U.S. FOOD & DRUG
ADMINISTRATION

Memorandum

To: File

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Subject: Bundling and Bracketing Approach for Review of ENDS Open E-liquid PMTAs

Background

The United States District Court for the District of Maryland ordered FDA to require that premarket authorization applications for all deemed new tobacco products on the market as of August 8, 2016,[1] be submitted to the Agency by September 9, 2020, and provided a one-year period during which products with timely received applications might remain on the market while FDA considers their applications ("compliance period").[2,3] Applicants are required to submit a premarket application for each new tobacco product including each ENDS open e-liquid with different characteristics such as characterizing flavor (CF), nicotine concentration, and propylene glycol to vegetable glycerin (PG:VG) ratio. FDA anticipates that a substantial portion of PMTA ENDS submissions[4] during the compliance period will consist of open e-liquids that contain hundreds to thousands of products with variations in CF, nicotine concentration, and PG:VG ratio based on the tobacco ingredient listing submitted by tobacco product manufacturers and importers. To increase the likelihood that more tobacco products will be reviewed and receive marketing orders before the end of the compliance period, the Office of Science (OS) is implementing a bundling-bracketing review approach for ENDs open e-liquids PMTAs.

Bundling refers to the process of dividing an applicant's PMTA submission into smaller subsets ("bundles") for scientific review. Since the start of OS review of premarket submissions for tobacco products, OS has been bundling PMTAs, SE Reports, and EX REQs. Additionally, OS has been conducting

[1]The order applies to deemed tobacco products that meet the definition of a 'new tobacco product' (defined in section 910(a)(1)) and were on the market on August 8, 2016, the effective date for the final deeming rule (81 FR 28976)
[2]American Academy of Pediatrics, et al. v. Food and Drug Administration, et al., No. 8:18-cv-883 (PWG), 2019 WL 3067492, at *7 (D. Md. July 12, 2019) (Dkt. No. 127)
[3]American Academy of Pediatrics, et al. v. Food and Drug Administration, et al., Case No. 8:18-cv-883 (PWG), (D. Md. Apr. 22, 2020), Dkt. No. 182
[4]A 'PMTA submission' can refer to an applicant's submission of individual PMTAs and/or a grouped submission for multiple tobacco products that share a significant amount of application content (e.g., a submission for products in the same subcategory such as ENDS open e-liquids).

limited bracketing during scientific review (e.g., applicant X makes cigarette with three different but similar cigarette papers, where the worst-case scenario paper data was bridged to the other two papers). Historically, bundling has occurred before initiation of scientific review while bracketing has occurred during scientific review.

Bracketing refers to the process of individually evaluating the highest and lowest variation of a given characteristic within the bundle (i.e., the highest and lowest nicotine concentration for purposes of this memo) and bridging the findings and conclusions to all other products within the bracket (e.g., products with nicotine concentrations between the highest and lowest nicotine concentration). The application of the bundling and bracketing approaches to the unique challenges of ENDS open e-liquids is the focus of this memo.

There is an expectation that applicants may submit applications that include numerous flavor combinations, nicotine concentrations, and solvent combinations that will exceed the capacity of the reviews to complete in a timely manner. Each of these combinations are considered new products but have many common characteristics that would best be reviewed using bracketing approaches. However, before reviewers can apply these approaches, the scientific review bundles will need to be developed to ensure proper representation of products. To accomplish this, while maintaining a fair and unbiased selection of products that will be reviewed, the bundle will be comprised of randomly selected open e-liquids proportional to the flavor categories represented in the overall PMTA submission. The updated OS approach described in this memo combines bundling and the identification of the bracketing products into a single process that occurs before scientific review.

Discussion

Role and Responsibilities

- Bundling and the identification of bracketing products will be conducted by the Division of Regulatory Project Management (DRPM) before the start of scientific review. Conclusions for the products identified to create the brackets will be extrapolated to all of the products within the bundle during DPS and DNCS scientific review.
- Due to the nature of their disciplines' reviews, Division of Population Health Science (DPHS) and Division of Individual Health Science (DIHS) reviewers will continue to review the entire PMTA in order to reach conclusions for any portion of the submitted products. As a result, DIHS/DPHS will review all the CFs in the PMTA and provide a comprehensive DIHS/DPHS review that indicates the findings of the review may apply across all tobacco products in the submission.
    - The reviewers will clearly identify and organize deficiencies that apply to the tobacco products bundle, and separate deficiencies that apply to the remaining tobacco products in the submission.
    - When there are subsequent bundles from a submission that has already been reviewed, abbreviated, focused DIHS and DPHS reviews should be completed. If the conclusions of the reviews still stand, then the reviews can simply reference the original reviews and state that the conclusions do not change from the original reviews. If there are changes to the conclusions in the original reviews to reflect CTP's current thinking and/or new information, the review should state the new conclusions and explain why the conclusion is different.

