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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

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Subject: Normalization of HPHC Yields between new and comparison products in ENDS PMTAs

Background

In order for a new tobacco product to receive marketing authorization through the premarket tobacco application (PMTA) pathway, FDA must determine that marketing the new tobacco product is appropriate for the protection of the public health (APPH). Section 910(c)(4) of the Federal Food, Drug, and Cosmetic Act states that this determination shall be made "with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product…" Determining these risks and benefits for users requires a consideration of the public health impact of the new tobacco product with respect to other tobacco products or product classes in the marketplace (comparison products or comparators). Per the PMTA for electronic nicotine

delivery systems (ENDS) Guidance (U.S. Department of Health and Human Services, 2019),[1] FDA recommends that comparison products include tobacco products from different categories (such as combusted cigarettes, referred to as cigarettes in this document) as well as other products from the same product category or subcategory as the new tobacco product. Thus, comparison products assist FDA's APPH determination by providing a context for how marketing the new tobacco product will affect the health impacts or risks posed by other commercially available tobacco products.

In PMTAs, applicants provide the comparison products and their relevant data (e.g., HPHC or biomarkers of exposure (BOE) data demonstrating potential reduced heath risk relative to other tobacco products, product use behavior data demonstrating reduced use of other relatively higher risk tobacco products) to demonstrate where the new tobacco product fits into the marketplace and why it would be APPH. Ideally, comparison products should fully capture the current tobacco product use of the target population for the new tobacco product. However, to demonstrate reduced risks of the new tobacco product, it is likely for applicants to select products from several categories such as combusted cigarettes, heated tobacco products (HTPs), smokeless and other ENDS as comparison products in ENDS PMTAs. As a product category, ENDS vary widely in design, emissions and use.[2] Given these differences between ENDS and other tobacco products, it is important to normalize any analytical results or toxicant testing between products in a manner that allows the best estimate of relative differences in toxicant yields. These toxicant yields can provide information relative to overall risk comparisons between products under review and comparator products, although factors such as route of exposure may also affect overall risk comparisons.

For chemistry reviewers, the evaluation of product toxicant yield focuses on identifying and quantifying harmful and potentially harmful constituents (HPHCs) and other toxicants present in the tobacco product or generated during product use. To collect this data, numerous standardized methods have been developed for testing the different categories of tobacco products (e.g., FTC, ISO, CORESTA No. 81). These standardized methods are effective at identifying the relative differences in emissions and contents among tobacco products and at identifying the effects of product design on these emissions. However, standardized methods are generally developed around a set of test conditions that allow the testing to be applied to the widest range of products. Although these test conditions approximate the parameters under which the tobacco products are used, they may not accurately capture how the products are actually used by consumers.[3] When comparing standardized test results between tobacco product categories, it is therefore important to normalize the analytical results or toxicant testing in a manner that allows the best estimate of relative differences in toxicant yields. This memorandum evaluates different strategies for comparing HPHCs and toxicant data between new and comparison tobacco products from different categories and provides guidance to reviewers on how to best normalize such data in ENDS PMTAs to inform the determination of the public health risks.

Discussion

HPHC and toxicant data are most helpful for product comparison when the data can be used to estimate the relative toxicant exposures to users. This can be facilitated by normalizing the toxicant data from the product to some measure that correlates with product use. A number of potential normalization factors have been used when comparing HPHC and toxicant data between tobacco products, including portion size, nicotine content, puff count, tobacco weight and total particulate matter (TPM). In the SE and EX pathways, product comparisons have often been between products in the same category (e.g. combusted cigarettes) as these pathways are limited to a one to one comparison and not a marketplace comparison. When comparing data between such similar tobacco products, it may be considered appropriate to normalize to many different product

[1] https://www.fda.gov/media/127853/download

[2] Williams M, Talbot P. Design Features in Multiple Generations of Electronic Cigarette Atomizers. *Int J Environ Res Public Health*. 2019;16(16):2904

