn, plate not counted.

JLI further clarified these results in its Deficiency Response:

> The data in the Ames assay report for Menthol 5.0%,[] corresponding to the conditions specified by FDA in Question 18 ("aerosol condensate generated from the proposed new product using standard puffing parameters . . . without liver S9 fraction, using Salmonella typhimurium strain TA98"), shows that the mean (+/- SD) revertant counts/plate for the triplicate vehicle control cultures was 25 (+/- 3). The highest observed mean (+/- SD) revertant counts/plate in the treated cultures was 50 (+/- 12) observed at a concentration of 3.13 µL/plate. This represents only a 2-fold increase in the number of mean revertant counts/plate while the positive criteria for TA98 strain is an increase of at least 3-fold over the vehicle control background frequency.

[255] *Id*. at 69 (Table 4.2).

[256] PMTA Section N.3.1.1. Report 03408REVA (Menthol 5%), sec. 10.3 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf) (emphasis added).

[257] *Id*. at 69 (Table 4.2).

> Therefore, the Menthol 5.0% aerosol condensate was not found positive for mutagenicity in strain TA98 in these treatment conditions, at any of the tested concentrations.
>
> Moreover, there were no test conditions for Menthol 5.0% (e-liquid, intense or non-intense condensate, with or without S9, in any of the test strains) where the mean number of revertants in treated cells achieved or exceeded the vehicle mean revertant count by the requisite factor for the different strains.[258]

With the testing criteria showing a negative mutagenic response, the data are reliable so long as the assay met acceptance criteria. According to the study protocol, the assay acceptance criteria are:

> The vehicle control and positive control plates from each tester strain (with or without S9) must exhibit a characteristic number of revertant colonies when compared against relevant historical control data generated at the Testing Facility (Ames_2019_01 or newer). In addition, vehicle control plates should display normal growth (i.e., normal background lawn) in the presence and absence of S9.[259]

As applied, the concurrent vehicle control, when compared to the laboratory's historical control data, met the assay acceptance criteria. The observed vehicle control value (25) was within the 95% confidence interval of the historical control data (15 ± 6; 95% confidence interval range, 3 – 27), with no obvious technical error.[260]

The study protocol and findings on acceptance criteria are further supported by OECD TG 471. There, the OECD guideline states that "[t]he strains should also yield spontaneous revertant colony plate counts within the frequency ranges expected from the laboratory's historical control data and preferably within the range reported in the literature."[261]

The vehicle control is within the 95% confidence interval of the historical mean.[262] Thus, the testing facility found that the assay met acceptance criteria, which means that the

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[258] JLI Deficiency Response to Question 18, p. 147 (footnote omitted).

[259] PMTA Section N.3.1.1. Report 03408REVA (Menthol 5%), p. 35, 66 (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf).

[260] *Id.* at 20.

[261] Organisation for Economic Co-operation and Development, OECD Guideline for the Testing of Chemicals, Test Guideline TG 471: Bacterial Reverse Mutation Test (1997), p. 3.

[262] PMTA Section N.3.1.1 Report 03408REVA (Menthol 5%) (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf).

concurrent vehicle control values were within the acceptable historical range as stated in the study report:

> In the mutagenicity and repeat mutagenicity assay, the means of the vehicle control data were comparable to the historical data. The means of all positive control data were at least 3-fold greater than the means of the vehicle control data and comparable to the historical data. These results demonstrated the validity and sensitivity of the test system for detecting chemical mutagens in the presence and absence of metabolic activation.[263]

Accordingly, the assay is valid and the data confirm that Menthol 5.0% is not mutagenic:

> The data from the vehicle and positive controls demonstrated the validity and sensitivity of this test system for detecting chemical mutagens with and without metabolic activation.
>
> Mean increases in the number of revertant colonies indicative of a positive response were not observed with Menthol 5% formulation in the *S. typhimurium* strains TA1537, TA98, TA100, TA1535 and TA102, with and without metabolic activation, under the conditions of this assay. Therefore, all preparation types (e-Liquid, Condensate – Standard Regime, Condensate – Intense Regime) of Menthol 5% are considered to be negative for inducing mutagenicity in this assay.[264]

***

A distinct but related flaw in the MDO is the process irregularity that led to this deficiency. If JLI had notice that CTP-OS was applying the wrong testing criteria and a full and fair opportunity to respond, it could have corrected the error through a simple exchange.

The MDO stated that, based on JLI's "study guidelines," Menthol 5.0% induced a mutagenic response in the in vitro Ames assay.[265] CTP-OS relied on the same basis (i.e., JLI's "study guidelines" for the Ames assay) in the Deficiency Letter.[266]

After reviewing the Deficiency Letter, JLI was confused about the basis for CTP-OS's finding. That is because, following the study protocol, OECD guideline, and testing criteria for a positive or negative response, Menthol 5.0% was not mutagenic under any condition.

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[263] *Id.* at sec. 5.

[264] *Id.* at sec. 6.

[265] FDA Marketing Denial Order for JLI's PMTAs, p. 11.

[266] FDA Deficiency Letter to JLI for PMTAs, Question 18.

In its Deficiency Response, JLI "respectfully disagreed" with CTP-OS's conclusion and then re-analyzed and re-justified the study's initial findings and conclusion: "Menthol 5.0% aerosol condensate was not found positive to mutagenicity in strain TA98 in these treatment conditions, at any of the tested concentrations."[267]

The true basis for CTP-OS's finding became clearer in the MDO. The MDO stated that Menthol 5.0% induced a "significant mutagenic response when compared to the *historical vehicle control group*."[268] That is, this issue of using the historical control data was raised for the first time in the MDO.

Process and program irregularities occurred throughout the decision-making process for JLI's PMTAs. Those discussed here are just another example.

B. Public-Health Considerations

CTP-OS's reluctance to consider the overall characterization of the health risk and net-population impact of the JUUL System undercuts a statutory and regulatory framework intended to protect and promote public health. This includes "efforts to develop, introduce, and promote less harmful tobacco products."[269]

The MDO for JLI's PMTAs prompts the question of whether FDA will fail to authorize products that have the most potential to serve the public-health goal of reducing tobacco-related death and disease. Instead, as it has recognized, the Agency should follow the iterative process for review it has previously developed and followed for prior PMTAs and that is necessary to assure FDA's product-specific decisions serve its public-health objectives.

1. Congress and FDA Have Recognized That Noncombustible Alternatives to Combustible Cigarettes Have the Potential to Reduce Tobacco-Related Death and Disease and That FDA Should Support the Development of Less Harmful Tobacco Products to Reduce Population-Level Harm

The Tobacco Control Act recognizes that there are potential public-health benefits if FDA authorizes new tobacco products that reduce tobacco-related death and disease compared to existing, grandfathered products — namely combustible cigarettes. It requires that PMTA reviews involve an evaluation of whether a proposed new product "presents less risk than other tobacco products."[270]

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[267] JLI Deficiency Response to Question 18, p. 147

[268] FDA Marketing Denial Order for JLI's PMTAs, p. 11 (emphasis added).

[269] Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, § 3(4), 123 Stat. 1782 (2009).

[270] 21 U.S.C. § 387j(b)(1)(A).

The Agency also has said that it "continues to support development of alternative tobacco products with the potential to reduce harm"[271] and recognizes the need for "striking an appropriate balance between regulation and encouraging development of innovative tobacco products that may be less dangerous than cigarettes . . . ."[272]

For ENDS products in particular, FDA has noted 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."[273] And subject to the Agency's review of additional information, "completely switching from combusted cigarettes to ENDS may reduce the risk of tobacco-related disease for individuals currently using combusted tobacco products, given the products' comparative placements on the continuum of nicotine-delivering products."[274]

2. An Iterative Process for PMTA Review Is Necessary to Assure Regulatory Decision-Making That Best Serves Public-Health Objectives

Congress and FDA have recognized that efficiency in agency decision-making is important to promote desired forms of innovation. Both have further recognized that an iterative approach to the review of product applications is critical to achieving that efficiency and reducing the risk of Type II error — i.e., the risk of failing to authorize products that do, in fact, have significant potential to protect and promote public health.

For example, Congress added statutory requirements for the collaborative review of device applications to "facilitate communications between FDA and persons who submit premarket approval applications to improve the efficiency of the device review process." These requirements were explicitly intended to "force the agency to critically consider the [premarket approval application] up front in the review cycle and not wait until late in the review process, which has all too often been the agency's pattern."[275]

Since then, the Agency itself has recognized the importance of notifying applicants of any deficiencies in drug or device applications as early as possible. For example, FDA has noted that this is important to "improve FDA's predictability and transparency, promote the efficiency and effectiveness of FDA's assessment process, minimize the number of assessment cycles necessary for approval," and, when warranted, "increase FDA's overall

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[271] 81 Fed. Reg. 28974, 29001 (May 10, 2016).

[272] FDA. (2017, July 27). FDA Announces Comprehensive Regulatory Plan to Shift Trajectory of Tobacco-Related Disease, Death. *FDA News Release*, retrieved from https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regulatory-plan-shift-trajectory-tobacco-related-disease-death.

[273] *Id.*

[274] 81 Fed. Reg. 28974, 29030 (May 10, 2016).

[275] Senate Report 105-43, at 25 (July 1, 1997) (accompanying enactment of 21 U.S.C. § 360e(d)(3)(A)).

rate of approval, and facilitate greater access to" products that are important from a public health perspective.[276]

3. FDA's More Limited Approach for JLI's PMTAs Runs Counter to Public Health: It Is Inefficient and Creates Risk that the Agency Will Fail to Authorize Products That Have Significant Potential to Reduce Harm

Prior FDA precedent on marketing decisions for PMTAs appears to have reflected recognition of these principles and their applicability to new products. As noted above, FDA's regulations, statements, and prior practice with respect to other products with the potential to reduce tobacco-related death and disease have reflected an emphasis on the need for iterative review.[277]

Presumably due to the pressures of an accelerated timeline imposed on the review of PMTAs for currently marketed products, the Agency's approach here and with other ENDS PMTAs appears to have been more limited.[278] The resulting risk of Type II error is not just theoretical — it seems to be bearing out in real time where FDA has provided applicants with little opportunity to address identified deficiencies. JLI is aware of at least eight other instances in the past year where the Agency's approach has led to the issuance of MDOs that were subsequently rescinded (in full or in part) or at least stayed pending further review.[279]

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[276] FDA, Guidance for Industry: Information Requests and Discipline Review Letters Under GDUFA, at p. 3 (2022); *see also* FDA, Guidance for Industry: Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act, at p. 2 (2001), (observing the importance of notifying the applicant of any deficiencies in an NDA or BLA "as early as possible after a discipline review had been completed," in order to enable the applicant to "begin preparing a response to the deficiencies, thereby decreasing the response time to the Agency and potentially expediting availability of products to consumers"); FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, at p. 10 (2018) (noting the "principle that FDA will consider the most efficient path toward completion of a comprehensive review that addresses application deficiencies and leads toward a first cycle approval when possible"); FDA, Guidance for Industry and FDA Staff: Types of Communication During the Review of Medical Device Submissions, at p. 5 (2014), (describing the purpose of FDA's program for "increased informal interaction between FDA and applicants" for device applications, which "is to facilitate the efficient and timely review and evaluation by FDA of premarket submissions").

[277] For example, see Section I, Figure 1.

[278] *See* Am. Acad. of Pediatrics v. FDA, Case No. PWG-18-883, 379 F. Supp. 3d 461 (D. Md. 2019); *see also* Norcia N. (2020), CTP's Office of Science (OS) Premarket Application Review Prioritization Plan, *Scribd*, retrieved at from https://www.scribd.com/document/575749534/CTP-s-Office-of-Science-OS-Premarket-Application-Review-Prioritization-Plan?secret_password=e79TH5ywGHVX4QlsN23O#download&from_embed (disclosing a redacted version of CTP's original PMTA review prioritization plan).

[279] FDA Premarket Tobacco Product Marketing Denial Orders, retrieved from https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/tobacco-products-marketing-orders#Marketing%20Denial.