Criteria

- The approach will be applied only to ENDS open e-liquid[5] PMTAs that contain:
  - More than 24 tobacco products;
  - Two levels of nicotine concentrations; and
  - More than one PG:VG ratio
- Some ENDS open e-liquid PMTAs will contain many products with numerous CFs.[6] Each CF can be categorized into common flavor categories (e.g., tobacco, menthol/mint, fruit, dessert) based on the color wheel (Figure 1).
- Division of Product Science (DPS) and Division of Nonclinical Science (DNCS) reviewers are able to conduct individual scientific review on a maximum of 24 CFs within any single PMTA due to resource limitations. However, there is no limit to the maximum number of tobacco products per PMTA for which the conclusions can be bridged.

Assumptions

- Open ENDS e-liquids in the same PMTA will contain the same-sourced ingredients (e.g., nicotine, PG:VG) in varying amounts, with the only distinct ingredients being flavor ingredients.
- PMTAs will contain representative harmful and potentially harmful constituent (HPHC) data for each tobacco product flavor.

Process

1. After a PMTA is accepted and filed, it is placed in the queue for triage randomization before the start of scientific review. If selected for scientific review, the application is reviewed to identify CFs and variations of nicotine concentration and PG:VG ratio.

2. Assign submitted CFs to flavor categories based on flavor wheel (Figure 2, Step 1).
   - For flavor categories and respective CFs, refer to Figure 1. Flavor wheels have been used as tools to classify flavors and aromas in the food, alcohol, and fragrance industries and can be adapted as a systematic tool for flavor classification in e-liquid tobacco products.
     - If a flavor category is not immediately apparent from the applicant-provided CF, tobacco product name, or brief descriptor (e.g., characterizing flavors such as unicorn blood or blue jazz), the assigned flavor category will be "Other."
   - After classifying CFs by flavor category, similar CFs should be grouped together (e.g., fruit flavors will be grouped together; "Other" flavors will be grouped together).
   - Less common flavor categories can be combined to create fewer flavor categories (e.g., "nuts" and "spices" may be combined into the "Other" category) on a case-by-case basis.

3. Calculate the percentage of tobacco products in each of the flavor categories within the application (Figure 2, Step 1).

$$\frac{Total\ \#\ products\ within\ a\ flavor\ category}{Total\ \#\ products\ in\ the\ application} x\ 100$$

   This calculation is done so that bundles can be representative of flavor categories present in the overall PMTA submission.

[5]Based on OS experience and the available scientific literature, the bracketing-bundling approach is applicable for ENDS open e-liquids only. OS will consider expanding the product scope as more experience and knowledge is gained.
[6]Characterizing flavor is based on the labeling and identifying information stated by the applicant in the application.

4. Randomly select 24 CFs, proportional to the percentage of flavor categories in the PMTAs based on step 3 (Figure 2, Step 2).

   Recall, the maximum number of individual tobacco products that can be scientifically reviewed in a bundle is 24. For each of the selected CFs, OS is only going to scientifically review two individual tobacco products, and bridge the conclusions to all remaining products in that CF.

   All of the nicotine variations and PG:VG ratios within each of the selected 24 CFs will enter scientific review as a single bundle.

5. Bracket products by reviewing two products for each of the 24 selected CFs: the highest and lowest nicotine concentrations, both with the highest VG[7] within PG:VG ratios (Figure 2, Step 3a, 3b).[8,9, 10,11]
   - Conclusions for the two individually scientifically reviewed products will be bridged to all other products in the bracket (Figure 2 and Figure 3).
   - In certain situations, a bracketing product[12] with the highest nicotine concentration may head towards a marketing denial order (MDO). If this occurs, the next appropriate nicotine concentration (e.g., the product with the next highest nicotine concentration) should be reviewed by DPS and DNCS as the bracketing product.

Public Health Benefits

Bundling divides PMTA submissions into more manageable subsets that will result in increased availability of OS review resources and increase the likelihood that more PMTA reviews will be completed during the one-year compliance period. Bracketing will facilitate efficiency in substantive scientific review as FDA can take action on a larger number of tobacco products than the actual number of tobacco products that are individually reviewed (through bridging) within the 180-day PMTA review timeline. The bundling-bracketing approach will increase the likelihood that FDA issues a greater number of marketing orders for tobacco products within the compliance period. This will benefit public health in two ways as it will (1) increase the likelihood that a variety of products for which marketing is determined to be APPH will be legally marketed by the end of the compliance period; increasing availability of tobacco products that help adult current TP users switch to potentially less harmful products; and (2) increase the likelihood that a greater number of TPs for which marketing was determined to not be APPH be removed from the market.

