U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

February 2, 2023

REFUSE TO FILE

TBD Liquids, LLC.
Attention: John Fitch, Owner
997 Piner Road
Santa Rosa, CA 95403

FDA Submission Tracking Numbers (STNs): PM0004179.PD1 – PM0004179.PD4

Dear John Fitch:

We completed a preliminary review of your PMTAs[1] and determined that these applications do **not** meet the filing requirements for a new tobacco product seeking a marketing order under section 910(b) of the FD&C Act.[2] As a result, we are refusing to file the applications for the new tobacco products identified in Appendix A, effective the date of this letter.

Your applications lack the following required information necessary for substantive scientific review per section 910(b) of the FD&C Act:

1. An adequate Environmental Assessment (EA) under 21 CFR 25.40 or a claim of a categorical exclusion under 21 CFR 25.35. All your PMTAs do not contain an adequate Environmental Assessment (EA) that addresses the relevant environmental issues. FDA's regulations implementing the National Environmental Policy Act (NEPA) of 1969 (21 CFR 25.15(a)) explain that "[a]ll applications or petitions requesting agency action require the submission of an [environmental assessment] or a claim of categorical exclusion." Granting a PMTA marketing order is not a class of action that has a categorical exclusion in place and, therefore, your application requires an EA. Although you included an EA, it does not address the relevant environmental issues and, therefore, is not adequate. Your EA lacks the environmental impacts of the proposed action, the environmental impacts related to the use of the product, and the environmental impacts related to disposal from use of the product. In future applications, provide this information in your EA for each product.

FDA considers each mixture or combination of ingredients (e.g., products with a 'Custom' nicotine concentration or of differing flavoring, PG, VG strength) to be a new tobacco product. Therefore, each new tobacco product would require its own premarket tobacco product application and would receive a separate marketing authorization decision from the FDA.

Refer to Appendix B for additional information to consider submitting in future submissions. The information provided in this letter may not represent a complete list of comments and potential deficiencies.

[1] Premarket Tobacco Product Applications (PMTAs)
[2] Federal Food, Drug, and Cosmetic Act (FD&C Act)

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.

We encourage you to submit all regulatory correspondence electronically via the CTP Portal[3,4] using eSubmitter.[5] 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[6]; 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.

If you have any questions, please contact Grace Kaiyuan, M.B.A., MT(ASCP), Regulatory Health Project Manager, at (240) 402 - 8240 or Grace.Kaiyuan@fda.hhs.gov.

Sincerely,

Todd L. Cecil -S

Digitally signed by Todd L. Cecil -S
Date: 2023.02.02 15:08:18 -05'00'

Todd Cecil, Ph.D.
Acting Director
Office of Science
Center for Tobacco Products

Enclosures:

Appendix A – New Tobacco Products Subject of This Letter
Appendix B – Additional Comments That May Be Considered for Future Submissions

[3] For more information about CTP Portal, see http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/Manufacturing/ucm515047.htm
[4] FDA's Electronic Submission Gateway (ESG) is still available as an alternative to the CTP Portal.
[5] For more information about eSubmitter, see https://www.fda.gov/industry/fda-esubmitter
[6] https://www.fda.gov/tobacco-products/about-center-tobacco-products-ctp/contact-ctp

Appendix A[7, 8]

New Tobacco Products Subject of This Letter

Common Attributes	
Submission date	September 09, 2020
Receipt date	September 09, 2020
Applicant	TBD Liquids, LLC.
Product manufacturer	TBD Liquids, LLC.
Product category	ENDS (VAPES)
Product subcategory	ENDS Component
Attributes	**New Tobacco Product**
STN	PM0004179
Static Product ID	PD1
Product Name	TBD Mango Salt
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mango
Additional Property	Nicotine: 15mg, PG/VG: 37/63, E-Liquid Volumes: 15mL, 30mL, 50mL, 120mL, 240mL
STN	PM0004179
Static Product ID	PD2
Product Name	TBD Mango Salt
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mango
Additional Property	Nicotine: 30mg, PG/VG: 37/63, E-Liquid Volumes: 15mL, 30mL, 50mL, 120mL, 240mL
STN	PM0004179
Static Product ID	PD3
Product Name	TBD Mango Salt
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mango
Additional Property	Nicotine: 50mg, PG/VG: 37/63, E-Liquid Volumes: 15mL, 30mL, 50mL, 120mL, 240mL

[7] Properties to uniquely identify the new tobacco products were provided by the applicant as of the date of this letter, and not confirmed by FDA.