The increased risk should also be particularly concerning where it applies to products, like the JUUL System, that are widely used by adults who are former cigarette smokers. Although FDA has authorized a number of other products with the potential to reduce harm compared to combustible cigarettes, those currently make up less than 3% of the total ENDS market.[280]

C. Legal Considerations

Authorization to market a new tobacco product requires a determination "that permitting such tobacco product to be marketed would be appropriate for the protection of the public health."[281] The APPH standard does not impose a "static set of requirements" or specific "criteria" that must be met.[282] It requires a "complex determination,"[283] that "considers many factors,"[284] and must be "based on all of the contents of the application."[285]

In making such a determination, the Agency also must abide by the familiar requirements of constitutional and administrative law. Due process and basic fairness require that the Agency act as an "impartial decision maker" when reviewing JLI's PMTAs.[286] Further, agency action is arbitrary and capricious under the Administrative Procedure Act (APA) if its "explanation for its decision . . . runs counter to the evidence before the agency,"[287] if the agency "departs from agency precedent without explanation,"[288] if the agency fails to "reasonably consider[] the relevant issues,"[289] or if the agency relies on impermissible considerations.[290] For instance, "political pressure invalidates agency action . . . when it shapes, in whole or in part, the judgment of the ultimate agency decisionmaker."[291]

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[280] Internal analysis based on syndicated market data from Information Resources, Inc. (IRI) for tracked channels through the first quarter of 2022. Tracked channels are limited to convenience, food/grocery, and drug. Based on internal estimates for tracked and non-tracked channels, JLI believes that authorized ENDS products comprise approximately 1.0–1.5% of the ENDS market.

[281] 21 U.S.C. § 387j(c)(2)(A).

[282] 86 Fed. Reg. 55300, 55385, 55386 (Oct. 5, 2021).

[283] *Id.* at 55335.

[284] *Id.* at 55314.

[285] *Id.* at 55320.

[286] *Goldberg v. Kelly*, 397 U.S. 254, 271 (1970).

[287] *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

[288] *Ramaprakash v. FAA*, 346 F.3d 1121, 1124 (D.C. Cir. 2003).

[289] *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021).

[290] *Int'l Ladies' Garment Union v. Donovan*, 722 F.2d 795, 814 (D.C. Cir. 1983).

[291] *Aera Energy LLC v. Salazar*, 642 F.3d 212, 220 (D.C. Cir. 2011).

The MDO did not meet these legal requirements.

First, FDA did not give the PMTAs a fair review. Instead, the Agency appears to have: (i) been subject to extraordinary political pressure exerted by several members of Congress; (ii) used the PMTA process as a mechanism to punish alleged past misconduct; and (iii) singled out JLI for adverse action.

Second, FDA did not give the PMTAs a complete review. Instead, the Agency issued the MDO based on ostensible deficiencies that: (i) overlooked information in the PMTAs; (ii) could have been addressed through the usual, iterative process that defines a full review of product applications; and (iii) applied a new and different standard that appears to have been created for, and applied only to, JLI's PMTAs.

1. FDA Failed to Conduct a Fair Review

a. The Administrative Decision-Making Process Was Subject to Attempts of Political Interference

Since JLI submitted its PMTAs, FDA has been under immense and unprecedented political pressure to reach a very specific decision — deny the applications and remove the products from the market. The record of attempted political interference from certain members of Congress is replete and overwhelming. Specific instances are detailed in Section I.

This sort of political pressure is precisely the sort of interference that courts have found to violate Due Process and the APA.[292]

There also appears to be an absence of effort by FDA to insulate its review of the PMTAs from undue political influence.[293] For instance, the D.C. Circuit has explained that an

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[292] *See Tummino v. Torti*, 603 F. Supp. 2d 519, 523-24 (E.D.N.Y. 2009) (actions taken to facilitate Senate confirmation of the Commissioner of Food and Drugs reflected "a lack of good faith and reasoned agency decision-making"); *see also Koniag, Inc., Village of Uyak v. Andrus*, 580 F.2d 601, 610 (D.C. Cir. 1978) (finding that a letter from a Representative regarding pending applications had compromised the appearance of agency impartiality); *D.C. Federation of Civic Ass'ns v. Volpe*, 459 F.2d 1231, 1246-49 (D.C. Cir. 1971) (finding improper political interference where a Representative threatened to withholding funding for one project unless the agency agreed to proceed with another project); *Pillsbury Co. v. FTC*, 354 F.2d 952, 963 (5th Cir. 1966) ("common justice to a litigant requires that we invalidate the order entered by a quasi-judicial tribunal that was importuned by members of the United States Senate").

[293] To the contrary, these blatant attempts to influence, coupled with victory laps by those interfering, have cast a pall over FDA's tobacco-regulatory program for ENDS products. See Section I for examples on and following June 23, 2022, when FDA issued the MDO.

Since the decision, FDA has commissioned the Reagan-Udall Foundation to conduct a comprehensive evaluation of its food and tobacco programs. Although not referenced in the Agency's press release announcing the external review, several have commented on the relevance of its decision on JLI's PMTAs. Perrone M. (2022, July 19) FDA Weighs Oversight Changes After Formula, JUUL Troubles. *AP News*, retrieved

agency can preserve impartiality by recusing the individuals and agency components interacting with Congress or other politicians.[294] An agency also can restore impartiality by referring an application to proceedings before an unbiased factfinder, such as an advisory committee or a formal evidentiary hearing.[295]

To mitigate these concerns, ensure transparency, and support a fair review on the science, JLI requests that this matter, the underlying scientific controversy, and its PMTAs also be reviewed by TPSAC.[296]

b. The MDO Was an Unauthorized Sanction

FDA's prior words and actions suggest that the reasons cited in the MDO as a basis to remove JUUL products from the market were pretextual.

In 2021, the Acting Commissioner of Food and Drugs testified before the Oversight Subcommittee on Economic and Consumer Policy at a hearing titled "An Epidemic Continues: Youth Vaping in America." During the hearing, the Acting Commissioner offered the opinion that JUUL products were "responsible for" a "youth vaping epidemic," were "hurting" a "generation" of Americans and were "a public health problem of significance." She also stated that the Agency's review of JLI's PMTAs would "take into account" allegations of past misconduct.[297]

Allowing allegations of past misconduct to influence the outcome of a PMTA review is impermissible. The Federal Food, Drug, and Cosmetic Act (FDCA), including the Tobacco Control Act, generally regulates products — not companies. Under the Tobacco Control Act, the grounds to deny a PMTA turn on the characteristics of the product, its proposed labeling, and its methods of manufacture.[298]

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from https://apnews.com/article/science-health-tobacco-industry-regulation-robert-califf-bbf49dd28719a34872771d82cd60cf02; McGinley L. (2022, July 19) Amid Controversies, FDA Seeks Advice on Food and Tobacco Companies. *Washington Post*, retrieved from https://www.washingtonpost.com/health/2022/07/19/fda-food-tobacco-review/.

[294] *See Aera Energy*, 642 F. 3d at 220-21 (discussing *Press Broadcasting Co. v. FCC*, 59 F.3d 1365, 1369-70 (D.C. Cir. 1995)).

[295] *See Aera Energy*, 642 F. 3d at 221 (discussing *ATX, Inc. v. DOT*, 41 F.3d 1522, 1525-28 (D.C. Cir. 1994)).

[296] 21 C.F.R. § 10.75(b)(2) (providing that an applicant may "request review of a scientific controversy by an appropriate scientific advisory panel . . . .").

[297] An Epidemic Continues: Youth Vaping in America: Hearing Before the Subcomm. on Econ. and Consumer Pol'y of the H. Comm. on Oversight and Reform, 117th Cong. (2021).

[298] *See* 21 U.S.C. § 387(j)(c)(2)(A)-(D).

In contrast, Congress has authorized agencies to weigh past misconduct in other federal licensing schemes.[299] Congress also authorized FDA to consider judicially established cases of misconduct when imposing certain sanctions.[300] Such provisions make clear that FDA cannot deny PMTAs as a sanction for alleged misconduct.[301] Indeed, FDA has acknowledged that the product review provisions of the FDCA do not authorize punitive action.[302]

Similarly, the press release announcing the MDO includes a quote from the current Commissioner claiming that JUUL products "have played a disproportionate role in the rise in youth vaping."[303] The MDO makes no reference to underage use, and it remains unclear whether the marketing decision even assessed population-level data on JUUL use — either from adults or youth.

These statements from the Agency were and are inappropriate. First, the implied claim that the JUUL System has special appeal to youth is, at the very least, outdated. The 2021 National Youth Tobacco Survey (NYTS) showed that 85% of youth ENDS users "reported currently using flavored products."[304] Unlike many of its competitors, JLI no longer markets, and did not seek authorization for, ENDS products with characterizing flavors other than tobacco and menthol. Further, among current users of ENDS products, JUUL was the fourth most commonly cited "usual brand" in 2021 (6.8%), following Puff Bar (26.8%), Vuse (10.5%), and Smok (8.6%).[305] Based on 2021 data, the overall prevalence of

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[299] *See, e.g.*, 49 U.S.C. §§ 31134(b), 31144(a).

[300] *See, e.g.*, 21 U.S.C. § 335a(a) (mandatory debarment applies if FDA determines that

[301] *See, e.g.*, *TransAmerica Mortgage Advisors, Inc. (TAMA) v. Lewis*, 444 U.S. 11, 20-21 (1979) ("[W]here a statute specifically provides a particular remedy or remedies, a court must be chary of reading others into it. 'When a statute limits a thing to be done in a particular mode, it includes the negative of any other mode'"); *White v. United States*, 989 F.2d 643, 647 (3d Cir. 1993) ("the structure of the Act indicates that Congress intentionally withheld" a particular power from agency).

[302] *See, e.g.*, *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1488 (D.C. Cir. 1995) ("FDA ruled that revoking its approval would serve no public health purpose and that neither the FDCA nor the citizen petition rules contemplated the use of the FDA's administrative procedures for punitive action against an animal drug manufacturer.").

[303] FDA. (2022, June 23). FDA Denies Authorization to Market JUUL Products. *FDA News Release*, retrieved from https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products.

[304] FDA. (2022, Mar. 10) Results from the Annual National Youth Tobacco Survey. Retrieved from https://www.fda.gov/tobacco-products/youth-and-tobacco/results-annual-national-youth-tobacco-survey.

[305] *See* E. Park-Lee, et al. (2021, Oct. 1) E-Cigarette Use Among Middle and High School Students – National Youth Tobacco Survey, United States, 2021, Notes from the Field, *Morbidity and Mortality Weekly Report*, *70*. 1387; CDC. (2021) National Youth Tobacco Survey. Retrieved from https://www.cdc.gov/tobacco/data_statistics/surveys/nyts/data/index.html.

JUUL use as the primary ENDS brand was 0.6% among high-school students and 0.4% among middle-school students. [306]

The APA also forbids FDA from using the PMTA process as a sanction. As noted above, the APA requires agencies to consider only those factors specified by Congress and forbids agencies from relying on impermissible considerations. The APA also decrees that agencies cannot impose any sanction without explicit statutory authority.[307] "Congress could not speak more clearly than it has in the text of the APA: 'a sanction may not be imposed or a substantive rule or order issued except within jurisdiction delegated to the agency and as authorized by law.'"[308]

c. JLI Was Singled Out for Disparate Treatment

Taken together, the MDO, decision-making process, barrage of targeted political pressure, and ad hoc punishment for alleged past conduct raise the proposition of JLI and its PMTAs being singled out for adverse action.

This disparate treatment may be best represented by how FDA communicated and handled the marketing decision, beginning with the press release. The subtitle of the press release reads: "Currently Marketed JUUL Products Must Be Removed from the US Market."[309] The first paragraph states both that "JLI must stop selling and distributing its products" and that JUUL products currently in retail inventories "must be removed, or risk enforcement action."[310] Further down, the press release reiterates that FDA "intends to ensure compliance by distributors and retailers."[311] No equivalent threatening statements were included in the press release announcing an MDO for one of JLI's competitors.[312]

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[306] *See id.*

[307] 5 U.S.C. § 558(b).

[308] *Am. Bus Ass'n v. Slater*, 231 F.3d 1, 7 (D.C. Cir. 2000) (finding that an agency could not rely on "inherent authority" to fashion a damages remedy).

[309] FDA. (2022, June 23). FDA Denies Authorization to Market JUUL Products. *FDA News Release*, retrieved from https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products.

[310] *Id.*

[311] *Id.*

[312] *See, e.g.*, FDA. (2022, Apr. 8). FDA Issues Marketing Denial Orders to Fontem US for myblu Products. *CTP Newsroom*, retrieved from https://www.fda.gov/tobacco-products/ctp-newsroom/fda-issues-marketing-denial-orders-fontem-us-myblu-products.

