U.S. Food & Drug Administration
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June 23, 2022

DENIAL

Juul Labs Inc.
Attention: Angela Ho-Chen, Director, Regulatory Affairs
1000 F Street NW, Suite 800
Washington, D.C. 20004

FDA Submission Tracking Numbers (STNs): Multiple STNs, see Appendix A

Dear Angela Ho-Chen:

We completed substantive scientific review of your PMTAs[1] and are denying issuance of marketing granted orders for the tobacco products identified in Appendix A. Refer to Appendix B for a list of amendments received in support of your applications.

Based on our review of your PMTAs, we determined that the applications for the new tobacco products, as described in your applications and specified in Appendix A, lack sufficient evidence to demonstrate that permitting the marketing of the products subject to these applications is appropriate for the protection of the public health (APPH). You cannot introduce or deliver for introduction these products into interstate commerce in the United States. Doing so is a prohibited act under section 301(a) of the FD&C Act, the violation of which could result in enforcement action by FDA.

Section 910 of the FD&C Act provides that FDA "shall deny an application" for a product to receive a PMTA marketing authorization if, "upon the basis of the information submitted to the Secretary as part of the application and any other information before the Secretary with respect to such tobacco product," FDA finds that "there is a lack of a showing that permitting such tobacco product to be marketed would be appropriate for the protection of the public health." Section 910(c)(2)(A). In assessing APPH, the statute requires FDA to consider the risks and benefits to the population as a whole, including both tobacco users and nonusers, and taking into account the increased or decreased likelihood that existing users of tobacco products will stop using such products and the increased or decreased likelihood that those who do not use tobacco products will start using such products. Section 910(c)(4).

As the statutory text makes clear, it is the applicant's burden to make a "showing"—with sufficient supporting information—that permitting the marketing of a new tobacco product would have a net benefit to public health based upon the risks and benefits to the population as a whole. Before determining that permitting the marketing of a new tobacco product would result in a net benefit to public health, FDA must weigh all potential public health benefits against all potential public health harms—including but not limited to the likelihood that the product will affect patterns of initiation and cessation of tobacco use. Concluding that there is a net benefit takes into account whether the

[1] Premarket Tobacco Product Applications (PMTAs) submitted under section 910 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

applicant has provided sufficient information regarding product design, chemistry, stability, manufacturing controls including process controls and quality assurance procedures, toxicology, abuse liability, and other factors that can affect the product's risks to individual users and nonusers, including relative to those of other tobacco products. In June 2019, we issued a Guidance for Industry, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems. Although not binding on FDA or the public, and an applicant can use an alternative approach if it satisfies the applicable legal requirements, the guidance gave FDA's current thinking on these applications. The guidance recommended "providing a full assessment of the toxicological and pharmacological profile associated with the new tobacco product." Guidance at 34. It noted the importance of providing, among other things: "[t]oxicological endpoints such as cytotoxicity, genotoxicity, carcinogenicity, and respiratory, cardiac, reproductive, and developmental toxicity"; "[i]nformation concerning substances that may be solvent extractable from the container closure system or leachable into the e-liquid when the e-liquid is in contact with the container closure system (e.g., information on whether toxic substances present in the container closure system can potentially transfer into the e-liquid or aerosol)"; "a conclusion as to whether there is a toxicological concern with respect to the ingredients, constituents… that will be delivered in the aerosol from the use." Guidance at 35. It noted that "where a thorough literature review does not address these points, these topics may need to be addressed in separate studies conducted by the applicant." Guidance at 35. Finally, the guidance recommended providing "an integrated summary discussing how permitting the marketing of the new tobacco product would be APPH from a toxicology perspective relative to any similar comparator tobacco products." Guidance at 37.

Without sufficient evidence of a product's toxicity risks, including in relation to the risks posed by other tobacco products, FDA cannot conduct a full evaluation of the overall risks and benefits of a new tobacco product. For example, FDA cannot adequately evaluate whether and to what extent relevant tobacco use behaviors would represent a public health benefit or a public health harm. Switching from one tobacco product to another tobacco product is not inherently beneficial or harmful. To illustrate, if a new tobacco product presents a greater level of risk than combustible cigarettes, switching from combustible cigarettes to the new product would represent a health harm to those who switch, not a health benefit. Only if FDA is able to conclude that a new tobacco product presents lower risk than combustible cigarettes can FDA consider that switching from combustible cigarettes to the new tobacco product represents a health benefit to those who switch.