[3] World Health Organization, WHO Study Group on Tobacco Product Regulation Second Report of a WHO Study Group, 2008

characteristics. Similarly, for ENDS PMTAs, where the comparison products are other ENDS products (same category), comparing data on a per gram of product (e.g., mg/g) or per unit of product (e.g., mg/cartridge) may be appropriate regardless whether the comparison products are pods, tanks, or cig-a-likes. However, when comparing between different categories of tobacco products, the choice of an appropriate normalization factor becomes more challenging. For ENDS products in particular, choosing the best normalization factor may be difficult because product and design variability contribute to a high variability in product use.[2] As a result, regardless of the types of new tobacco products (e.g., pods, tanks, cig-a-likes), normalizing HPHCs and toxicants data to product use is ideal for highlighting potential differences in emissions or content if this information is provided by the applicant for the new and comparison products.

Normalization factor when product use data has been provided by the applicant

If the applicant provides product use data in a PMTA for the new and comparison products, it is recommended that the reviewer should consider normalizing the toxicant data to the provided use for each product over an equivalent unit of time (see example below). Product use data can come from published literature or clinical/survey studies conducted by the applicant showing that, for example, an average use for cigarette smokers is 10 cigarettes a day, 10 pouches per day for smokeless users, and 400 µL of e-liquid per day consumed by the new product (ENDS) users. Normalizing the HPHC and toxicant data to product use allows products of different categories to be compared equally and more clearly highlights relative differences in product emissions or content to determine the public health impact. The additional advantages of normalizing to product use are that it is applicable to all tobacco products and allows a convenient means of comparing portioned and unportioned products. However, the suitability of this approach relies upon the suitability of the product use data provided. It is possible that applicants may provide product use data from published literature instead of directly collected data. Regardless of the source, reviewers may need input from other disciplines such as social science, behavioral and clinical pharmacology, or epidemiology regarding the suitability of the data provided. If the product use data cannot be verified, validated, or lacks sufficient information then reviewers should consider normalizing HPHC and toxicant yields to nicotine yields.

An example of normalizing to product use:

Assume an applicant submits an application for a new closed ENDS product and uses a combusted cigarette and a smokeless tobacco product as comparison products. The applicant provides HPHC data measured in the aerosol for the ENDS product (in mass per amount of e-liquid aerosolized), in the mainstream smoke for the combusted cigarette (in amount per cigarette) and in the tobacco filler for the smokeless product (in amount per pouch). The applicant further provides product use data from a clinical study of cigarette smokers and smokeless tobacco users that were asked to switch from their usual tobacco products to the new product. The applicant states that the cigarette smokers reported an average use of 10 cigarettes a day (half a pack) and the smokeless users reported an average use of 10 pouches per day. Over the course of the study, the applicant reports that users of the new tobacco product consumed 400 µL of e-liquid on average per day. Multiplying the emission data from each product by the provided product use data converts the toxicant data into toxicant yield for each product per day.

Normalizing to nicotine yields when use data has not been provided by the applicant

Given the difficulty in obtaining robust data for product use, many applications may lack product use information for the new or comparison products. In this case, reviewers should consider normalizing HPHC levels to nicotine yields. If nicotine yields are not provided, then normalizing to nicotine content is an alternative although potentially less suitable option as it does not represent the amount of nicotine delivered to users; the efficiency of nicotine to transfer into aerosol varies depending on the products and nicotine types (e.g., free base nicotine, nicotine salt) and is different than that of combustible cigarettes.