Conclusion

We anticipate that many PMTA submissions for ENDS open e-liquids during the one-year compliance period will contain hundreds to thousands of open e-liquids with variations in characteristics such as characterizing flavor (CF), nicotine concentration, and propylene glycol to vegetable glycerin (PG:VG)

[7] If 100% VG is the bracket, the reviewer should consider looking at the HPHC data for at or closest to 30:70 PG:VG.

[8] N Engl J Med 2015; 372:1575-1577, DOI: 10.1056/NEJMc1502242

[9] FDA CTP CDRH Research project (VG degradation data showed highest levels of acrolein, formaldehyde, and acetaldehyde with increasing levels of VG)

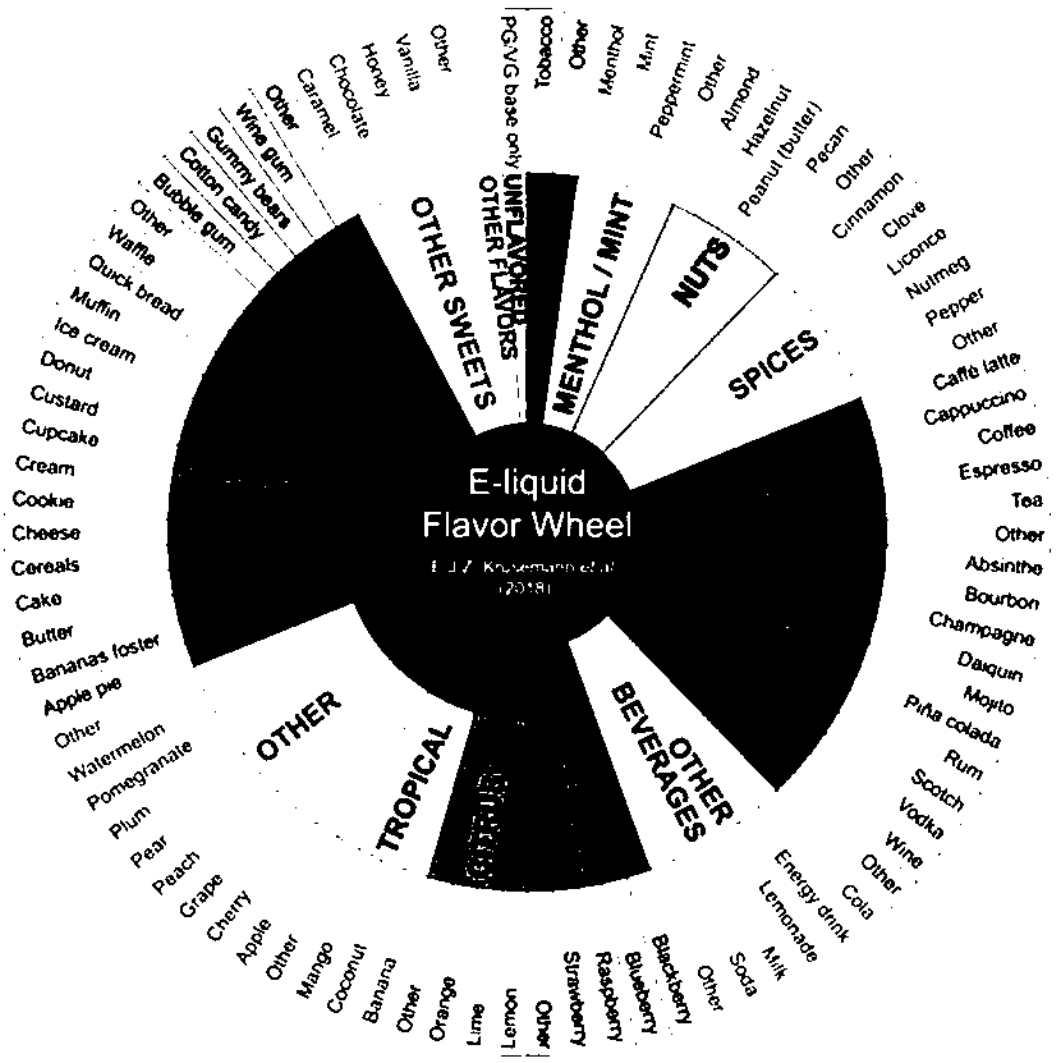
[10] Tobacco products with the same CFs which contain variations in other characteristics (such as salt formulation), will not be bracketed due to changes in product composition and therefore, would require individual review.