In addition, FDA considers the risks of the new tobacco product in relation to other similar tobacco products (e.g., products in the same product category). For example, if an ENDS product poses lower risk than combustible cigarettes, but higher risk than other ENDS, the potential public health benefit from cigarette smokers switching could be offset by increased harm to users who choose the new tobacco product over less harmful ENDS products. These kinds of analyses, among other related considerations, would inform FDA's determination as to whether marketing of the product would have a net benefit to public health based upon the risks and benefits to the population as a whole. Other considerations could include how the product is actually used (e.g., nonuser initiation, dual use) and effects on nonusers (e.g., accidental or secondhand exposure).

As described in more detail in the deficiencies below, we found that you did not provide sufficient information for FDA to assess the toxicological risks posed by the new products, and the information that you provided raised concerns. Among other deficiencies, the evidence you provided was internally inconsistent; lacked key information; relied in significant part on methodological choices that, without adequate justification, ignored crucial indications of toxicity; and used a different methodology to assess the toxicity of the new products than it did for comparison products in key respects. As a result, FDA was

unable to make any meaningful determinations regarding the risks of the new products relative to their benefits and compared to the risks of other tobacco products, including combustible cigarettes and other ENDS, which is necessary for FDA to make a determination as to likely net public health impact. Without such information, FDA is not able to adequately evaluate whether and to what extent relevant tobacco use behaviors (e.g., initiation with the new products, switching from combustible cigarettes to the new products, switching from other ENDS products, dual use of the new products with other tobacco products) would represent a public health benefit or a public health harm. Without the ability to make any meaningful determinations regarding the toxicological risks presented by the new products, the public health impact of the initiation, switching, and cessation data in the applications cannot be evaluated under the APPH standard, regardless of what those data otherwise show. In light of these uncertainties, it is possible that marketing of the new products would have a neutral impact, result in net public health benefit, or result in net public health harm. 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).

In light of the unaddressed deficiencies regarding potential toxicological risks and in the interest of issuing a decision without the additional delay that further analysis would have required, FDA did not assess whether there might be additional deficiencies relating to initiation, switching, and cessation.

We provide the following bases for our determination:

1. **Identity of leachable constituents produced by the Juul System (PM0000864, PM0000872, PM0000874, PM0000876, PM0000878, PM0000879); mainstream aerosol yields of these leachable constituents in the Juul System; issues in the risk assessment provided to assess toxicity of these leachable constituents in the mainstream aerosol yield of the Juul System**

   You have not provided proper identification of leachable constituents (leachables) in the new products nor have you provided mainstream aerosol yield data for these leachables generated by the new products (PM0000864, PM0000872, PM0000874, and PM0000876) when used with PM0000878 and/or PM0000879. As a result, FDA cannot perform an accurate and complete risk assessment of the new products.

   In your original submission for these PMTAs, you submitted a toxicological evaluation of identified leachables from your new products PM0000864, PM0000872, PM0000874, PM0000876 when used with PM0000878 and/or PM0000879. The devices (PM0000878 and PM0000879) are responsible for aerosolizing and delivering the e-liquid to the user. HPHCs and mutagenic and genotoxic constituents from the JUULpods can be transferred into the mainstream aerosol via the devices. The device functional parameters (i.e., coil temperature, power delivery and maximum puff duration) control and mediate the transfer of these genotoxic leachables into the mainstream aerosol. In this toxicological evaluation, you identified the presence of two genotoxic leachables found to produce an excess cancer risk outside of generally accepted margins of "tolerable cancer risks." These leachables were identified by you as Ethyl-4-hydroxyquinoline-3-carboxylate (EHQC) and Propylpyridine,1H-pyrrole-1-hexanoic acid,2,5-dihydro-2,5-dioxo-related compound) (PHDC). Further, you declined to provide testing results of these leachables in the mainstream aerosol generated under intense and non-intense use of your new tobacco products. Nor did you provide a comparison with similar testing for

suitable comparison products.

In response to FDA's Deficiency letter, you revised the identity of the leachable EHQC to 1,8,9-trihydro-2-(3-carboxypropylamine-N-yl)-3-ethylcarboxylate-4-quinolone (TCEQ) and revised the identity of the leachable PHDC to Nornicotine, N-carboxyglycerol-5'-(methoxy-1-(p-hydroxybenzene-O4-yl-acetic acid)) (NNMA). The information you provided to support these revised identifications (revised chemical structures, chemical formulas and mass spectral data) is incompatible with chemical analysis and mass spectral data you previously submitted regarding the identification of these leachables. Additionally, information you provided elsewhere in the response to FDA's Deficiency letter identifies the revised leachable TCEQ as a different chemical, (4-((3-(ethoxycarbonyl)-4-oxo-1,4,6,7-tetrahydroquinolin-2-yl)amino)butanoic acid) (ETBA) (app-17-03-n-3-3-whole-pod-leach-tra-report.pdf; pages 105 and 306). This conflicting data further undermines your revised identification of EHQC as TCEQ. You continued to decline to provide testing results of these leachables in the mainstream aerosol.