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

STN	PM0004179
Static Product ID	PD4
Product Name	TBD Mango Salt
Package Type	Bottle
Package Quantity	1 Bottle
Characterizing Flavor	Mango
Additional Property	Nicotine: Custom, PG/VG: 37/63, E-Liquid Volumes: 15mL, 30mL, 50mL, 120mL, 240mL

Appendix B

Additional Comments That May Be Considered for Future Submissions

Although not a basis for our refuse-to-file decision, the following additional comments are intended to provide information that we encourage you to consider including in future submissions:

1. For any **clinical studies** included in your PMTA, we recommend that you provide:
    a. Documentation and evaluation of any **adverse experiences** that occur
    b. Data on any non-compliance, protocol deviations, and subject withdrawals or drop-outs

2. For **literature reviews**, FDA recommends providing details on the methodology used. It is helpful when the literature review includes details on how the review was conducted by providing a protocol that includes, but is not necessarily limited to:
    a. The objectives, primary outcomes, methods, databases searched
    b. The dates of searches, search terms, inclusion and exclusion criteria, number of articles identified
    c. A discussion of how study bias, weight of the evidence, and quality of the data were evaluated
    d. The generalizability of the findings to the U.S. population
    e. The strategy for assessing study quality and strengths and limitations
    f. Your overall conclusions and interpretation of findings

    FDA recommends that you consider how specific characteristics of your new tobacco products (e.g., nicotine content, flavors) may impact user behavior, exposure, and health effects. These characteristics may impact your ability to bridge published literature findings to your new tobacco products. When characterizing health risks, consider including studies and other scientific evidence that identify biomarkers and health outcome measurements or endpoints specifically related to these health risks.

    Consider whether relying solely on peer-reviewed published literature will support a full and robust evaluation (including, for example, toxicological and clinical evaluations) of your new products relative to other tobacco products already being marketed. Your new products may include differences such as novel ingredients not seen in the current marketplace and the scientific literature. Consequently, there may be limited data in the literature that can be applied to your products and support your PMTAs. Providing a rationale for why data from studies of other tobacco products are applicable to the evaluation of your new products is important. Depending on the results of the literature reviews and literature-based risk assessments, information gaps may remain for this evaluation. In this case, you may consider whether additional studies (e.g., clinical, in vitro, or in silico toxicological studies) using your specific products may be useful in providing evidence to support your PMTA.

3. If you draw inferences regarding the long-term health effects of your new tobacco product based on published **epidemiological studies**, FDA recommends that you provide a rationale for using specific studies and consider generalizability of the studies This rationale may include:
    a. Study design
    b. Type of products
    c. Study population
    d. Exposure and outcome measures

e. Study Duration
f. Statistical power for detection of pre-defined differences and/or testing hypotheses
g. Potential bias and confounding

4. FDA may request to conduct **inspections** of your manufacturing sites, as well as the sites and entities involved with clinical and nonclinical research relied upon to support FDA's review of your PMTAs. To ensure that the appropriate records and personnel will be available during the inspection, FDA will notify the firms and/or clinical investigators prior to the inspection start date. You should include a full description of each manufacturing and testing facility involved in the manufacturing, packaging, storing, and/or testing of the new tobacco product(s) in your application, including each manufacturing and testing facility's: address, point of contact, and assigned Firm Establishment Identifier (FEI) number. Your PMTAs should also include a full description of all manufacturing and testing activities, processes, and controls performed at each facility. You should provide a narrative description, accompanied by a list and summary of all standard operating procedures (SOPs) and examples of relevant forms and records for all manufacturing activities.

   For studies that you conducted or that were conducted on your behalf, we recommend submitting the following information:
   a. A list of all sites and clinical investigators that conducted the study, including contact information and physical address(es)
   b. All versions of protocols and amendments that were used in the study, including investigator instructions if any were produced in addition to the protocol
   c. Line data, including data definition files that include the names of the variables, codes, and formats in each dataset
   d. The location of all source data
   e. A list of all contractors who participated in the study, the role of each contractor, and the initiation and termination dates of the participation of each contractor
   f. A signed full report of all findings

   For **clinical studies**, to the extent available or reasonably obtainable, provide the following:
   a. Documentation of all actions taken to ensure the reliability of the study and the protection of human subjects (e.g., documentation of study oversight by an Investigational Review
   b. Board duly constituted and operating under 21 CFR part 56 and documentation of informed consent procedures, such as appropriate procedures found in 21 CFR part 50)
   c. All versions of study materials (e.g., consent forms, questionnaires, and stimuli) used
   d. All versions of case report forms used
   e. Individual case report forms related to participant deaths, other serious and unexpected adverse experiences, withdrawals, and participant discontinuation where the study participant was exposed to the tobacco product that is the subject of the application or similar products

5. FDA recommends analysis of **harmful and potentially harmful constituents (HPHCs)** to help understand the health risks of a tobacco product. If you choose to submit HPHC data, FDA recommends your application contain a full description of all HPHC testing conducted for your tobacco product(s) as well as a full list of HPHC test methods and instrumentation including information for in-house/custom equipment, standards, and adaptors used to generate test

data.