Table 7 Differences in FDA Press Releases and Communications on MDOs

	Juul Labs, Inc.	Fontem US
Headline	FDA Denies Authorization to Market JUUL Products *Currently Marketed JUUL Products Must Be Removed from the US Market*	FDA Issues Marketing Denial Orders to Fontem US for myblu Products
Enforcement	"Today, the U.S. Food and Drug Administration issued marketing denial orders (MDOs) to JUUL Labs Inc. for all of their products currently marketed in the United States. As a result, the company must stop selling and distributing these products. In addition, those currently on the U.S. market must be removed, or risk enforcement action." "Any products subject to an MDO may not be offered for sale or distributed in the United States, or the FDA may take enforcement action." "In addition to ensuring that JUUL complies with this order, as with unauthorized products generally, the FDA intends to ensure compliance by distributors and retailers. Specifically, the FDA notes that all new tobacco products on the market without the statutorily required premarket authorization are marketed unlawfully and are subject to enforcement action." "As the FDA has stated in the past, unauthorized electronic nicotine delivery system (ENDS) products for which no application is pending, including for example, those with an MDO, are among our highest enforcement priorities. Therefore, the FDA encourages retailers to discuss products in their inventory with their suppliers including the current status of any particular tobacco product's marketing application or marketing authorization. Manufacturers will be the best source of that information and retailers should rely on manufacturers directly to inform decisions about which products to continue selling."	"Tobacco products subject to a negative action regarding a premarket submission, including those subject to an MDO, may not be offered for sale, distributed or marketed in the US. Such products may not be introduced or delivered for introduction into interstate commerce, and if the product is already on the market, the product must be removed from the market." "Currently, FDA's highest enforcement priorities are ENDS products for which no application is pending, including, for example, those with an MDO or those for which no application was submitted. "

	Juul Labs, Inc.	Fontem US
Youth Use	"We recognize these make up a significant part of the available products and many have played a disproportionate role in the rise in youth vaping."	"Additionally, the applications did not demonstrate that the potential benefit to smokers who switch completely or significantly reduce their cigarette use would outweigh the risk to youth."
Black-Market Products	"There is also no way to know the potential harms from using other authorized or unauthorized third-party e-liquid pods with the JUUL device or using JUULpods with a non-JUUL device. The FDA recommends against modifying or adding substances to tobacco products."	N/A
Health and Safety	"JUUL users are encouraged to report any unexpected health problems or product problems to the FDA through the Safety Reporting Portal and to seek medical attention as necessary."	N/A
Switching	"There are many resources to help smokers who want to quit. Quitting all tobacco products is the best possible path to good health. Some current JUUL users who will not have access to JUUL products following this action or current smokers who want to transition away from cigarettes and cigars may decide to switch to other ENDS products that have been reviewed and authorized by the FDA based on their potential to benefit adult smokers."	N/A

Even after the U.S. Court of Appeals for the D.C. Circuit had entered a temporary administrative stay (June 24, 2022) and the Agency issued its own administrative stay of the MDO (July 5, 2022), FDA continued to threaten JLI's business. The Agency sent a written statement to press outlets asserting that JLI cannot "legally market, ship, or sell [its] products."[313] Press outlets continued to repeat FDA's statement through at least July 11, 2022, without correction from the Agency,[314] even though the statement was

[313] Norcia, N. (2020, July 6) FDA Backs Away From Its Own JUUL Decision With 'Additional Review. *FilterMag*, retrieved from https://filtermag.org/fda-juul-additional-review; Zimmerman M. (2020, July 6) FDA Stays JUUL Marketing Denial Order, More Review Needed. *Bloomberg Law*, retrieved from https://news.bloomberglaw.com/health-law-and-business/fda-stays-juul-marketing-denial-order-says-more-review-needed.

[314] Padres, A. (2002, July 11) JUUL Nears Its Last Gasp — After It Hooked a Generation on Vaping. *Wired*, retrieved from https://www.wired.com/story/juul-nears-its-last-gasp/.

inconsistent with FDA's representations to JLI and the D.C. Circuit.[315] Sending and then failing to retract an arguably contumacious statement reflects a significant level of hostility towards JLI and its applications.

The Agency also has taken extraordinary steps to stimulate safety reports related to JUUL products — steps not taken for any other ENDS product subject to an MDO. The June 23 press release conceded that "FDA has not received clinical information to suggest an immediate hazard associated with the use of the JUUL device or JUULpods."[316] Nevertheless, the press release went on to state, "JUUL users are encouraged to report any unexpected health problems or product problems to the FDA through the Safety Reporting Portal."[317] As FDA repeatedly has recognized, that sort of encouragement causes bias by stimulating over-reporting.[318] That the Agency would inject bias into the safety reporting data for the JUUL System speaks volumes.

Making matters worse, JLI did not learn of FDA's marketing decision from the MDO or even the Agency's press release. Instead, JLI and the rest of the world learned of FDA's decision a day before the MDO was released because the decision was leaked to a reporter by unnamed FDA officials.[319] This unprecedented breach of the confidentiality owed to a pending product application was a stunning violation of FDA regulations.[320]

The Agency's disparate treatment of JLI and its PMTAs has been noticed by many. For instance, STAT News noted that "the agency may have railroaded [JLI's] application

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[315] Joint Motion to Hold Case in Abeyance, *Juul Labs, Inc. v. FDA*, No. 22-1123, ECF No. 1953737, ¶ 3 (July 6, 2022) ("FDA does not intend to take enforcement action against the products subject to JLI's marketing denial order while the administrative stay is in place.").

[316] FDA Denies Authorization to Market JUUL Products, FDA News Release (June 23, 2022). Retrieved at https://www.fda.gov/news-events/press-announcements/fda-denies-authorization-market-juul-products.

[317] *Id.*

[318] *See, e.g.*, Duggirala, et. al. (2018, Aug. 20) Data Mining at FDA. Retrieved from https://www.fda.gov/media/91848/download, p. 16-17 ("Challenges, inherent in safety report databases, that limit the interpretability of signals have already been discussed elsewhere and include: … *Over-reporting*. Over-reporting can be due to media publicity, litigation, or the product being newly marketed."); FDA, *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, at 9 (Mar. 2005) (acknowledging the need for "caution" because voluntary reporting databases "are subject to a variety of reporting biases" including "reporting stimulated by publicity or litigation").

[319] Maloney J. (2022, June 22) FDA to Order JUUL E-Cigarettes Off U.S. Market: Agency Has Cleared Way for Rivals Reynolds American, NJOY Holdings to Keep Selling Tobacco Flavored E-Cigarettes. *Wall Street Journal*, retrieved from https://www.wsj.com/articles/fda-to-order-juul-e-cigarettes-off-u-s-market-11655904689.

[320] *See* 21 C.F.R. § 1114.47(b)(2)–(3).

under political pressure."[321] And the Wall Street Journal aptly described FDA's treatment of JLI as "a death sentence without a trial."[322]

2. FDA Failed to Conduct a Complete Review

Even if FDA's review had not been affected by impermissible considerations, it would remain legally deficient because it was incomplete. The statute requires that the Agency examine all "valid scientific evidence," and balance all of the relevant data, before taking action on a PMTA.[323] The statute also requires that, when "practicable," a marketing denial order must inform the applicant of all "measures required to remove such application from deniable form."[324] The APA imposes a similar obligation.[325]

FDA itself has recognized that its decision must be "based on all of the contents of [an] application."[326] For example, the Agency's final rule for PMTAs and associated preamble specifically recognize that toxicology data feed into a comprehensive assessment of individual health risk, which should take into account a wide range of relevant information. For example, the final rule states that a PMTA must include comprehensive information about individual health risks, including information about a product's toxicological profile and the health effects of its constituents.[327] The preamble further emphasizes this point by stating that the types of investigations relevant to an assessment of health effects "include human exposure studies, in silico computational toxicology techniques, risk assessments, in vitro toxicology studies, published reports of in vivo toxicology studies, and, if necessary, new in vivo toxicology studies."[328]

FDA's approach to prior PMTAs further establishes that toxicological issues of the kind identified here are not sufficient to preclude a final decision on a PMTA, or even to preclude an ultimate finding of APPH. The MGOs for IQOS, VERVE, Logic, and Moonlight VLN Cigarettes all reflect marketing authorizations despite findings that the applicant's toxicological assessment was inadequate or identified potential issues of toxicological concern. For each of these authorizations, FDA also evaluated the body of evidence in the

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[321] Florko N. (2020, July 7) In a High-Profile Misstep, the FDA Backtracks on Its Ban on JUUL. *STAT News*, retrieved from https://www.statnews.com/2022/07/07/fda-backtracks-ban-on-juul-high-profile-misstep/.

[322] Editorial Board (2022, July 7) The FDA Misses Its Hit on JUUL. *Wall Street Journal*, retrieved from https://www.wsj.com/articles/the-fda-botches-its-hit-on-juul-labs-robert-califf-lawsuit-11657224457.

[323] 21 U.S.C. § 387j(c)(5)(A)-(B).

[324] *Id.* § 387j(c)(3).

[325] *See, e.g.*, *Genuine Parts Co. v. EPA*, 890 F.3d 304, 312 (D.C. Cir. 2018) (agencies "'must examine all relevant data'") (quoting *State Farm*, 463 U.S. at 43)).

[326] 86 Fed. Reg. at 55320.

[327] See 21 C.F.R. § 1114.7(k)(1)(i)(A) & (B).

[328] 86 Fed. Reg. at 55360-61.

respective applications to assess individual health-risk profile of the products and, in large part, found that the data showed low levels of exposure to specific constituents of concern and overall reductions in HPHCs compared to combustible cigarettes.

For example:

IQOS: In granting authorization for IQOS (a heated tobacco product), FDA pointed to data on four "probably or possible" carcinogenic chemicals and many other chemicals with potentially genotoxic, carcinogenic, or other health effects found to be present in higher concentrations in IQOS aerosols as compared to cigarette smoke.

The Agency found that the applicant's "assessment of [the four] carcinogens is not considered adequate."[329] Specifically, FDA stated that the applicant's comparison of estimated exposures from use of tobacco products to occupational exposure limits was inappropriate because those limits are not intended to be used in evaluating health hazards.[330] The Agency also found that the applicant's comparison to maximum dietary intake was inappropriate because "sensitive effects and target organs drastically differ depending on whether a toxicant is ingested or inhaled."[331]

On the in vitro and in vivo studies, FDA found that "limitations of these assays affect the conclusions that can be drawn from test results" and made it "difficult to determine" the carcinogenic potential of long-term exposure.[332]

Despite these toxicological issues, FDA concluded that:

- "[T]he levels of exposure to these possible carcinogens appear low and when considered with other data does not preclude a conclusion that the products are appropriate for the protection of public health."[333]

- "[A]lthough there is potential for genotoxicity with some of these compounds, the exposure levels appear low and the available data does not

[329] FDA TPL Review of Philip Morris Products S.A.'s PMTAs PM0000424–PM0000426, PM0000479, p. 32. FDA specifically found that the applicant's comparison of estimated exposures from use of tobacco products to occupational exposure limits was inappropriate because those limits are not intended to be used in evaluating health hazards. FDA also found the applicant's comparison to maximum dietary intake was inappropriate because "sensitive effects and target organs drastically differ depending on whether a toxicant is ingested or inhaled."

[330] *Id*.

[331] *See id.*

[332] *Id*. at 37–39.

[333] *Id.* at 32.

preclude a conclusion the products are appropriate for the protection of public health."[334]

- "Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in [combustible cigarettes]."[335]

VERVE: In granting authorization for VERVE Discs and Chews (an oral tobacco product), FDA noted that "[n]o original toxicology studies were submitted by the applicant for any of the VERVE® products."[336] Rather, the applicant relied on hazard and exposure assessments of individual ingredients, with which the Agency took methodological issue because they relied on toxicity values intended for foods, not tobacco products.[337] As part of its analysis of HPHCs, FDA also found increased levels of arsenic as compared to cigarettes but concluded that these "levels are not of toxicological concern."[338]

Despite these toxicological issues, FDA concluded that:

- "The data provided by the applicant for the four VERVE® products do not raise toxicological concerns because of overall reduction of exposure to HPHCs compared to information available for other tobacco products that comprise the current U.S. tobacco market."[339]

- "This determination was made in the absence of original toxicology study data; extensive literature reviews, health assessments, and ingredient assessments provided by the applicant support that the VERVE products will not raise concern from the toxicological perspective."[340]

Logic: In granting authorization for Logic (an ENDS product), FDA stated that "the applicant concluded that the potential risks to consumers from identified and partially identified leachable compounds are acceptable but risk for the unknown leachable

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[334] *Id.*

[335] *Id*. at 42.

[336] FDA TPL Review of U.S. Smokeless Tobacco Company LLC's PMTAs PM0000470–PM0000473, p. 25.

[337] *See id.*

[338] *Id*. at 8.

[339] *Id.* at 34.