In addition, in response to the Deficiency letter, you provided a new risk assessment indicating that these revised leachables are not present at levels of toxicological concern. However, there are two overarching concerns with this submitted risk assessment. First, because you have not established the identity of these revised leachables, the risk assessment that you submitted evaluating these leachables cannot be used to determine the toxicity of the new products. Second, we find significant methodological issues that preclude our consideration of your findings. The risk assessment you provided uses a less conservative approach (Carthew et al., 2009[2]) than what was used in the original risk assessment, (Escher et al., 2010[3].) When the original, more conservative, approach was used, these leachables were found to be present at a level of toxicological concern. In your original risk assessment, you stated that the more conservative risk assessment approach used in Escher et al., 2010 "would appear to be more representative for the extractables and leachables risk assessment" as this risk assessment evaluated industrial chemicals, whereas the risk assessment approach used in Carthew et al., 2009 is based on an evaluation of consumer products ingredients. We agree that the dataset used to develop the Escher et al., 2010 risk assessment approach included industrial chemicals that are likely more representative of the types and classes of chemicals encountered in an assessment of leachables akin to those present in the aerosol yield of the JUUL System. The risk assessment approach used in Carthew et al., 2009 is based on an evaluation of consumer products ingredients, which consists of chemicals intentionally added to products. As the leachable chemicals "leach" from the components of the JUULpods and are not added intentionally to the products as ingredients, the Escher et al., 2010 method is more appropriate than the Carthew et al., 2009 method which is geared towards the risk assessment of added ingredients. Because the Carthew et al., 2009 method specifically focuses on ingredients, it does not have the specificity needed to evaluate the types of leachable chemicals typically studied in a leachables assessment (for example, polymers and heavy metals). Additionally, the dataset used to derive the Carthew et al. 2009 approach and evaluate subsequent health risks does not include chemicals relevant to the assessment of leachables; it specifically excludes genotoxic carcinogens, in vivo mutagens, heavy metals and polymers from the risk assessment, "as they

[2] Carthew P, Clapp C, Gutsell S. Exposure based waiving: The application of the toxicological threshold of concern (TTC) to inhalation exposure for aerosol ingredients in consumer products. Food and Chemical Toxicology. 2009;47:1287-1295.
[3] Escher SE, Tluczkiewicz I, Batke M, et al. Evaluation of inhalation TTC values with the database RepDose. Regulatory Toxicology and Pharmacology. 2010;58:259-274.

were not considered representative of the ingredients that are, or could be used, in aerosols for consumer use." You demonstrated in the provided mainstream aerosol HPHC yield data for the new products that the aerosol generated using PM0000864, PM0000872, PM0000874, and PM0000876 with PM0000878 contains genotoxic constituents, in vivo mutagens and heavy metals. Therefore, Carthew et al., 2009's less conservative approach used in your revised risk assessment of these leachables is inappropriate for evaluation of the new products, as this approach does not accurately model the potential health risks associated with use of the new products.

You have not explained why the less conservative approach used in Carthew et al., 2009 is appropriate to perform a risk assessment of these revised leachables. Additionally, you did not provide an explanation for why the revised risk assessment was limited to assessing systemic toxicity and did not include local toxic effects, which have a lower threshold for occurrence. Overall, your additional risk assessment has not adequately addressed the toxicology concerns regarding these leachable constituents, and you did not provide an explanation for using a less conservative approach than the approach used in your initial risk assessment.

In order for FDA to perform a full toxicological evaluation of these leachable constituents, the correct identity of these leachables needs to be determined. Accordingly, you needed to have:

a) Provided consistent and non-conflicting information to support your identification of these leachable constituents. These data are needed to ensure that an accurate toxicological risk assessment is performed.
b) Provided a toxicological risk assessment of these identified leachable constituents that used an appropriate methodology consistent with your original approach. This is needed to ensure the health risks associated with use of the new products are accurately evaluated using a reasonably conservative risk assessment methodology.
c) Provided testing results of these two leachable constituents in the mainstream aerosol generated from appropriately aged new JUULpod products (PM0000864, PM0000872, PM0000874, and PM0000876) with the new JUUL devices (PM0000878 or PM0000879) under intense and non-intense use conditions, and a comparison with similar testing for suitable comparison products. These aged JUULpod products should undergo 1) accelerated aging for 22 weeks at 30°C and relative humidity of 65%, equivalent to 9 months ambient conditions and 2) accelerated aging for 22 weeks at 40°C and relative humidity of 75%, equivalent to 18 months ambient conditions. For example, the new products used to generate the aerosol should have been prepared in the same manner (i.e., the same parameters to simulate shelf aging) as previously done to evaluate leachable constituents. These data are needed to assess the toxicological risks associated with the presence of these leachable constituents in the mainstream aerosol generated from the new product and enable FDA to determine relevant health risks to consumers of the new products.

2. Methodological issues impacting scientific validity of results provided from your in vitro micronucleus assay genotoxicity study comparing the genotoxic potential of the new products to other tobacco products

You submitted in vitro toxicological studies to assess the genotoxic potential for the new products (PM0000864, PM0000872, PM0000874, PM0000876, PM0000878 and PM0000879) in comparison to other tobacco products. These in vitro studies utilized both the e-liquids and

aerosol condensates. However, the methodology you 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 unjustified deviations from the guidelines that you selected in order to conduct the in vitro micronucleus assay. Specifically there was: (a) uneven application of acceptance criteria (including inconsistent cell counting) for the scoring and evaluation of positive and negative genotoxic responses and (b) use of different methodologies to evaluate the new products and the comparison products.

The devices (PM0000878 and PM0000879) are responsible for aerosolizing and delivering the e-liquid to the user. HPHCs, mutagenic and genotoxic constituents within the e-liquid can be transferred into the aerosol via the device. The device functional parameters mediate and control the delivery of these toxic constituents to the user and are a critical factor in assessing user exposure to genotoxic constituents. This means that the inability to perform a full and accurate toxicological evaluation of the new product e-liquids (PM0000864, PM0000872, PM0000874 and PM0000876) precludes the completion of a full and accurate toxicological evaluation of the JUUL devices (PM0000878 and PM0000879) as these devices play a critical role in the production and delivery of genotoxic constituents to the product user.

(a) Uneven application of acceptance criteria (including inconsistent cell counting) for the scoring and evaluation of positive and negative genotoxic responses for the new products

In your study protocol, you stated that the in vitro micronucleus assay was performed according to Organization for Economic Cooperation and Development (OECD) guidelines as described in OECD Test Guideline 487 (TG 487) for the in vitro micronucleus assay. TG 487 describes the purpose and principles of the assay, the methodology used to conduct the in vitro micronucleus assay, acceptability criteria for the acceptance of assay results, and criteria for the evaluation and interpretation of assay results. The acceptability criteria in TG 487 sets standards needed for accepting the results of the assay. Within the acceptance criteria in TG 487, there is no requirement to verify a clearly positive or clearly negative response. You initially evaluated the new products for genotoxic potential using 2000 cells per concentration as required by TG 487, but diverged from this required cell count when there was a positive result for genotoxicity. Specifically, if a new product yielded a negative result, this negative result was accepted as final. However, if a positive result was produced for the new product, the assay result was rejected and the new product was re-evaluated using 4000 cells per concentration. Equivocal responses for the new products were further evaluated by counting an additional 2000 cells “to clarify the response” however, you did not provide a rationale or supporting statistical calculations to demonstrate why counting additional cells, in lieu of conducting a repeat or modified experiment, was appropriate and justified. This inconsistent methodology used to evaluate the genotoxic potential of the new products raises concerns as your select re-evaluation of new products yielding positive genotoxicity results caused assay results to be changed to lower risk categories (i.e., negative or equivocal for genotoxicity).

Furthermore, your inconsistent testing methodology and select application of more rigorous criteria for the evaluation of the new products that were found to be positive for genotoxicity is not supported by TG 487 or by your submitted study protocol. Based on these criteria, the positive genotoxicity responses identified for the new products should have been accepted and not subjected to an additional, more rigorous evaluation. We note that in response to this toxicological concern (raised by FDA in Cycle 1, Deficiency 19 of FDA’s Deficiency letter), you

state that, in specific situations, the number of cells counted and scored for micronuclei formation was increased to establish the biological relevance of the results. However, assessing the biological relevance of the genotoxicity assay results does not require rejecting these valid results and you did not provide a justification or explanation for why these results were rejected. You rejected genotoxicity results for clearly positive responses that you subjectively deemed to be "very weak" or "very small", despite the fact that the responses met all assay acceptance criteria described in TG 487 and your provided study protocol. In lieu of rejecting clearly positive responses for assays conducted in line with the guidelines set out in your study protocol, you could have discussed toxicologically relevant factors (e.g., the presence of detoxification pathways in vivo that are absent within this in vitro model system) that may mitigate the occurrence of toxicity in vivo. However, you did not address such toxicologically relevant factors in your response, or explain how the counting (use) of additional cells and re-evaluation of the assay results is an appropriate method to assess the biological relevance of a positive genotoxicity response. The 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 meaningful toxicological conclusions on the genotoxic potential of the new products from being made.