To this end, consider whether testing additional ingredients or constituents of toxicological concern, perhaps through a non-targeted analysis, would provide better representation of the total hazards of your product. Additionally, you should provide a rationale for why the constituents you choose to test provide adequate information to characterize the hazard of the new product. In the event that the new product includes both increased and decreased levels of measured HPHCs relative to the comparator product(s), FDA suggests that you consider conducting additional hazard or risk evaluation of the HPHCs for FDA to assess potential health risks and help FDA make a determination whether marketing of your products is APPH.

6. FDA recommends providing **product stability testing** data spanning the complete shelf life of the tobacco product to adequately support the proposed shelf life and recommended storage conditions for the finished tobacco product. If you choose to submit partial long-term testing data at the time of the PMTA submission, you may also want to provide scientific evidence and justification as to why this information is sufficient, reasonable to extrapolate into complete long-term stability data, and adequate in determining the microbial stability of the tobacco product over its complete shelf life.

   Regarding **microbial stability testing**, FDA recommends that studies include testing of all attributes that are likely to influence the microbiological stability of the product and at time-points that span the complete shelf life (i.e., beginning, middle, and end) of the finished tobacco product. Complete stability testing data (including sample size, sample manufacture and test date, test intervals, test methods, data sets, and a summary of results) from samples that are representative of the manufacturing scale of production is recommended.

7. **Individual perceptions, intentions, and behaviors** (e.g., appeal, likelihood of initiation and cessation) may differ as a function of the unique characteristics of each product in a PMTA. Therefore, it is helpful to provide sufficient information for each distinct product (e.g., each flavor and nicotine combination) such that FDA may evaluate whether the marketing of each distinct new product is appropriate for the protection of public health (APPH) or provide rationale and justification for how “common” (e.g., brand-level) data can be bridged or extrapolated to each of the distinct products. You may also include additional data or information sources other than “common” data that address relevant perceptions, intentions, and behaviors for each of the different varieties of new products submitted for review to assist with bridging or extrapolating "common" data to the distinct product under review. Although not required by FDA, if you choose to conduct your own studies to expand upon the available “common” data, consider how the study design, hypothesis, sample size, and results for each product will contribute to the PMTA and help FDA make a determination whether marketing of your product(s) is appropriate for the protection of public health (APPH).

8. FDA supports the **use of different types of studies, methods, instruments, and analyses** to determine whether marketing of a tobacco product is appropriate for the protection of public health. FDA will make this determination with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product. If you use data from studies or other sources which do not include your new product, FDA recommends that you provide a detailed rationale to explain why you choose to infer data on other products to your new products; whether perception and intention to use your new products predict actual use; and

why bridging data from other products is relevant to your new products. FDA also recommends that you do all of the following:

a. Define nonuser subgroups based on similar strategies found in published articles using nationally representative surveys and studies
b. Provide detailed description of your study design and analyses (e.g., hypotheses, study population and subgroups, sample size and statistical power calculation, definition of exposure and outcome measures, methods of statistical analyses, and determination of statistical significance)
c. Identify strengths and limitations of your approach
d. Discuss how the information you provided supports that marketing of your new products is appropriate for the protection of public health (APPH) (e.g., how non-probability nature of studies informs statistical inference)

9. **Secondary analyses of national survey data** may also be used to support a PMTA. If you take this approach, FDA recommends that you explain why data for the secondary analyses are applicable to your new product(s) in the population of interest. FDA also recommends that you provide a statistical analysis plan (if available) with sufficient details, including but not necessarily limited to, data used for the secondary analyses, date of data access, design of the study or studies, hypotheses to be tested, primary and secondary objective, sample size and statistical power calculation, study population and subgroups, inclusion and exclusion criteria, a definition or description of each variable, exposure and outcome measures, statistical analyses performed, level of statistical significance, software used for the statistical analyses, interpretation of results, assessment of bias, and identification of strengths and limitations of the analyses.