[340] *Id.*

compound was above the benchmark value of 1.0 which indicates potential risks of concern."[341]

Despite these toxicological issues, FDA concluded that:

- "Although the simulated leachable compounds for all new products can be hazardous, at the low levels present, if there is any contribution towards cancer hazard, these risks are outweighed by decreases in HPHCs by 83–99% in all new products."[342]

Moonlight VLN Cigarettes: In granting authorization for Moonlight Cigarettes (a combustible product), FDA found that the products' toxicological profiles, including both cancer risks and toxicant-associated noncancer hazards, were "likely similar" to traditionally marketed cigarettes.[343] The Agency also stated that smoke from Moonlight cigarettes included higher levels of four HPHCs than traditional products.[344] FDA nevertheless accepted the supposition that the risks for users "could be lower compared to marketed cigarettes" if users decreased their cigarettes per day and puffing volumes after switching to Moonlight products.[345]

Despite these obvious toxicological issues, FDA concluded that:

- "[T]he potential for a relative benefit compared to [traditional cigarettes] exists for smokers who switch completely to VLN™ cigarettes, then reduce cigarette use, and eventually totally quit."[346]

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Similar considerations of JLI's PMTAs weigh in favor of authorization. Specifically, the PMTAs had data showing: (i) the leachables in question were not found in aerosols at all; (ii) "[t]oxicological evaluation of the mainstream aerosol yields of HPHCs included on the HPHC list, and other quantified chemical constituents found that levels of these compounds in the new products are not present at levels of concern";[347] and (iii) "significant reductions in blood and urinary BOEs indicate that exposure to carcinogens

[341] FDA TPL Review of Logic Technology Development LLC's PMTAs PM0000529–PM0000531, PM0000535–PM0000537, PM0000540–PM0000541, p. 37.

[342] *Id*.

[343] FDA TPL Review of 22nd Century Group Inc,'s PMTAs PM0000491–PM0000492, p. 7.

[344] *Id.* at 26.

[345] *Id.* at 7.

[346] *Id.* at 34.

[347] FDA TPL Review of JLI's PMTAs (Toxicology), p. 11.

and other toxicants present in cigarette smoke were greatly reduced with exclusive use of the new products compared to [combustible cigarette] smoking."[348]

The MDO's statements to the contrary —

- *finding* that "unaddressed deficiencies regarding potential toxicological risks" left FDA unable "to adequately evaluate whether and to what extent relevant tobacco use behaviors" associated with the JUUL System "would represent a public health benefit or a public health harm,"

- *asserting* that FDA cannot determine whether the JUUL System presents "higher risk than other ENDS," and

- *claiming* that FDA cannot determine whether the JUUL System "presents lower risk than combustible cigarettes,"

— reflect a fundamental failure to conduct a complete review of JLI's PMTAs. This failure runs in the face of CTP-OS finding that the aerosol HPHC yields were 98–99% lower in JUUL products compared to combustible cigarettes[349] and authorizing an actual combustible cigarette (albeit with "very low nicotine") that had a similar toxicological profile as other combustible cigarettes.[350]

Further, the issues raised by the MDO could have and should have been addressed through a limited request for additional information or even a teleconference. The Agency's regulations contemplate that a complete review may involve multiple amendments, submitted on an iterative basis, to address any perceived shortcomings in an application.[351] FDA has stated that its historic practice has been to send an average of four deficiency letters per PMTA bundle.[352] The current regulations were based on an expectation that the Agency would send at least two deficiency letters per PMTA bundle.[353]

Rather than engage with JLI on an iterative basis, FDA sent only a single deficiency letter in March 2021, to which JLI timely responded in June 2021. At any point in the ensuing year, FDA could have raised additional concerns — including all the concerns alleged in the MDO — with JLI. The Agency chose not to do so and instead issued the MDO. The departure from the usual iterative process deprived JLI of its right to a full and complete review.

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[348] *Id*. at 13.

[349] FDA 1st Cycle Chemistry Review of JLI's PMTAs, p. 35.

[350] FDA Market Granted Order for 22nd Century's PMTAs PM0000491 and PM0000492.

[351] *See* 21 C.F.R. § 1114.9(a).

[352] *See, e.g.*, 84 Fed. Reg. 50566, 50627-28 (Sept. 25, 2019).

[353] *See, e.g.*, *id.* at 55403.

V. CONCLUSION

For the reasons stated in this § 10.75 request, JLI seeks supervisory review of CTP-OS's MDO and related deficiencies based on the complete administrative file and, as a result, rescission of the MDO to place JLI's PMTAs back into substantive review. This will enable FDA to complete its statutorily-required, science- and evidence-based review and determine whether the JUUL System is APPH. JLI also requests the additional relief detailed in Section I.

Respectfully submitted,

Enclosures: Appendices 1–3

cc: Michele Mital, Deputy Director, Center for Tobacco Products (michele.mital@fda.hhs.gov)

Nathan Hurley, Ombudsman, Center for Tobacco Products (CTPOmbudsman@fda.hhs.gov)

Appendix 1

I. INTRODUCTION

Extractable and leachable investigations are routinely undertaken across a range of sectors (e.g., pharmaceuticals and medical devices) to evaluate the potential of contacting materials to leach unwanted substances into consumer products. Although there are no set standards for leachables in tobacco products, JLI undertook a robust program of extractables and leachables (E&L) evaluations on the components comprising the JUULpod (i.e., component analysis) and also on representative whole pod configurations (i.e., whole pod analysis), following regulatory guidance and widely-accepted standards on E&L for similar container closure systems. Complete details of the E&L analysis, including the test materials, contract laboratories, and analytical methods, are summarized in PMTA Section H.1.1.4 Quantitative Risk Assessment.

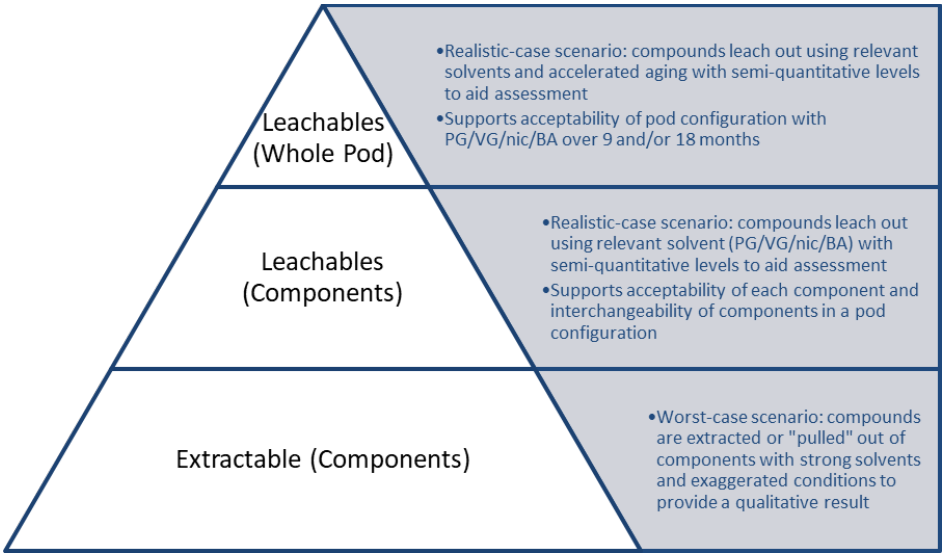
II. ADDITIONAL INFORMATION ON JLI'S APPROACH TO E&L EVALUATIONS

JLI's E&L evaluations followed a step-wise approach:

- First, JLI screened for any potential chemicals that could be introduced into the e-liquid from the container closure system (JUULpods) and components within the aerosol path through the studies depicted in Figure 1;
- Second, JLI conducted a health risk assessment of the leachables identified in the simulated e-liquid studies and flagged any potential toxicological concerns; and
- Third, JLI monitored and evaluated leachable constituents in the JUUL System aerosol over the expected shelf life of the products.

This data ultimately fed into the whole product risk assessment, which forms the basis for the final determination of the product's toxicological risks.

Figure 1 E&L Assessment of JUULpod Components and Whole Pod



Source: PMTA Section H.1.1.4 Quantitative Risk Assessment, p. 30 (h-1-1-4-quantatitative-risk-assessment.pdf)

For the whole pod leachable studies, representative JUULpods (filled with an unflavored e-liquid [simulated e-liquid]) were subject to an accelerated aging process before the respective and then evaluated for leachable compounds. The accelerated aging parameters were as follows:

- Twenty-two (22) weeks at 30°C and 65% relative humidity, reflecting an approximate 9-month shelf life at ambient conditions according to ASTM F1980-07; and

- Twenty-two (22) weeks at 40°C and 75% relative humidity, reflecting an approximate 18-month shelf life at ambient conditions according to ASTM F1980-07.

The resulting extracts from the simulated e-liquids were analyzed by gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), and inductively coupled plasma-mass spectrometry (ICP-MS).[1] The detected leachables were chemically identified and semi-quantified; expressed as µg/component, or device (for the whole pod), for each analytical method, so that each of the identified leachables then could be incorporated into the health risk assessment.

[1] For a complete description of methods, see PMTA Sections N.3.4 Whole Pod Leachables Report 238874 and Whole Pod Leachables Report 238873 (n-3-4-[redacted]-whole-pod-leachable-report-1.pdf and n-3-4-[redacted]-whole-pod-leachable-report-2.pdf).

III. ADDITIONAL INFORMATION ON COMPOUND IDENTIFICATION IN JLI'S E&L EVALUATIONS

For identification, compounds were determined using automated library matches, based on extracting mass spectra for each peak. The initial identifications were made without *a priori* information from JLI on the product materials or manufacturing. While a non-targeted open scan such as this has the benefit of avoiding bias, it may also lead to false positive detection.[2]

Additionally, as noted in the [redacted] leachables reports provided in JLI's PMTAs[3] similar compounds can display similar mass spectra, so it may not be possible to assign definitive compound structures to all detected compound(s) based on library matching alone. Similarly, some compounds may not be distinguishable from other members of their respective class. [redacted]

As is typical for library matching outputs, the initial identification process resulted in a range of confidence levels for identifications – including tentative and partial tentative identifications.[5] The [redacted] leachables reports noted that compounds tentatively identified by the library match as "compound name - related compound" provided information of the structural and chemical features of the assigned compound, but could represent another compound in the same class. The molecular mass and semi-quantitative concentration were reported for each compound as detected by library match, but no confirmatory

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[2] *See, e.g.,* Eric M. Sussman, Berk Oktem, Irada S. Isayeva, Jinrong Liu, Samanthi Wickramasekara, Vaishnavi Chandrasekar, Keaton Nahan, Hainsworth Y. Shin, and Jiwen Zheng (2002). Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices. *ACS Biomaterials Science & Engineering,* 8 (3) ("One potential drawback to surrogate standard selection based on a priori information is bias towards analytes that respond strongly in the selected chemical analysis workflow, and thus, qualification may not apply to the chemical space of unexpected analytes. An alternative approach is to select surrogate standards to cover a wide range of physicochemical properties… many methods and tools are available for improving the identification of substances in NTA, including manual spectral interpretation…")

[3] PMTA Sections N.3.4 Whole Pod Leachables Report 238874 and Whole Pod Leachables Report 238873 (n-3-4[redacted]-whole-pod-leachable-report-1.pdf and n-3-4-[redacted]-whole-pod-leachable-report-2.pdf); JLI Deficiency Response Appendix 17 GRPT-02187 Whole Pod Leachables Report 238874 Version 2 and GRPT-02186 Whole Pod Leachables Report 238873 Version 2 (app-17-01-n-3-4[redacted] whole-pod-leachable-report-1.pdf and app-17-02-n-3-4-[redacted] whole-pod-leachable-report-2.pdf*)*

[4] PMTA Section N.3.4 Whole Pod Leachables Report 238874 and Whole Pod Leachables Report 238873, p. 4 (n-3-4-[redacted]-whole-pod-leachable-report-1.pdf and n-3-4[redacted]-whole-pod-leachable-report-2.pdf); JLI Deficiency Response Appendix 17 GRPT-02187 Whole Pod Leachables Report 238874 Version 2 and GRPT-02186 Whole Pod Leachables Report 238873 Version 2, p.4 (app-17-01-n-3-4-[redacted]-whole-pod-leachable-report-1.pdf and app-17-02-n-3-4-[redacted]-whole-pod-leachable-report-2.pdf).

[5] "tentative" is a defined term per industry standard, and is used by the contract laboratory [redacted] to apply when no database or library information on the precise compound exists.

chemical analysis was undertaken at this point, and the underlying mass data was not provided in the [redacted] leachables reports.

Regarding library match scores, in the LC-MS section of the [redacted] report, included the following statement:

[redacted]

It is well recognized that a non-targeted open scan library matching process is imperfect. Tentative matches, particularly those based only on classes of compounds, may not be exact. A common interdisciplinary approach for addressing analytical uncertainty is manual evaluation to confirm the identity and quantity of the analyte.[7] Additionally, because score is not a direct indication of confidence, the veracity of updated identifications should not be questioned on the basis of the library match score alone, but instead on the comprehensive review of the mass spectra and fragmentation patterns.

IV. ADDITIONAL INFORMATION ON TOXICOLOGICAL RISK ASSESSMENTS FOR LEACHABLE COMPOUNDS

With these identifications from [redacted] JLI's contractor [redacted] conducted toxicological risk assessments for the leachable compounds. The assessments evaluated the critical toxicological endpoints [redacted] for each identified leachable compound.