(b) Use of a different methodology to evaluate the comparison products.

Additionally, the data you provided from the in vitro micronucleus assay shows that the new products were not evaluated using the same methodology as the comparison products. The new products, as described above, were evaluated using 2000 cells, or re-evaluated using 4000 cells if there was a equivocal or positive result. In contrast, all the comparison products were evaluated for genotoxic potential using a single assay at 4000 cells per concentration without appropriate justification. Furthermore, you did not count additional cells or further evaluate equivocal responses reported for the comparator products.

The differences in methodology created situations where there may be meaningful differences in statistical power between the genotoxicity assays. Statistical analysis of the assay results is a key component of evaluating the genotoxic potential of a test article, therefore differences in statistical power can directly affect the ability to correctly identify positive or negative genotoxic test articles. As you state in your response, "[s]coring 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." However, you did not provide statistical power calculations for your study. This information is needed to demonstrate that the increased counting of cells for select groups is appropriate for the statistical analyses being performed and to show that these modifications do not adversely impact the validity of assay. This is necessary information as the affected statistical analysis is a key deciding factor in determining whether or not the product being evaluated is identified as being positive or negative for genotoxicity. However, even if this additional information describing the statistical power of the analysis was provided, significant concerns regarding inconsistencies in the assay methodology and rejection of valid assay results remain. You provided new data in response to Deficiency 19 of FDA's Deficiency Letter to show that the increased counting of cells, from 2000 to 4000 cells per concentration, identified a similar percentage of micronuclei formation, which indicate similar genotoxic responses. This 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. Furthermore, you state that "[s]ince all the [in vitro micronucleus] studies were conducted

consistent with the OECD TG 487 guidelines, the differences in the number of cells scored for some of the test articles and comparison test samples do not impact the scientific validity of the assay and the ability to correctly identify genotoxic versus non-genotoxic test articles." In contrast to what you stated, there is a conflict with the OECD guidelines as OECD only states the minimum standards to evaluate and score a single test article. OECD guidelines emphasize that when multiple cell cultures are evaluated, the same number of cells from each culture must be scored. The methodology used to evaluate the genotoxic potential of a group of test articles needs to be comparable to generate reliable, valid results and is necessary when making relative comparisons of genotoxic potential between test articles. As demonstrated in your submitted data, your assessment of genotoxic potential for the new products varied significantly as additional cells were counted.

For 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. For example, from the data you provided, it is unknown if any of the comparison products would have been positive for genotoxicity at 2000 cells per concentration and unknown if the new products that were found to be negative at 2000 cells per concentration would have produced a positive response at 4000 cells per concentration. You did not provide an adequate scientific justification or explanation for why the differences in methodology for the in vitro genotoxicity evaluation of the new products and the comparison products does not impact the scientific validity of the assay. The inability to adequately compare the in vitro genotoxicity assay results between the new and comparison products prevents a complete and accurate toxicological evaluation of the new products.

In summary, the unequal treatment of test articles is demonstrated in your data by the acceptance of negative genotoxicity responses for the new products without further investigation while positive genotoxicity responses were further evaluated using more rigorous criteria (i.e., rejecting "very weak" or "very small" responses). Additionally, the unequal treatment of new and comparison products within your in vitro genotoxicity assay and your rejection of valid assay results prevents FDA from performing a conclusive toxicological evaluation of the new products.

Accordingly, in order for FDA to evaluate the genotoxicity of the Juul System you needed to have:

a) Specifically, addressed how the differences in assay methodology do not impact the scientific validity of the assay or cause differences in the ability to correctly identify genotoxic versus non-genotoxic test articles, or
b) Provided data comparing the genotoxic potential of the new products and the comparison products using a consistent methodology.

This information is needed to ensure that an accurate and complete toxicological evaluation of the new products can be conducted, that the different cell counting and scoring methodologies you used did not prevent the identification of genotoxic compounds, and that scientifically valid comparisons are made between the new and comparison products.