10. FDA does not endorse any specific model for **population modeling,** but supports the application of comprehensive frameworks that have the capacity to assess the impact of the marketing of the new products that inform the risks and benefits to the population as a whole (FD&C Act Section 910(c)(4)). The chosen framework should be able to assess the likelihood of initiation among never users and former users, cessation among current tobacco users, switching completely, dual use, and likelihood of product use by youth. FDA recommends your population modeling use appropriate inputs and assumptions and provide evidence for the products effects on both users and nonusers of tobacco products; taking into account increased or decreased likelihood that those who do not use tobacco products will start using such products. FDA also recommends that you clearly articulate the methods used to develop your models and provide sufficient information to allow FDA to conduct a comprehensive scientific review of your modeling strategy, evaluate the development of the models, and determine how the predictions (outputs) from the models are used to address the risks and benefits to the population as a whole. Providing details for your population modeling may help FDA to confirm the information provided with the application, including but not necessarily limited to:
    a. The model development plan
    b. Data sources used in the development of input parameters
    c. Information on the development and validation of your methods for using data from the Actual Use Survey and Perceptions and Behavioral Intentions Study (e.g., your algorithm for predicting purchase rates and likelihood of smokers completely switching from cigarettes to your new products)
    d. Explanation of why the selected data sources are relevant to your new products and the U.S. population

e. Assumptions for development of models
f. Computer codes associated with the computer implementations of the models that allows verification of outputs
g. Model validation (e.g., sensitivity analysis)
h. Model parameters from literature with descriptions of how the literature search was conducted and how results of the search were consolidated into the models
i. Generalizability of results to the U.S. population
j. Strengths and limitations of the models - including potential limitations on the interpretation of model results of a chosen framework given the data input selected
k. Scenarios considered
l. Any other potential factors that may affect the results

11. In a PMTA submission that includes multiple new tobacco products, it is important that you clearly identify which content pertains to each distinct product and show that the PMTA content requirements of Section 910(b)(1) of the FD&C Act are satisfied for each distinct product. FDA considers each ENDS product with a differing flavor variant and/or nicotine strength to be a different new tobacco product.

12. When submitting a PMTA that cross-references a **Tobacco Product Master File** (TPMF), we recommend you include written authorization from the TPMF owner that grants you authorization to reference the TPMF, specify the TPMF submission tracking number, and clearly identify the content that you are referencing in the TPMF. Please read the Guidance for Industry on Tobacco Product Master Files for additional information on TPMFs and how to request authorization to reference one in your PMTA.[9]

13. A PMTA must include specimens of the **labeling** proposed to be used for the new tobacco product (FD&C Act Section 910(b)(1)(F)). The following would be helpful to FDA review of the submitted labeling: specimens that are legible, reflect the actual size and color for use with the new tobacco product and include any warning statements appropriate for the product class where applicable and comply with all other applicable labeling requirements under the FD&C Act.

14. An environmental assessment (EA) must be submitted as part of a PMTA. According to 21 CFR 25.40(a), an EA should include all of the following:
    a. Discussion of the need for the proposed action (i.e., FDA issuance of marketing granted order for your tobacco product)
    b. Discussion of alternatives as required by section 102(2)(E) of the National Environmental Protection Act (NEPA)
    c. Environmental impacts of the proposed action and alternatives
    d. Listing of the agencies and persons consulted
    e. Relevant environmental issues relating to product use and disposal from use.

    Additionally, CTP requests discussion of relevant environmental issues relating to product manufacturing.

    Additionally, per 21 CFR 25.40(a), an EA shall focus on relevant environmental issues for your

[9] Guidance for Industry: Tobacco Product Master Files. May 2016. https://www.fda.gov/media/97632/download.

tobacco product and is to be a concise, objective, and well-balanced document that allows the public to understand the agency's decision.

You may refer to the following resources on the CTP website for more information with respect to EAs for tobacco products:

a. *Environmental Assessment & Claims of Categorical Exclusion*,[10] presented during the 2018 Tobacco Product Application Review – A Public Meeting[11]
b. *Lessons Learned from PMTA Reviews,*[12] presented during the 2019 Deemed Tobacco Product Applications – A Public Meeting (information on EAs begins on slide 33)[13]
c. FDA's Premarket Tobacco Product Marketing Orders website[14] for examples of EAs that comply with 21 CFR Part 25
d. Guidance for Industry: National Environmental Policy Act; Environmental Assessments for Tobacco Products; Categorical Exclusions – Small Entity Compliance Guide.[15]

15. In addition, while alternative formats may be used, inclusion of a certification in your EA such as the one below containing a signed and dated statement would promote efficiency in the review process.

> "The undersigned official, on behalf of [insert company name] certifies that the information presented is true, accurate, and complete."
>
> _____
> (Date)
>
> _____
> (Signature of responsible official)
>
> _____
> (Name and title of responsible official, printed)

[10] https://www.fda.gov/media/117503/download
[11] https://www.fda.gov/tobacco-products/ctp-newsroom/tobacco-product-application-review-public-meeting
[12] https://www.fda.gov/media/133444/download
[13] https://www.fda.gov/tobacco-products/ctp-newsroom/deemed-tobacco-product-applications-public-meeting-10282019-10292019
[14] https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders
[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/national-environmental-policy-act-environmental-assessments-tobacco-products-categorical-exclusions