It is widely recognized that nicotine is the principal addictive substance in tobacco products and most tobacco product users are addicted to nicotine.[4] In keeping with this, tobacco product users tend to have an optimal level of nicotine that provides sufficient user satisfaction and avoids symptoms of withdrawal.[5] When tested under conditions meant to replicate the use of a single cigarette or a single typical portion of smokeless tobacco, combusted cigarettes, oral snuff and chewing tobacco produced similar peak plasma nicotine levels (~15 – 30 ng/mL), although over different time courses.[6] There is a general consensus in the literature that tobacco users adjust their behavior to maintain this level of nicotine. This has been seen in studies looking at reduced nicotine cigarettes. When smokers use combusted cigarettes containing a lower nicotine content (e.g., "light" cigarettes) than their typical cigarettes, they tend to alter their puff topography and cigarette use behavior to compensate and increase their nicotine intake.[7,8] This effect has also been observed in cigarette smokers who use ENDS for the first time. ENDS naïve cigarette smokers were seen to adapt their puff topography over time in order to achieve the same plasma nicotine levels seen after using combusted cigarettes.[9]

The tendency of tobacco users to moderate and maintain their nicotine levels indicates that normalizing to nicotine yield should provide a reasonable estimate of relative product use and should be applicable to all inhaled tobacco product categories including "light" cigarettes but not for very low nicotine (VLN) cigarettes (0.2-0.7 mg/cig nicotine); studies show minimal evidence of compensatory smoking for VLN smokers, which may be driven by the estimated nicotine availability making compensation impossible.[8] This normalization approach utilizes data that is generally provided by the applicant in a PMTA and facilitates comparisons between portioned and unportioned products. Because nicotine yield is a function of puffing conditions, it is recommended that reviewers normalize HPHC and toxicant yields to nicotine yields measured under equivalent conditions. For combusted cigarette data, ISO (non-intense) HPHC yields should therefore be normalized to ISO nicotine yield and CI (intense) HPHC yields should be normalized to CI nicotine yields. For ENDS, HPHC yields should be normalized to the nicotine yield obtained under the same power, temperature and flow settings.

It should be recognized that several factors can affect how well nicotine yield correlates with product use. While tobacco users appear to have a desired plasma nicotine concentration, how readily a given dose of nicotine achieves this level (i.e., how efficiently the nicotine is delivered) depends upon the route of administration (e.g., oral versus inhaled) and the nicotine formulation (freebase versus salt form).[10] Normalization to nicotine yield is expected to best reflect relative product use in those cases where the new and comparison products have similar nicotine yields, deliver nicotine via a similar route of administration and have comparable forms of nicotine.

Other normalization factors and their limitations

As technology has evolved ENDS, their ability to deliver nicotine has improved. While the first marketed ENDS typically delivered less nicotine than cigarettes, current ENDS may now match the nicotine delivery in

[4] USDHHS, Public Health Service. The Health Consequences of Smoking—Nicotine Addiction: A Report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service, Centers for Health Promotion and Education, Office on Smoking and Health. DHHS Publication No. 88- 8406, 1988.

[5] Benowitz N. Clinical pharmacology of nicotine: Implications for understanding, preventing, and treating tobacco addiction. Clin Pharmacol Ther. 2008;83(4):531–541.

[6] Benowitz NL, Porchet H, Sheiner L, Jacob P 3rd. Nicotine absorption and cardiovascular effects with smokeless tobacco use: comparison with cigarettes and nicotine gum. *Clin Pharmacol Ther*. 1988;44(1):23-28.

[7] USDHHS. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. Smoking and Tobacco Control Monographs, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; 2001

[8] Benowitz, NL, Donny, EC, et al; Edwards, The Role of Compensation in Nicotine Reduction. *Nic & Tob Res*, 2019 21(Supplement_1), S16-S18

[9] Lopez A, Hiler M, et al; Effects of Electronic Cigarette Liquid Nicotine Concentration on Plasma Nicotine and Puff Topography in Tobacco Cigarette Smokers: A Preliminary Report, Nic & Tob Res, 2016, 18, (5):720-723

[10] O'Connell G, Pritchard, JD, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. *Intern Emerg Med* , 2019, 14, 853–861

cigarettes.[11] For ENDS products that have similar nicotine yields to cigarettes and are designed to deliver nicotine at a similar rate, puff count becomes a surrogate measure of nicotine yield. In these circumstances, normalization to puff count may be suitable. However, this method should only be used when the ENDS product and the cigarette comparator have comparable nicotine yields per puff.