3. Regarding the Genotoxic Potential of PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) used with the devices PM0000878 and PM0000879:

You submitted data from the in vitro micronucleus assay (n-3-1-2-micronuc-men-5-rpt-03420reva-report.pdf, n-3-1-2-micronuc-vt-3-rpt-03425reva.report.pdf, n-3-1-2-micronuc-vt-5-rpt-03399reva-report.pdf) to demonstrate that PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) do not induce genotoxic responses, and that PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) are relatively less genotoxic than a combustible cigarette comparison product. However, 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. You did not provide an adequate rationale or justification to address why these initial genotoxicity assay results from valid assays were rejected. The 3R4F combustible cigarette comparison product was found to be equivocal for genotoxicity. These results indicate that PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) with PM0000878 and PM0000879 may be relatively more genotoxic than the combustible cigarette comparison product.

In an attempt to address this positive genotoxicity result for PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%), you provided data from an in vivo genotoxicity study. You did not provide additional information or in vivo study data to further evaluate the genotoxicity of PM0000876 (Virginia Tobacco 5%). The in vivo study evaluated the potential for PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) to induce DNA damage in vivo, assessed using the Comet assay, and to induce genotoxicity in vivo, assessed using the micronucleus assay. The data you provided in the DNA damage/Comet assay indicated that PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) had negative responses for both induction of DNA damage and genotoxicity in vivo. However, the results were highly variable and may not reliably indicate the occurrence of DNA damage.[418] Additionally, the in vivo study did not include a combustible cigarette comparison product; therefore, no comparisons of genotoxic potential between PM0000872 (Menthol 5%) or PM0000874 (Virginia Tobacco 3%) and a combustible cigarette can be made using your provided in vivo data. The inclusion of a combustible cigarette comparison product within the in vivo genotoxicity study is needed to perform a complete toxicological evaluation of PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%), as your in vitro genotoxicity study indicated PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) with PM0000878 and PM0000879 may be more genotoxic than the 3R4F combustible cigarette comparison product. The relative genotoxicity of PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) with PM0000878 and PM0000879 versus a combustible cigarette comparison product needs to be conclusively addressed in order to perform a complete toxicological evaluation of PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%).

It 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

[18] While relatively large standard deviations are commonly observed in the DNA damage/Comet assays, the high variability of the data can compromise the statistical analysis and can limit the conclusions that can be drawn (Langie et al., 2015).

genotoxicity results should be considered biologically insignificant or irrelevant. Differences in the design and execution of in vitro and in vivo studies can cause changes in the concentrations of HPHCs and other health hazardous constituents within the test system (i.e., cell culture or animal model), which will affect dose-response relationships, tissue level exposure to hazardous constituents, toxicokinetics and toxicodynamics. Differences in the biological system used to evaluate genotoxicity in vitro and in vivo (i.e. availability of detoxification pathways, occurrence of bioactivation, contributions of gender and/or species-specific effects) may also contribute to producing conflicting results between in vitro and in vivo studies. You did not provide a justification or explanation addressing these toxicologically relevant factors and how they pertain to the conflicting genotoxicity results of PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) with PM0000878 and PM0000879 in your additional information. A comparison of the in vitro and in vivo studies using additional information or bridging data from scientific literature is needed to put the positive in vitro genotoxicity result for PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) with PM0000878 and PM0000879 in the context of the in vivo biological system.

Therefore, you needed to have:

a) Provided 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,
b) Provided scientific data and a rationale to address the conflicting genotoxicity results for PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) from the in vitro and in vivo genotoxicity study data you provided. These data can include measurements of HPHCs and other chemical constituents from PM0000872 (Menthol 5%) and PM0000874 (Virginia Tobacco 3%) with PM0000878 and the 3R4F combustible cigarette comparison product to compare the cell and tissue levels of potentially hazardous constituents between the positive in vitro and negative in vivo genotoxicity studies, an assessment of relevant pharmacokinetic/toxicokinetic parameters, detoxification mechanisms, metabolic and bioactivation pathways, and/or an evaluation of dose-response relationships for relevant HPHCs and other health hazardous constituents that may be present within the in vitro and in vivo genotoxicity assays.
c) Provided scientific data and a rationale to address the positive in vitro genotoxicity score from the initial genotoxicity assay of PM0000876 (Virginia Tobacco 5%) using 2000 cells. This assay met the acceptance criteria listed in your study protocol, however, you rejected the positive genotoxicity result and re-evaluated PM0000876 (Virginia Tobacco 5%). You did not provide an adequate rationale or justification to address why these initial genotoxicity assay results from valid assays were rejected. You also did not provide an explanation as to why this rejection of valid assay results does not adversely impact the scientific validity of the assay.