[redacted] used highly health precautionary assumptions to characterize potential individual health risk from constituents that could be introduced from the JUULpod materials into the e-liquid and potentially exposed to users through the aerosol:

- Consumer exposures were estimated using heavy use scenarios, [redacted]

[6] PMTA Sections N.3.4 Whole Pod Leachables Report 238874 and Whole Pod Leachables Report 238873 (n-3-4-[redacted]-whole-pod-leachable-report-1.pdf and n-3-4-[redacted]whole-pod-leachable-report-2.pdf).

[7] *See, e.g.,* Eric M. Sussman, Berk Oktem, Irada S. Isayeva, Jinrong Liu, Samanthi Wickramasekara, Vaishnavi Chandrasekar, Keaton Nahan, Hainsworth Y. Shin, and Jiwen Zheng (2002). Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices. *ACS Biomaterials Science & Engineering,* 8 (3).

- It was also conservatively assumed that 100% of the leachables detected could be transferred from the e-liquid solutions into the aerosol and be inhaled by the consumer.

- As there is no set standard for levels of toxicological concern for leachables in tobacco products, the risk values used for flagging potential toxicological concern were based on the standards for drug impurities (e.g., ICH M7).

- While comprehensive literature searches were performed to identify relevant and reliable toxicity data for all identified leachables, where substance-specific data were lacking, appropriate (Q)SAR assessments, expert judgment and read-across approaches were considered and applied.

For each of the different JUULpod components, the risk assessment concluded that the potential exposure to the detected leachables was unlikely to pose a health risk to even heavy-use consumers.[8]

For the whole pod studies, JLI noted that "uncertainties" remained concerning the toxicological risk posed by certain "data-deficient" leachable compounds. Relevant to this discussion, Ethyl hydroxyquinoline carboxylate, aminobutyric acid related compound (EHQC) and Propylpyridine, 1 H-pyrrole-1-hexanoic acid,2,5-dihydro-2,5-dioxo-related compound (PHDC) were flagged as candidate target compounds based on the ICH M7 standard for drug impurities to "monitor and evaluate in future analyses" in the aerosol during real-time stability testing.[9] However, even when using highly conservative assumptions and assuming 100% transfer to aerosol, the levels of both EHQC and PHDC in the simulated leacheable e-liquid resulted in maximum estimated exposures below the allowable cancer risk level of 1 in 10,000 in ISO 10993-17 (ISO, 2002) for leacheables in medical devices.

As a next step in the risk assessment framework, JLI noted "all identified compounds will be reported in the non-targeted analyses" of the products' aerosol. If any of the candidate target compounds were identified in the then-ongoing semi-quantitative non-targeted analyses, "targeted approaches may be necessary to confirm identification and quantification."[10] Ultimately, it is the levels in the aerosol rather than the projections based on levels of detection in the simulated e-liquid that allows for the most accurate assessment of potential risk. Not all the detected potential leachables of concern will

[8] PMTA Section N.3.3 Component Leachables Technical Risk Assessment Report (n-3-3-comp-leach-tra-report.pdf*)*

[9] PMTA Section N.3.3 Whole Pod Leachables Technical Risk Assessment Report, p. 219-220, 400 (n-3-3-whole-pod-leach-tra-report.pdf).

[10] Section N.3.3 Whole Pod Leachables Technical Risk Assessment Report, p. 221, 401 (n-3-3-whole pod-leach-tra-report.pdf).

transfer to the e-liquid and then the aerosol to which the user is exposed during product use.

V. ADDITIONAL INFORMATION ON UPDATED COMPOUND IDENTIFICATIONS

To support monitoring and evaluation in future analyses, shortly after the leachables analysis was received in February 2020, JLI requested [redacted] provide mass spectra of EHQC and PHDC compounds for further manual evaluation of the compound structure.

JLI questioned whether these two compounds were incorrect identifications for three reasons:

- The compounds were detected only in the whole-pod leachables studies and not in upstream component leachables or extractables studies;
- The compounds were not fully rationalized (i.e., only partial tentative identifications); and
- The compounds had no known relation to the product properties and were not classified as formulation related (e.g., nicotine or benzoic acid reaction products).

To address tentative findings such as these, a common interdisciplinary approach is careful follow-up analysis to confirm the identification. Manual spectral interpretation is a common method available for improving the identification.[11] As is best practice according to USP 1663, Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, the identifications were refined based on manual spectral interpretation in collaboration with JLI analytical chemistry specialists and the contracted laboratory using combined product knowledge and chemical analysis with generally accepted analytical chemistry techniques.[12]

Chemical analysis considered the assigned molecular structure and rationalization of the chemical structure, and full tentative identifications were proposed based on the

[11] Eric M. Sussman, Berk Oktem, Irada S. Isayeva, Jinrong Liu, Samanthi Wickramasekara, Vaishnavi Chandrasekar, Keaton Nahan, Hainsworth Y. Shin, and Jiwen Zheng (2022). Chemical Characterization and Non-targeted Analysis of Medical Device Extracts: A Review of Current Approaches, Gaps, and Emerging Practices. *ACS Biomaterials Science & Engineering,* 8 (3), 939-963.

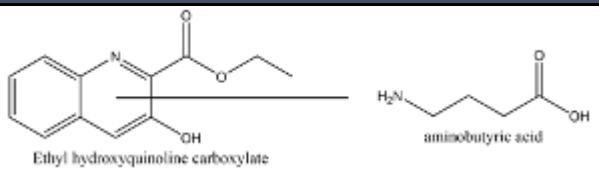
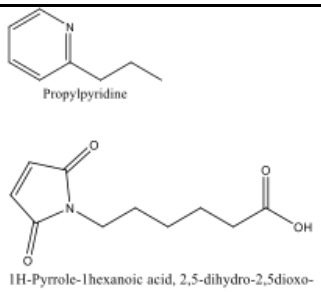
[12] USP. Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems <1663>. In: USP-NF. Rockville, MD: USP; August 1, 2018. DOI: https://doi.usp.org/USPNF/USPNF_M7126_03_01.html. ("[I]t is strongly recommended that the test article assessor and the test article vendor collaborate in such a way that the test article assessor has access to critical information which will aid in the design and implementation of an effective and efficient extraction study.")

fragment patterns and possible fragment ions from the mass spectra. In cases where assigned molecular formula did not align with the mass spectral data, improved molecular formula and structure was proposed. Importantly, no new analytical data were generated; rather, the original data was reprocessed with the same software but with updated structural information (e.g., ions) identified during the manual evaluation to facilitate better matches. As a result, the original [redacted] Whole Pod Leachables reports,[13] which had been completed on February 26, 2020, were amended on May 13, 2020 to update the two partial tentative identifications to full (Table 1) to full tentative identifications (Table 2). These updated reports were included in the Deficiency Response. [14]

[13] PMTA Sections N.3.4 Whole Pod Leachables Report 238874 (n-3-4-[redacted]-whole-pod-leachable-report-1.pdf) and Whole Pod Leachables Report 2388733 (n-3-4-[redacted]-whole-pod-leachable-report-2.pdf).

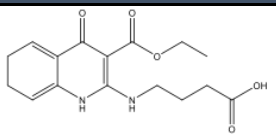
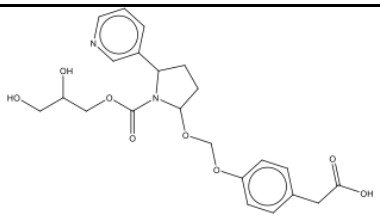
[14] JLI Deficiency Response Appendix 17 GRPT-02187 Whole Pod Leachables Report 238874 Version 2 **(**app-17-01-n-3-4-[redacted]whole-pod-leachble-report-1.pdf) and GRPT-02186 Whole Pod Leachables Report 238873 Version 2 (app-17-02-n-3-4[redacted]-whole-pod-leachable-report-2.pdf).

Table 1 Previous Compound Identifications

Previous identification	Previous identification structure
Ethyl hydroxyquinoline carboxylate, aminobutyric acid related compound [EHQC]	 Position not assigned Chemical Formula: $C_{16}H_{20}N_2O_5$ Molecular Weight: 320.35
Propylpyridine,1H-Pyrrole-1hexanoic acid, 2,5-dihydro-2,5dioxo-related compound [PHDC]	 Position not assigned Chemical Formula: $C_{18}H_{24}N_2O_4$ Molecular Weight: 332.40[a]

[a] Assumed charge carrier adduct at 445.16 m/z

Table 2 Updated Compound Identifications

Previous identification	Updated identification	Updated identification structure
Ethyl hydroxyquinoline carboxylate, aminobutyric acid related compound [EHQC]	1,8,9-Trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone [TCEQ] *also known as* 4-((3-(ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid [ECOTHQB or ETBA]*	 Chemical Formula: $C_{16}H_{20}N_2O_5$ Molecular Weight: 320.35 Predicted Boiling Point: 993.25 [K][a]
Propylpyridine,1H-Pyrrole-1hexanoic acid, 2,5-dihydro-2,5dioxo-related compound [PHDC]	Nornicotine, *N*-carboxyglycerol-5'-(methoxy-1-(*p*-hydroxybenzene-*O*4-yl-acetic acid)) [NNMA]	 Chemical Formula: $C_{22}H_{26}N_2O_8$ Molecular Weight: 446.46 Predicted Boiling Point: 1266.27 [K][a]

Source: PMTA Section N.3.4 Whole Pod Leachables Report 238874 (n-3-4-[redacted]-whole-pod-leachable-report-1.pdf); JLI Deficiency Response Appendix 17 GRPT-02187 Whole Pod Leachables Report 238874 Version 2 **(**app-17-01-n-3-4-[redacted]-whole-pod-leachble-report-1.pdf)

[a] Boiling point prediction by commercially available ChemOffice

*Note: as shown in the associated identification structure, TCEQ and ECOTHQB/ETBA are the same structural compounds, with different naming conventions

While these updated identifications were completed prior to JLI's initial PMTA submission, the updated reports could not be included in the PMTAs due to publishing deadlines. However, it should be noted that JLI incorporated the updated identifications in

the JUULpod material toxicological risk assessment and Quantitative Risk Assessment summaries.[15]

VI. ADDITIONAL INFORMATION ON UPDATED COMPOUND IDENTIFICATIONS

In Question 17 of CTP-OS's Deficiency Letter on the PMTAs, CTP-OS requested additional data on three leachables: EHQC, PHDC, and phenol.[16] CTP-OS noted that JLI's risk assessment had identified these leachables as candidate target compounds "to monitor and evaluate in future analyses" of the products' aerosol.[17] With respect to EHQC and PHDC, CTP-OS stated "you identified these constituents as having an excess cancer risk outside of generally accepted margins of 'tolerable cancer risk' or possessing some mutagenic and carcinogenic potential when inhaled." [18] CTP-OS asked that JLI "provide testing results of these three constituents in the mainstream aerosol generated under intense and non-intense use of your new tobacco products, and a comparison with similar testing for suitable comparator products" so that it could "perform a full toxicological evaluation of these leachable constituents." [19] CTP-OS stated that "these data will inform toxicological risks associated with the potential presence of these leachable constituents in the respirable aerosol generated from the new tobacco product and enable CTP-OS to determine relevant health risks to consumers of the new tobacco products." [20]

In response to questions regarding the leachables of concern in the Deficiency Letter, JLI provided the information to support the refined identifications of EHQC and PHDC:

- EHQC was updated to 1,8,9-tryhydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone (hereinafter, TCEQ); and
- PHDC was updated to Nornicotine, N-carboxyglycerol-5'-(methoxy-1-(p-hydroxybenzene-O4-yl-acetic acid)) (hereinafter, NNMA) (collectively, the leachables of concern).

To address CTP-OS's concerns as noted in the Deficiency Letter, JLI also provided a new risk assessment for the updated compounds.[21] Although CTP-OS requested "testing

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[15] PMTA Section N.3.3 JUULpod Material Toxicological Risk Assessment (n-3-3-juulpod-material-toxicologic-risk-assess.pdf); Section H.1.1.4 Quantitative Risk Assessment (h-1-1-4-quantitative-risk-assessment.pdf).

[16] JLI Deficiency Response to Question 17.

[17] *Id.*

[18] *Id.*

[19] *Id.*

[20] *Id.*

[21] I*d.,* p. 132.

results of the constituents in the mainstream aerosol," because none of the two potential leachables of concern were detected in the non-targeted analyses of the aerosol over the estimated shelf-life of 12 months, JLI did not go on to conduct and provide targeted aerosol data for the otherwise non-detectable leachables.