[11] FDA CTP CDRH Research project (VG degradation data showed highest levels of acrolein, formaldehyde, and acetaldehyde with increasing levels of VG)

[12] "Bracketing products" are those that represent the highest and lowest nicotine concentrations. "Bracketed products" are those that fall in between the highest and lowest nicotine concentrations.

ratios. OS is implementing a bundling-bracketing approach for ENDS open e-liquids that will reduce the size of each PMTA submission by dividing it into smaller review bundles and will reduce the need for individual scientific review for each ENDS open e-liquid product due to characteristic variations. The current approach will increase the likelihood that FDA can issue more marketing orders on a greater number of tobacco products which would provide public health benefit.

Figure 1. E-liquid flavor wheel classification, depicting characterizing flavors (outer ring) categorized by flavor category (inner ring)[13]



[13] Krüsemann EJZ, Boesveldt S, de Graaf K, Talhout R. An E-Liquid Flavor Wheel: A Shared Vocabulary Based on Systematically Reviewing E-Liquid Flavor Classifications in Literature. *Nicotine Tob Res*. 2019;21(10):1310-1319. doi:10.1093/ntr/nty101

Figure 2. Open E-Liquids Bundling-Bracketing Process with Example

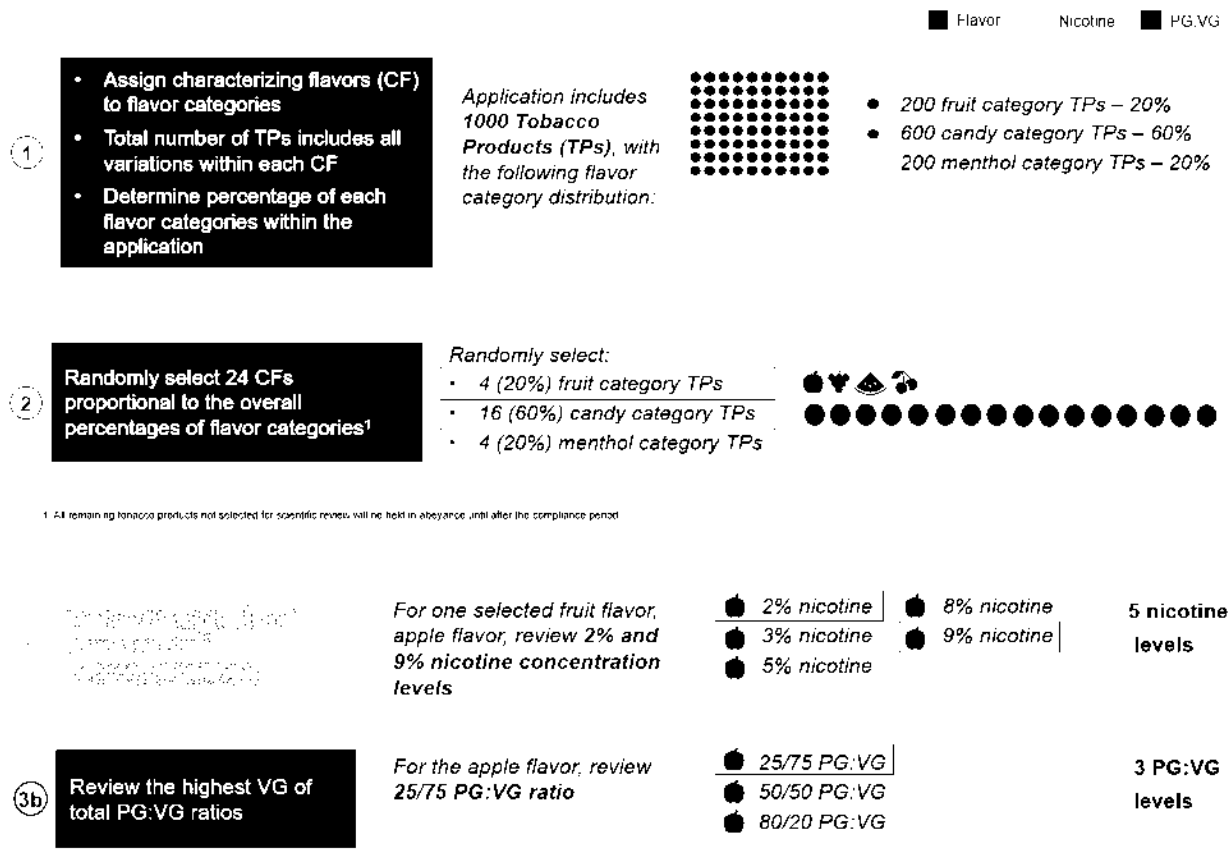


Figure 3. Example determination of TPs with Bundling-Bracketing