This additional information is needed to evaluate the biological significance and relevance of the positive in vitro genotoxicity result for PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) with PM0000878 and PM0000879. The devices (PM0000878 and PM0000879) are responsible for aerosolizing and delivering the e-liquid to the user. HPHCs, mutagenic and genotoxic constituents within the e-liquid can be transferred into the aerosol via the device. The device functional parameters mediate and control the delivery of these toxic constituents to the user and are a critical factor in evaluating the genotoxicity of the

new products. This information is also needed to assess the risk of genotoxicity associated with use of PM0000872 (Menthol 5%), PM0000874 (Virginia Tobacco 3%) and PM0000876 (Virginia Tobacco 5%) with PM0000878 and PM0000879, which received positive results for in vitro genotoxicity, relative to the 3R4F combustible cigarette comparison, which received an equivocal result for in vitro genotoxicity and was not included within the in vivo genotoxicity study.

4. **Regarding the Mutagenic Potential of PM0000872 (Menthol 5%) used with the devices PM0000878 and PM0000879:**

   You submitted data from the in vitro bacterial reverse mutation assay (Ames assay; n-3-1-1-ames-men-5-rpt-03408-reva-report) to identify if a test article is able to induce DNA mutations. 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. According 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. Your data submitted indicates that PM0000872 (Menthol 5%) used with the devices PM0000878 and PM0000879 induced a mutagenic response. The devices (PM0000878 and PM0000879) are responsible for aerosolizing and delivering the e-liquid to the user. HPHCs, mutagenic and genotoxic constituents within the e-liquid can be transferred into the aerosol via the device. The device functional parameters mediate and control the delivery of these toxic constituents to the user and are a critical factor in evaluating the mutagenicity and genotoxicity of the new products. Thus, the information set out below is needed to assess the risk of mutagenicity associated with use of PM0000872 (Menthol 5%), used with the devices PM0000878 and PM0000879.

   You also needed to have:

   a) Provided additional data, information or a scientific rationale for PM0000872 as used with the JUUL devices PM0000878 and PM0000879 to demonstrate that these results from the in vitro bacterial reverse mutation assay are not biologically relevant or biologically significant. This could have included data and results from a repeated in vitro bacterial reverse mutation assay, a discussion of the mutations induced within the TA98 strain by test articles and their in vivo relevance, the anticipated mutagenic and detoxification responses that would occur in vivo following exposure to PM0000872 (Menthol 5%) and how the assay results from PM0000872 (Menthol 5%) can be interpreted in relation to suitable comparison products (i.e., combustible cigarettes). This additional information is needed to assess the risk of mutagenicity posed by PM0000872 (Menthol 5%) and will establish the in vivo relevance of this in vitro mutagenicity assay result.

If you choose to submit new applications for these tobacco products, you must fulfill all requirements set forth in section 910(b)(1). To do so, you may cross-reference information submitted in:

- The new tobacco product applications, PM0000864.PD1, PM0000872.PD1, PM0000874.PD1, PM0000876.PD1, PM0000878.PD1 and PM0000879.PD9 subject to this Denial. (see 21 C.F.R. 1114.17)

- A Tobacco Product Master File submission (see 21 CFR 1114.7(b)(2) or 1114.17(c)(2); and guidelines at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/tobacco-product-master-files)

Your new PMTAs should clearly identify the PMTA submission type as a resubmission and include all information necessary to respond to all deficiencies identified in this letter (see 21 CFR 1114.17(d)). Please note, however, that the list of deficiencies identified in this letter is not necessarily exhaustive. We found that the toxicological deficiencies identified above are dispositive of your applications because they preclude a finding that permitting the marketing of your new tobacco products is APPH. Accordingly, FDA has not reached a final agency decision on other aspects of your application, including for example, the potential benefit to adults as compared to the risk to youth posed by your tobacco or menthol products. If you decide to resubmit and cross-reference this PMTA, in addition to evaluating your response to the listed deficiencies, FDA will assess your submission to determine whether it meets the requirements of the FD&C Act and the PMTA rule[5] and whether the application as a whole supports a finding that the marketing of your product(s) is appropriate for the protection of the public health.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal[6,7] using eSubmitter.[8] Alternatively, submissions may be mailed to:

Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The CTP Portal and FDA's Electronic Submission Gateway (ESG) are generally available 24 hours a day, seven days a week; submissions are considered received by DCC on the day of successful upload. Submissions delivered to DCC by courier or physical mail will be considered timely if received during delivery hours on or before the due date[9]; if the due date falls on a weekend or holiday, the delivery must be received on or before the preceding business day. We are unable to accept regulatory submissions by e-mail.