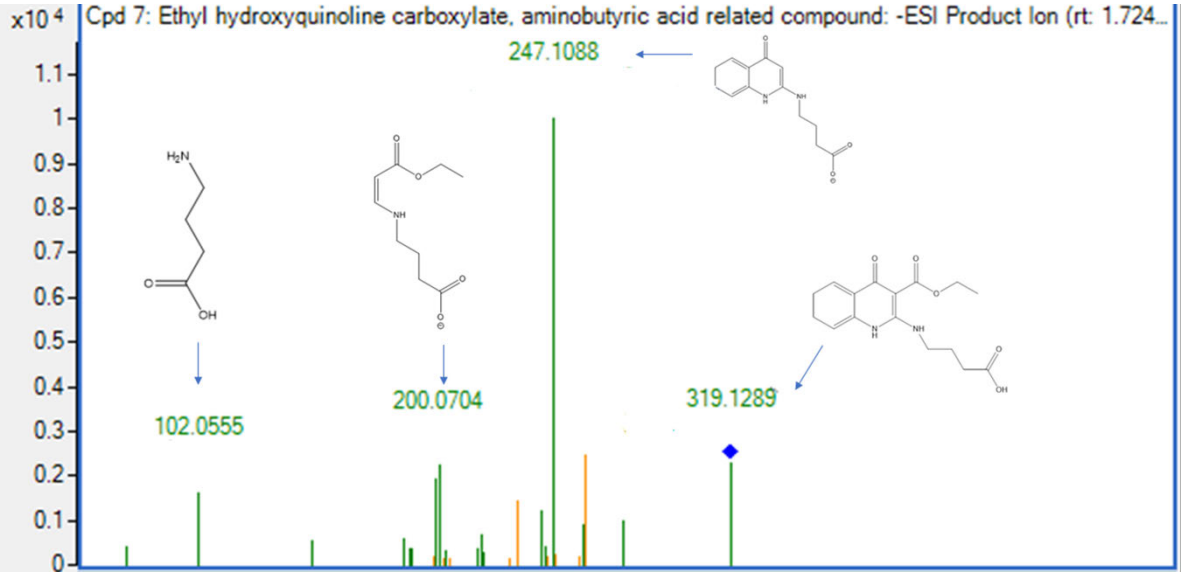
1. EHQC → TCEQ

Ethyl-4-hydroxyquinoline-3-carboxylate, aminobutyric acid related compound, referred to as "EHQC," was a partial tentative identification detected by LC-MS analyses in the simulated e-liquid leachables study.

Because this was a partial tentative identification through the automated library match process, there was not data on potential toxicity of the compound. For purposes of risk assessment, JLI focused on ethyl-4-hydroxyquinoline-3-carboxylate and the structurally related analogue, 4-hydroxyquinoline, as a health-precautionary surrogate. The risk assessment assumed that EHQC poses an equivalent carcinogenicity hazard as quinoline.

After the manual evaluation of the mass spectral data and subsequent data reprocessing (as described in Section V above) the identification of EHQC was refined to 1,8,9-Trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone (TCEQ). Based on the mass spectral evidence, the nitrogen-associated ring contains both an ethylcarboxylate (see Figure 2, fragment ion at 247.1088 m/z) and an aminobutyric acid group (see Figure 2, fragment ion at 102.0555 m/z). This is further supported by the fragment ion observed at 200.0704 m/z (see Figure 2, fragment ion at 200.0704 m/z) which contains both groups. Therefore, this refined full tentative identification is a better match than the initial partial tentative identification, which is incompatible with the underlying mass spectral data.

Figure 2 Annotated ESI(-) Fragmentation Spectrum – Retention Time 1.724 Minutes (EHQC/TCEQ)



Source: JLI Response to Deficiency Letter: Appendix 17.1 GRPT-02187 - Whole Pod Leachables Report 238874 Version 2 and Appendix 17.2 GRPT 02186 - Whole Pod Leachables Report 238873 Version 2

The MDO stated that JLI provided "conflicting" data that undermines the revised identification of EHQC to TCEQ, in that EHQC is reidentified as two separate and distinct chemicals (TCEQ and ETBA). However, as the MDO acknowledged, TCEQ and ETBA have the same chemical structure. The difference in compound name is a result of differences in compound naming conventions only. JLI acknowledges that the different naming conventions may be cause for confusion, but the semantic differences do not undermine the chemical identifications. JLI provides the following breakdown of naming conventions:

- The updated compound identification was reported as 1,8,9-Trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone (TCEQ) in the updated [redacted] leachables reports and Deficiency Response.

- The same compound structure was reported as 4-((3-ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid in the updated risk assessment report.

- JLI also referred to and evaluated 4-((3-ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid in both the [redacted] Risk Assessment

report[22] and in H.1.1.4 Quantitative Risk Assessment contained within the initial PMTAs, and used the shorthand "ECOTHQB" to describe this compound.

Note that JLI's PMTAs did not use the shorthand ETBA at any point. Rather, in the course of CTP-OS's review, it refers to 4-((3-ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid as "ETBA."[23]

Whether TCEQ, ECOTHQB, or ETBA, the chemical names 1,8,9-Trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinoloneand 4-((3-(ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid all refer to the same chemical structure using different naming conventions. To further illustrate this point, JLI provides a thorough depiction of the chemical structure identifications in Section VII below.

Any perceived conflict in the chemical names (TCEQ versus ETBA or ECOTHQB) does not make a difference in determining the toxicological risks associated with this leachable compound. Specifically for purposes of the leachables health risk assessment, JLI conducted a thorough literature search, which revealed no relevant substance-specific toxicity data or **structurally** analogous surrogate compounds (via in silico methods as described in response to Deficiency 17), so any risks would have been captured not only in name but also substance.

2. PHDC → NNMA

Propylpyridine, 1H-pyrrole-1-hexanoic acid,2,5-dioxo-related compound (PHDC) was a partial tentative identification detected by LC-MS analyses in the simulated e-liquid leachables study.

JLI identified propylpyridine, 1H-pyrrole-1-hexanoic acid,2,5-dioxo-related compound (PHDC) consistently across the initial PMTA submission documents and updated the identification to Nornicotine, N-carboxyglycerol-5'-(methoxy-1-(p-hydroxybenzene-O4-yl-acetic acid)) (NNMA) in the Deficiency Response and supporting documents. With respect to this compound identification, CTP-OS specifically noted that "...with respect to the leachable constituent, PHDC, the applicant's re-identification is not

[22] PMTA Section N.3.3 JUULpod Material Toxicological Risk Assessment (n-3-3-juulpod-material-toxicologic-risk-assess.pdf)

[23] ECOTHQB was also identified in the individual component leachables analysis and was discussed in the Quantitative Risk Assessment summary section, which was based on the updated reports, although the updated reports were not included in the initial submission due to publishing deadlines. Despite the fact that ECOTHQB was analyzed as a leachable in the initial PMTA submission, applying the same risk assessment approach requested by the agency, CTP-OS noted no deficiencies related to it.

scientifically supportable for the following reasons: The provided chemical structures and chemical formulas between the original and revised identification are inconsistent."[24]

First, JLI agrees the original compound assignment of Propylpyridine,1H-Pyrrole-1hexanoic acid, 2,5-dihydro-2,5dioxo- related compound was not compatible with the mass spectra collected during the initial analysis of the e-liquids.

As depicted in Figure 3, three pieces of information critical to understanding the revised identification can be observed from the mass spectra:

- The largest peak in the mass spectrum (353.1136);
- The highest mass peak in the mass spectrum (445.1584); and
- The peak in the mass spectrum that relates to nicotine (143.0602).

All three fragments are structurally linked to the updated structure [NNMA] and would not be explained by the original molecular formula [PHDC] — which was based on a charge carrier adduct for the original molecular formula — and was revised to a deprotonated molecular ion [M-H] for the updated structure.

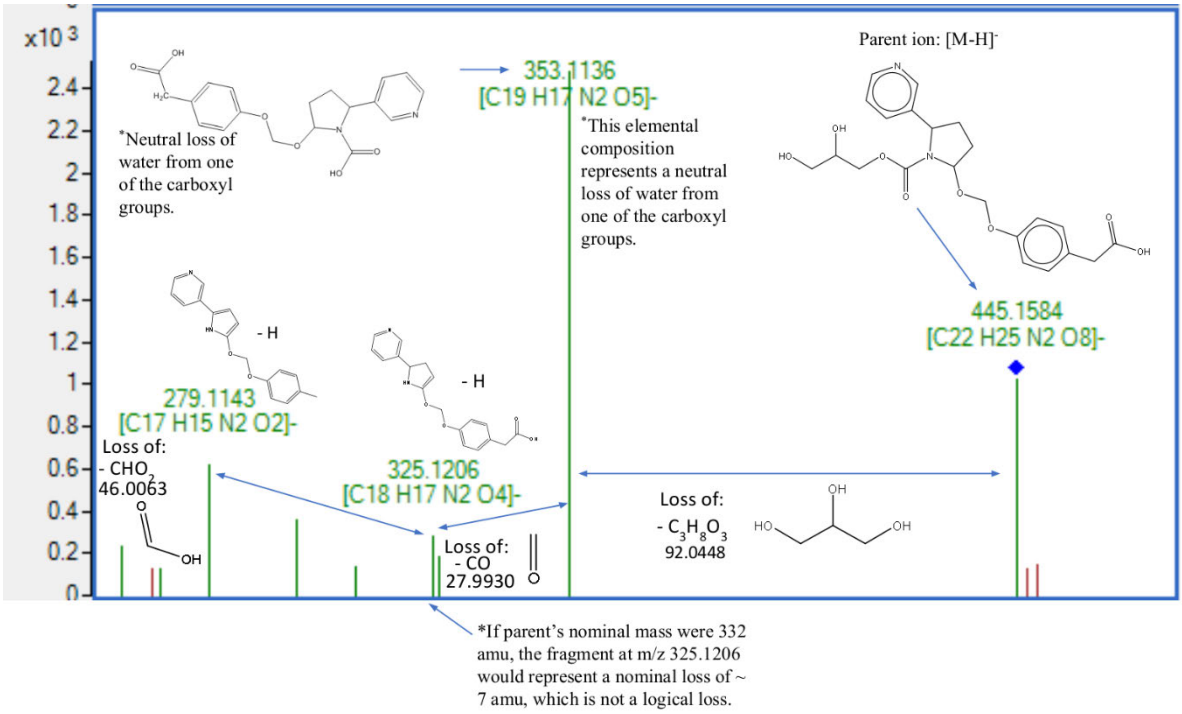
As reflected in the updated [redacted] reports submitted with the Deficiency Response, the updated identification is also associated with a revised molecular mass assignment, from a mass range of 332.1726 – 332.1757 Da and molecular formula of $C_{18}H_{24}N_2O_4$ to a mass range of 446.1654 – 446.1707 Da and a molecular formula of $C_{22}H_{26}N_2O_8$. The mass of the compound was calculated as if it had been detected with a trifluoracetic acid (CF_3CO_2H) adduct, which has an exact mass of 113.9923.

It is common in the field of mass spectrometry to report the molecular formula and molecular mass of the compound detected, not the mass of the compound plus the mass of the adduct. For this reason, the mass of the molecule was first reported in the range of 332.1726 – 332.1757 (mass detected minus the mass of the adduct) and then revised to the range of 446.1654 – 446.1707 (reflecting the absence of an adduct). This field-specific practice is perhaps at the heart of the misunderstanding, as CTP-OS indicates "there are no indications that change in exact mass of the product ion... can be explained by a neutral loss or other relevant mechanism."[25] Here, the corrected molecular mass assignment was driven by the mis-identified charge carrier adduct, thus resulting in revisions to the molecular formula of the compound.

[24] FDA TPL Review of JLI's PMTAs (Toxicology) PM0000864, PM0000872, PM0000876, PM0000878, PM0000879, p. 16

[25] FDA 2nd Cycle Toxicology Review of JLI's PMTAs p. 8

Figure 3 Annotated ESI(-) Fragmentation Spectrum – Retention Time 2.44 Minutes (PHDC/NNMA)



Source: JLI Deficiency Response to Question 17 Figure 3, p. 136.

Second, in addition to being more consistent with fragments measured in the mass spectrum, the updated identification of NNMA is more consistent with known chemical reactions that occur in the e-liquid over time. The revised compound consists of a nicotine-based core structure, with a condensation of propylene glycol and evidence of reaction with benzoic acid.

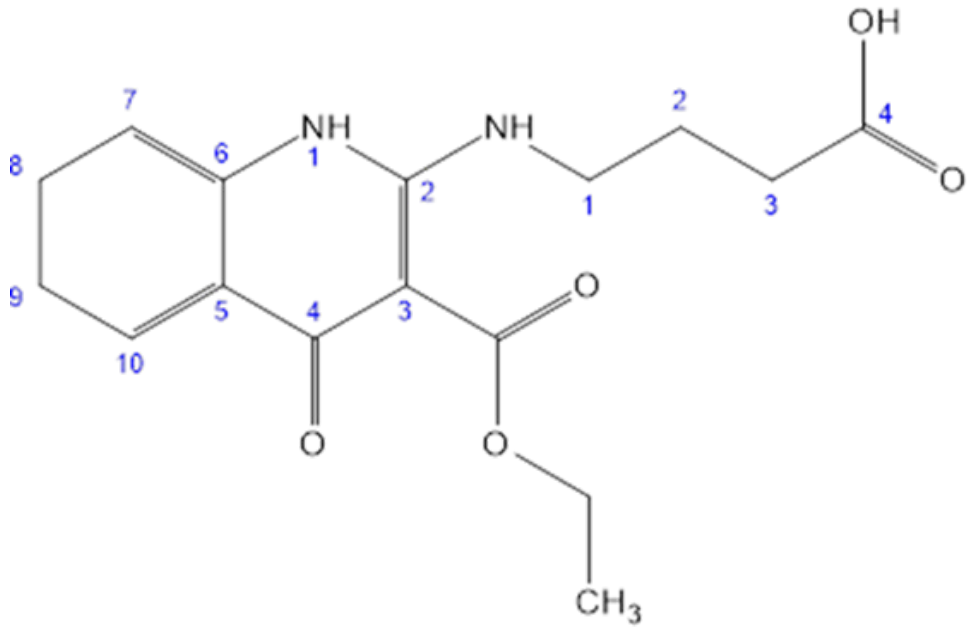
Overall, as explained by these clarifications, JLI is confident that the updated compound identifications are correct and supported by the underlying documents and analyses within the PMTAs (including the Deficiency Response). They are aligned with:

- The structurally linked fragments, as shown in the mass spectra data obtained from the vendor and provided to CTP-OS;
- The proposed chemical reactions that occur in the e-liquids over time; and
- Chemical structures across naming conventions.

VII. ADDITIONAL INFORMATION ON CHEMICAL STRUCTURE IDENTIFICATION

1,8,9-trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone and 4-((3-(Ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid are the same chemical structure, as explained below.

Figure 4 1,8,9-trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone

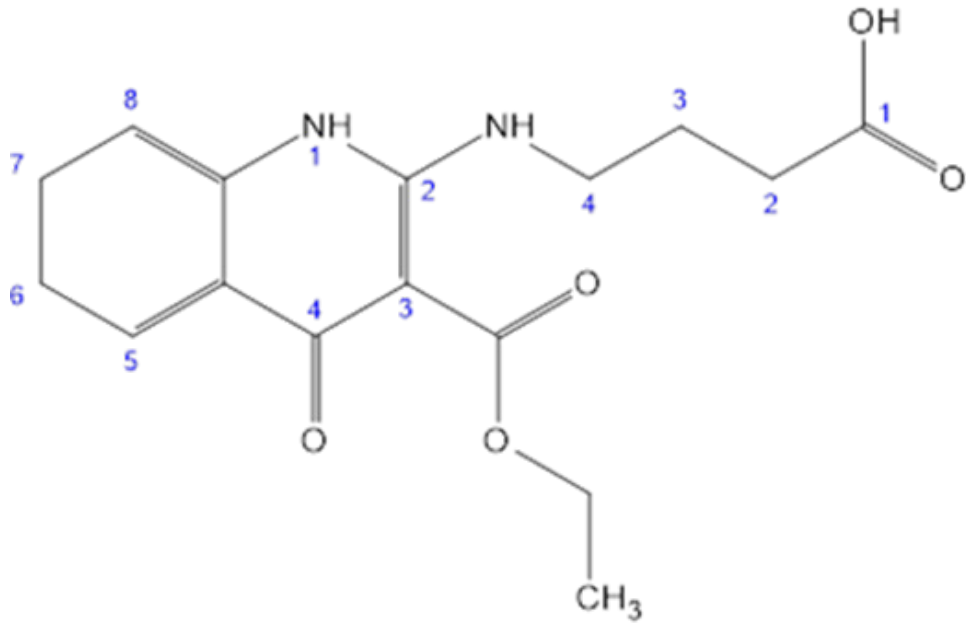


1,8,9- trihydro and 4- quinolone indicate an unsaturated quinoline ring structure. 4-quinolone is a quinolone that is 1,4-dihydroquinoline substituted by an oxo group/ketone at position 4. This nomenclature includes counting all positions on the ring as shown above. 1,8,9- trihydro indicate unsaturation/lack of a double bond at positions 1,8, and 9 on the quinolone ring system.

2-(3-carboxypropylamine-N-yl): 3-carboxypropylamine is also known as 4-Aminobutanoic acid. "2-"indicates this functional group is located at the 2 position of the quinolone ring system. The suffix -yl is used when naming organic compounds that contain a single bond replacing one hydrogen; therefore, "N-yl" indicates the attachment of this functional group is on the Nitrogen.

"3-ethylcarboxylate" indicates an ethyl carboxylate functional group at the 3-position of the quinolone ring system.

Figure 5 4-((3-(Ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid



"4-oxo-1,4,6,7-tetrahydroquinolin" indicates a quinoline ring structure whereby the 4 position includes a ketone/oxo group. The numbering of the 4-quinolone ring system is consistent with IUPAC (International Union of Pure and Applied Chemistry) rules for naming fused ring systems nomenclature; numbering begins with the heterocyclic atom (Nitrogen); the numbering proceeds clockwise around the structure. Fused Carbons (those joining the two ring systems) are not explicitly numbered. 1,4,6,7-tetrahydro indicates that these numbered positions lack a double bond(alkene) within the ring.

"3-ethoxycarbonyl" indicates an ethyl carboxylate functional group at the 3-position of the quinolone ring system.

Parentheses are used in chemical nomenclature to set off parts of a name dealing with specific structural features to provide the structure of a compound as clearly as possible. Thus, the parentheses in the above chemical name indicate that there is a structural feature at the 4-position of butanoic acid. The location of the attachment of the structural feature is provided as 2-yl, indicating 4-amino butanoic acid is located off the 2-position of the quinolone ring.

Appendix 2

I. ADDITIONAL INFORMATION ON THE IN VITRO MICRONUCLEUS ASSAY ACCEPTANCE CRITERIA

As described in JLI's PMTA Section H.1.1.2 Toxicology, genotoxic potential was assessed using the in vitro micronucleus (MN) assay with the human lymphoblastoid cell line TK6 in accordance with the 2016 OECD Guideline Test No. 487: In Vitro Mammalian Cell Micronucleus Test (OECD TG 487).[1] The potential for JUUL product and comparator ENDS product e-liquids and aerosol condensates and 3R4F smoke condensates to induce MN was evaluated using three OECD recommended treatment conditions. The same assay acceptance criteria, as well as the data evaluation and scoring methodologies, for the in vitro micronucleus (MN) assay applied across test products as set forth in each study protocol provided in the PMTAs.[2] (See Table 1).

Table 1 Criteria Used for Data Interpretation

Study Protocol
4.2. Criteria for a Positive Response The test article would be considered positive for inducing micronuclei if a statistically significant and dose dependent increase ($p \leq 0.05$) in the mean percentage of micronucleated cells was observed at 1 or more dose levels when compared to the concurrent vehicle control. A response would be considered statistically significant for dose-response trend in the Cochran-Armitage test if $p \leq 0.05$. At least 1 concentration should be increased outside the historical control range of the vehicle control. 4.3. Criteria for a Negative Response The test article would be considered negative for inducing micronuclei if no statistically significant increase ($p \leq 0.05$) was observed in the mean percentage of micronucleated cells at any of the test concentrations when compared to the concurrent vehicle control and there is no concentration-related increase when evaluated in the Cochran-Armitage

[1] Organisation for Economic Co-operation and Development. OECD Guideline for Testing Chemicals Test Guideline. TG487: In vitro Mammalian Cell Micronucleus Test. 2016.

[2] PMTA Section 3.1.2 Report 03399REVA (Virginia Tobacco 5%) (n-3-1-2-micronuc-vt-5-rpt-03399reva-report.pdf); PMTA Section 3.1.2 Report 03425REVA (Virginia Tobacco 3%) (n-3-1-2-micronuc-vt-3-rpt-03425reva-report.pdf); PMTA Section 3.1.2 Report (Menthol 5%) (n-3-1-2-micronuc-men-5-rpt-03420reva-report.pdf); PMTA Section 3.1.2 Report 03445REVA (Menthol 3%) (n-3-1-2-micronuc-men-3-rpt-03445reva-report.pdf); Comparators: PMTA Section 3.1.2 Report 03588REVA (Comparator - Vuse Alto Menthol 5%) (n-3-1-2-[redacted]-mn-rpt-03588reva-report.pdf); PMTA Section 3.1.2 (n-3-1-2-[redacted]-mn-rpt-03594reva-report.pdf); PMTA Section 3.1.2 Report RPT-04735REVA (Comparator – NJOY Ace Mint 5%)(n-3-1-2-[redacted]-mn-rpt-04735reva-report); PMTA Section 3.1.2 PT-00931496 3R4F In Vitro Micronucleus Assay in TK6 Cells (n-3-1-2-[redacted]-rpt-00931496-3r4f-mn-report.pdf); PMTA Section 3.1.2 Report 04730REVA (Comparator - NJOY Ace Classic Tobacco 5%) (n-3-1-2-micronuc-com-04730reva-report.pdf); PMTA Section 3.1.2 Report 03583REVA (Comparator - Vuse Alto Original Tobacco 5%) (n-3-1-2-micronuc-comp-rept-03583reva-report.pdf); PMTA Section 3.2.1 Report 04715REVA (Comparator - Blu PlusClassic Tobacco 2.4% (n-3-1-2-mn-blu-plus-classic-tobacco-report.pdf); PMTA Section Report 04720REVA (Comparator - Blu Plus+Menthol 2.4%) (n-3-1-2-mn-blu-plus-menthol-report.pdf)

test. All test article concentrations should be comparable to the historical control range of the vehicle control. 4.4. Criteria for an Equivocal Response Cases which do not clearly fit into the positive or negative criteria may be judged equivocal. In these cases the Study Director, based on sound scientific judgment, may take additional factors into consideration in evaluating the test results.
OECD TG 487, concerning the number of cells to be scored: Page 11, under Analysis (paragraph 45): "In cell lines tested without cytoB treatment, micronuclei should be scored in at least 2000 cells per test concentration and control, equally divided among the replicates, if replicates are used. " pg. 14, under Evaluation and interpretation of results (paragraph 60): "In case the response is neither clearly negative or clearly positive as described above and/or in order to assist in establishing the biological relevance of a result, the data should be evaluated by expert judgement and/or further investigations. Scoring additional cells (where appropriate) or performing a repeat experiment possibly using modified experimental conditions (e.g. concentration spacing, other metabolic activation conditions [i.e. S9 concentration or S9 origin]) could be useful."

Source: Deficiency Response 19, Table 1, p. 155

II. ADDITIONAL INFORMATION ON CELL COUNTING AND THE RATIONALE PROVIDED IN JLI'S DEFICIENCY RESPONSE 19

As discussed in Section IV.2.i of the 10.75 request, JLI agrees with CTP-OS's assessment that the results from the in vitro MN studies for JUUL products with 2,000 cells can be considered "valid assay results".[3] JLI provides additional information, as previously provided to CTP-OS in its Deficiency Response, on its approach for increasing cell counts for certain JUUL products.

Based on OECD TG 487 Guidelines, three sample concentrations were selected for the MN evaluation based on level of cytotoxicity. The JUUL products were initially evaluated using the scoring of 2,000 cells per concentration. OECD TG 487 recommends counting at least 2,000 cells per concentration and states that "in order to assist in establishing the biological relevance of a result", "scoring additional cells… could be useful."[4] As explained by JLI in Deficiency Response 19, the number of cells scored for some JUUL products was increased from 2,000 cells to 4,000 cells per concentration for some test articles, in order to further establish biological relevance for results of potential concern.

[3] FDA TPL Review of JLI's PMTAs (Toxicology), p. 6.

[4] Organisation for Economic Co-operation and Development. OECD Guideline for Testing Chemicals Test Guideline. TG487: In vitro Mammalian Cell Micronucleus Test. 2016.

Specifically, JLI chose additional cell counting as the mechanism for further evaluation, which provided greater statistical power but did not introduce a systematic bias, as the initial 2,000 and additional 2,000 cell samples were drawn from the same experiment. Additionally, scoring 4,000 cells instead of 2,000 cells may provide greater statistical power to distinguish between a weak positive response and potentially false positive results.[5] Therefore, after concluding the JUUL product studies, JLI decided to evaluate all comparator products based on scoring 4,000 cells per concentration.