[5] See 86 FR 55300, October 5, 2021.
[6] For more information about CTP Portal, see https://www.fda.gov/tobacco-products/manufacturing/submit-documents-ctp-portal
[7] FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.
[8] For more information about eSubmitter, see https://www.fda.gov/industry/fda-esubmitter
[9] https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/contact-ctp

If you have any questions, please contact Rodney Hammond, MPH, CHES, Regulatory Health Project Manager, at (240) 796 - 4667 or Rodney.Hammond@fda.hhs.gov.

Sincerely,

Digitally signed by Matthew R. Holman -S
Date: 2022.06.23 09:54:44 -04'00'

Matthew R. Holman, Ph.D.
Director
Office of Science
Center for Tobacco Products

Enclosures:

Appendix A – New Tobacco Products Subject to This Letter
Appendix B – Amendments Received for These Applications

Appendix A[10,11]

New Tobacco Products Subject to This Letter

Common Attributes of PMTA	
Date of Submission:	July 29, 2020
Date of Receipt:	July 29, 2020
Product Manufacturer:	JUUL Labs Inc.
Product Category:	ENDS (VAPES)
PM0000864.PD1: JUULpods (Menthol 3.0%)	
Product Sub-Category:	Closed E-Liquid
Package Type:	Cartridge
Package Quantity:	1 Cartridge
Characterizing Flavor:	Menthol
E-liquid volume	0.7 mL
Nicotine concentration:	3.0%
PG/VG ratio:	30/70
Additional property:	Blister Pack
PM0000872.PD1: JUULpods (Menthol 5.0%)	
Product Sub-Category:	Closed E-Liquid
Package Type:	Cartridge
Package Quantity:	1 Cartridge
Characterizing Flavor:	Menthol
E-liquid volume	0.7 mL
Nicotine concentration:	5.0%
PG/VG ratio:	30/70
Additional property:	Blister Pack
PM0000874.PD1: JUULpods (Virginia Tobacco 3.0%)	
Product Sub-Category:	Closed E-Liquid
Package Type:	Cartridge
Package Quantity:	1 Cartridge
Characterizing Flavor:	Tobacco
E-liquid volume	0.7 mL
Nicotine concentration:	3.0%
PG/VG ratio:	30/70
Additional property:	Blister Pack
PM0000876.PD1: JUULpods (Virginia Tobacco 5.0%)	
Product Sub-Category:	Closed E-Liquid
Package Type:	Cartridge
Package Quantity:	1 Cartridge
Characterizing Flavor:	Tobacco
E-liquid volume	0.7 mL
Nicotine concentration:	5.0%
PG/VG ratio:	30/70
Additional property:	Blister Pack

[10] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.

[11] Brand/sub-brand or other commercial name used in commercial distribution.

PM0000878.PD1: JUUL Device	
Product Sub-Category:	Closed E-Cigarette
Package Type:	Box
Package Quantity:	1 ENDS Device
Characterizing Flavor:	None
Length:	[redacted]
Diameter:[12]	N/A
Wattage:	[redacted]
Battery Capacity:	200 mAh
E-liquid volume	0.7 mL
Nicotine concentration:	N/A
PG/VG ratio:	N/A
Additional properties:	Width: [redacted] Depth: [redacted] Color: Slate Universal Serial Bus (USB) Charging Dock
PM0000879.PD9: JUUL Locked Device	
Product Sub-Category:	Closed E-Cigarette
Package Type:	Box
Package Quantity:	1 ENDS Device
Characterizing Flavor:	None
Length:	[redacted]
Diameter:[12]	N/A
Wattage:	[redacted]
Battery Capacity:	256 mAh
E-liquid volume	0.7 mL
Nicotine Concentration:	N/A
PG/VG ratio:	N/A
Additional properties:	Width: [redacted] Depth: [redacted] Color: Slate USB Charging Dock

[12] Applicant provided depth as an alternative for diameter given the product proportions.

Appendix B
Amendments Received for These Applications

Submission Date	Receipt Date	Applications being amended	Reviewed	Brief Description
November 30, 2020	November 30, 2020	All STNs	Yes	Response to November 9, 2020 FDA Information Request
June 22, 2021	June 22, 2021	All STNs	Yes	Response to March 26, 2021 Deficiency Letter