The counting of an additional 2,000 cells applied to two out of the twenty-four JUUL System aerosol test conditions and four out of the twelve JUUL System e-liquid test conditions:

- Virginia Tobacco 5.0% e-liquid induced positive results after 4-hour exposure with and without metabolic activation. Results were negative when evaluating 4,000 cells.

- Virginia Tobacco 3.0% aerosol condensate induced a positive (ISO 20768 puffing regimen) and equivocal (JUUL-specific intense puffing regimen) result after 4-hour exposure with metabolic activation. Results were both equivocal when evaluating 4,000 cells.

- Menthol 5.0% e-liquid induced a positive result after 4-hour exposure with and without metabolic activation. Results remained positive when evaluating 4,000 cells.

With additional cell counting, three of the six in vitro MN assay results did not change. One initially positive result was determined to be equivocal when an additional 2,000 cells were evaluated. These results led to further investigation in vivo.

Only in the case of one product, Virginia Tobacco 5.0% e-liquid, did the results go from positive at 2,000 cells to negative at 4,000 cells. The responses from both the 2,000 and combined 4,000 cell count evaluations was similar over the tested concentrations (i.e., %MN varying mostly within the historical control range). This, in addition to the negative results obtained with the 4000-cell count, which would provide greater statistical power, suggested that the minimal increases detected in the initial positive result based on the 2,000-cell count (although statistically significant relative to the concurrent control), were likely within the overall variability of the assay and thus not likely biologically meaningful.[6]

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[5] Thybaud V, Lorge E, Levy DD, van Benthem J, Douglas GR, Marchetti F, Moore MM, Schoeny R. Main issues addressed in the 2014-2015 revisions to the OECD Genetic Toxicology Test Guidelines. Environ Mol Mutagen. 2017 Jun;58(5):284-295. (Deficiency Response Appendix 19.1).

[6] JLI Deficiency Response 19, p. 161-162.

Overall, the MN studies were conducted in accordance with the OECD TG487 guidelines, and JLI maintained that the differences in the number of cells scored did not impact the scientific validity of the assay and the ability to correctly identify genotoxic versus non-genotoxic test articles.

A summary of outcomes and justifications for additional cell counting is provided below in Table 2.

Table 2 Summary of in vitro MN testing outcomes and justification for increased cell scoring and follow-up

Product	Test Materials	Testing condition	Initial Results (2,000 cells) & Justification for Increased Cell Scoring	Results after Increased Cell Scoring (4,000 cells)	Results for *in vivo*
PM0000874 (Virginia Tobacco 3.0%)	Condensate	4 hr + S9 (non-intense)	**Positive** (3/3 conditions met) • Increases not linear (decreasing at the middle dose); • MN% of the vehicle control was low near the historical control range; and • MN% of the high dose only slightly exceeding the upper limit of the historical control range	**Equivocal** (2/3 conditions met) • Increases statistically significant over control; dose-dependent trend); but • All observed MN% within the historical negative control range	**Negative** In vivo inhalation (MN and Comet)
		4 hr + S9 (intense)	**Equivocal** (2/3 conditions met) • Increase over the vehicle control, dose-response trend); but • Vehicle control within the historical control range	**Equivocal** (2/3 conditions met; same as in the initial outcomes)	
PM0000876 (Virginia Tobacco 5.0%)	E-Liquid	4 hr - S9	**Positive** (3/3 conditions met) • Increases not linear (decreasing at the middle dose); and • %MN of only the high dose slightly exceeding the upper limit of the historical control range	**Negative** • No doses were significantly higher than the control; • No trend; and • All within the historical control range)	Not Tested[7]

[7] No in vivo study was conducted for Virginia Tobacco 5.0%. However, because acute nicotine toxicity is the limiting factor for the in vivo inhalation studies conducted at the maximum tolerated dose, a higher exposure concentration can be achieved using the Virginia Tobacco 3.0% (because of the lower nicotine dose). Virginia Tobacco 3.0% and Virginia Tobacco 5.0% contain the same flavor ingredients and at such levels that all exposures would be lower with a Virginia Tobacco 5.0% test product due to the difference in nicotine levels — i.e., the in vivo study using Virginia Tobacco 3.0% exposed animals to a higher chemical load for each ingredient than a Virginia Tobacco 5.0% would and thus provides a "worst case" baseline.

		4 hr + S9	**Equivocal** (2/3 conditions met) • Increase over vehicle control (only the middle dose slightly above the historical control range); but • No significant trend	**Negative** • No doses were significantly higher than the control; • No trend; and • All within the historical control range	
PM0000872 (Menthol 5.0%)	E-Liquid	4 hr - S9	**Positive** (3/3 conditions met) • %MN of only the high dose slightly exceeding the upper limit of the historical control range	**Positive** (3/3 conditions met, same as in the initial outcomes)	**Negative** In vivo inhalation (MN and Comet)
		4 hr + S9	**Positive** (3/3 conditions met) • %MN of only the high dose exceeding the upper limit of the historical control range, with significant cytotoxicity (60%)	**Positive** (3/3 conditions met, same as in the initial outcomes, including cytotoxicity)	

Source: Deficiency Response 19, table 1, p. 156-157

III. ADDITIONAL INFORMATION ON THE VARIABILITY OF THE IN VIVO COMET ASSAY

For Deficiency 3, the MDO stated that "the results were highly variable and may not reliably indicate the occurrence of DNA damage" in the in vivo genotoxicity studies.[8] This finding, among others, prevented CTP-OS from performing a full toxicological evaluation of JUUL products and relative to comparator products.[9] The variability of the study results was not raised in the Deficiency Letter.[10]

As noted by CTP-OS, variability is typical for in vivo DNA damage/Comet assays.[11] The variability observed in the studies provided by JLI are not unusual and are within the range to support a valid statistical analysis.[12] Thus, the observed levels of variability are

[8] FDA Marketing Denial Order for JLI's PMTAs, p. 9.

[9] *Id.*

[10] FDA Deficiency Letter to JLI for PMTAs.

[11] FDA TPL Review of JLI's PMTAs (Toxicology), p. 26.

[12] *See* PMTA Section N.3.2 Technical Summary (n-3-2-in-vivo-technical-summary.pdf).

not a "deficiency" and did not prevent CTP-OS from drawing meaningful toxicological conclusions from the study results. Questioning the variability of the results for the in vivo Comet assay was raised for the first time in the MDO.

Appendix 3

I. ADDITIONAL INFORMATION ON THE IN VITRO BACTERIAL REVERSE MUTATION ASSAY PROTOCOL AND RESULTS

A summary of relevant information from the Deficiency Letter, Deficiency Response, the 1st and 2nd Cycle Toxicology Reviews, and the MDO and TPL highlights where CTP-OS deviated from the study protocol and OECD guideline by applying the wrong testing criteria to reach the incorrect conclusion that Menthol 5.0% is mutagenic.

In Question 18 of the Deficiency Letter, CTP-OS found that:

> Data from the in vitro bacterial reverse mutation assay . . . show that the aerosol condensate generated from the proposed new product using standard puffing parameters, induced a significant mutagenic response, without liver S9 fraction, using Salmonella typhimurium strain TA98. According to your study guidelines, a three-fold increase in TA98 revertants are to be seen in at least two or more successive concentrations, or the response should be repeatable at a single concentration. The data submitted in this study met your criteria for a positive result.[1]

But the data submitted from this study did not meet the "criteria for a positive result"[2] based on the study protocol as informed by the OECD guideline. In its Deficiency Response, JLI noted that it "respectfully disagreed" with CTP-OS's conclusion and then re-analyzed and re-justified the study's initial findings and conclusion:

> The data in the Ames assay report for Menthol 5.0%,[] corresponding to the conditions specified by FDA in Question 18 ("aerosol condensate generated from the proposed new product using standard puffing parameters . . . without liver S9 fraction, using Salmonella typhimurium strain TA98"), shows that the mean (+/- SD) revertant counts/plate for the triplicate vehicle control cultures was 25 (+/- 3). The highest observed mean (+/- SD) revertant counts/plate in the treated cultures was 50 (+/- 12) observed at a concentration of 3.13 µL/plate. This represents only a 2-fold increase in the number of mean revertant counts/plate while the positive criteria for TA98 strain is an increase of at least 3-fold over the vehicle control background frequency. Therefore, the Menthol 5.0% aerosol condensate was not found positive for mutagenicity in strain TA98 in these treatment conditions, at any of the tested concentrations.[3]

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[1] FDA Deficiency Letter to JLI, p. 9.

[2] *Id.*

[3] JLI Deficiency Response to Question 18, p. 147.

Nonetheless, the MDO still found that Menthol 5.0% "induced a significant mutagenic response when compared to the *historical vehicle control group*."[4] Based on the criteria for the Ames assay in the study protocol, in accordance with OECD TG 471, the vehicle control is the proper comparison for the assay, while the historical control is important in assessing assay acceptance criteria.

The 1st and 2nd Cycle Toxicology Reviews are instructive on the apparent confusion. In the 1st Cycle Toxicology Review, there is no reference to a "vehicle control" as part of the testing criteria to assess a mutagenic response. Rather, in paraphrasing the study guidelines, CTP-OS references "vehicle background frequency" — omitting the operative word "control". Table 1 below compares how the study protocol for testing criteria were represented in the 1st Cycle Toxicology Review with the actual language in the study protocol.

Table 1 Comparison of the Testing Criteria as Referenced in the 1st Cycle Toxicology Review Versus as Stated in the Study Protocol

1st Cycle Toxicology Review	Study Protocol
"The increases in revertants should be at least two times the vehicle background frequency for strains with high spontaneous reversion levels (i.e., TA100 and TA 102) and at least three times for strains with low spontaneous reversion levels (i.e., TA98, TA1535, TA1537)."[5]	"The increases should be at least two times the vehicle *control* background frequency for strains with high spontaneous levels (i.e., TA 100 and TA 102) and three times for those with low spontaneous levels (TA 1537, TA98, and TA1535)."[6]

It is reasonable to infer that CTP-OS interpreted "vehicle background frequency" — in its paraphrasing of the testing criteria — to mean historical control data. From there, CTP-OS did exactly that by comparing the test-article data against the historical control data to assess a positive or negative mutagenic response for Menthol 5.0%. Specifically, the 1st Cycle Toxicology Review found that:

> Based on the applicant-provided data, the *historical control data* for strain TA98 in the bacterial reverse mutation assay is a mean of 15 revertants. The data from PM0000872 at 3.13 µL/plate and 6.25 µL/plate indicate 3.3-fold and 3.2-fold increase in revertants, respectively. While this is an unexpected result,

[4] FDA Marketing Denial Order for JLI's PMTAs, p. 11 (emphasis added).

[5] FDA 1st Toxicology Review of JLI's PMTAs, p. 12.

[6] N.3.1.1 Report 03408REVA (Menthol 5%), Section, 10.3 [n-3-1-1-ames-men-5-rpt-03408reva-report.pdf] (emphasis added).

> it meets the criteria for a positive mutagenic response, as specified by the applicant (n-3-1-1-ames-men-5-rpt-03408reva-report.pdf; pg. 14).[7]

Presumably this prompted Deficiency Letter Question 18 discussed above. After receiving JLI's Deficiency Response, CTP-OS acknowledged the vehicle control data in the Ames assay for the first time in the 2nd Cycle Toxicology Review.[8] But there, unlike in the 1st Cycle Toxicology Review and Deficiency Letter, and for the first time without any notice to JLI, CTP-OS seemed to take issue with the potential variability in the vehicle control data compared to the historical control data:

> Because the submitted result for the vehicle concurrent control is nearly two standard deviations larger than the corresponding historical control (i.e., 25 (3) vs. 15 (6)), this indicates that the applicant-provided data for the vehicle control group (i.e., 25 (3)) may not be representative of historical data (i.e., 15 (6)); therefore comparison to this control group should be made with caution.[9]

There was no additional analysis of the vehicle control data. Instead, the 2nd Cycle Toxicology Review went on to conclude that Menthol 5.0% induced a mutagenic response based on the historical control data: "PM0000872 induced a significant mutagenic response compared to a *historical vehicle control group* in the in vitro bacterial reverse mutation assay (Ames assay)."[10]

This conclusion was incorporated into the MDO. There was no explanation or justification as to why the criteria in the study protocol and OECD guideline were not followed in assessing the mutagenic potential (or lack thereof) of Menthol 5.0%.

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[7] FDA 1st Toxicology Review of JLI's PMTAs, p. 13 (emphasis added).

[8] FDA Cycle 2 Toxicology Review of JLI's PMTAs, p. 11. In the 2nd Cycle Toxicology Review, CTP-OS appears to refer to the vehicle-control data as the "vehicle concurrent control" and the historical-control data as the "historical vehicle control."

[9] *Id.*

[10] *Id.* at 28 (emphasis added).