Total particulate matter (TPM) has also been used when comparing emissions between cigarette products and when comparing ENDS products to cigarettes. In cigarettes, TPM is a complex mixture of compounds including water, semi volatile tobacco additives such as humectants and numerous semi volatile and non-volatile byproducts of combustion and pyrolysis. In general, smoke nicotine correlates with TPM and the average ratio of smoke nicotine to TPM is relatively consistent across products.[12] As a result, normalization to TPM has been used to account for variability between products. However, it should be noted that changes in design parameters and the use of tobacco additives such as glycerol can significantly alter the ratio of TPM to nicotine[13] and confound the interpretation of TPM normalized results.

In ENDS, TPM is approximately equal to the quantity of e-liquid aerosolized and varies with power level and product design. Nicotine delivery from an ENDS is determined by the quantity of e-liquid aerosolized and the concentration of nicotine in the aerosolized e-liquid.[14] Although TPM in any given ENDS product does correlate to nicotine delivery, the ratio of nicotine yield to TPM varies widely among products. Therefore, TPM in an ENDS cannot, by itself, be used as an independent estimate of nicotine yield or, consequently, product use. Normalizing HPHC yields to TPM when comparing ENDS products to combusted cigarettes is not expected to be as representative of relative product use as normalizing to nicotine yield.

Conclusions

Comparison products play a key role in determining if the new tobacco product is APPH. From a product chemistry perspective, HPHC and toxicant yield comparisons provide a context for assessing the relative health impact or risk posed by the new tobacco product compared to other available products in the marketplace. While standardized methods provide a basis for comparison within a tobacco product category, these methods may not fully capture the actual use behavior. This highlights the importance of data normalization between the new and comparison products which, if not done appropriately, can result in the misinterpretation of product risks. Proper normalization of HPHC and toxicant data allows for a more relevant comparison of these quantities and yields between different tobacco product categories and can highlight any potential health risks associated with the new tobacco product in the context of an ENDS PMTA. Therefore, reviewers should consider the following normalization principles, which are listed in a decreasing order of priority and based on available data in a PMTA (see **Table *1*** for summary), when comparing HPHC and toxicant yields between ENDS and comparison tobacco products from different categories:

1. If the applicant provides suitable use behavior data for the new and comparison tobacco products (e.g. cigarettes smoked per day and e-liquid consumed per day), HPHC and other toxicant data should be normalized to the amount of each product used within the same interval of time.
2. If the applicant does not provide suitable use data, but does provide nicotine in smoke/aerosol yield, then HPHC and other toxicant data should be normalized to the respective nicotine yields of the new and comparison tobacco products.
3. If the applicant does not provide product use or nicotine yield data, then HPHC and other toxicant yields should be normalized to the respective nicotine contents of the new and comparison tobacco products.

[11] Schroeder MJ, Hoffman AC. Electronic cigarettes and nicotine clinical pharmacology. *Tob Control*. 2014;23 Suppl 2(Suppl 2)
[12] Fresenius, R. Analysis of tobacco smoke condensate, *J Anal App Pyrolysis*, 1985, 8: 561_575.
[13] Lui, C. Glycerol Transfer in Cigarette Mainstream Smoke, *Beitr Tabakforsc. Int*, 2004, 21(2):111-6
[14] Talih S, Balhas Z, Salman R, et al. Transport phenomena governing nicotine emissions from electronic cigarettes: model formulation and experimental investigation.*Aerosol Sci Technol*. 2017;51(1):1-11

4. If the applicant does not provide product use data and the comparison tobacco product is a combustible cigarette with similar nicotine yield per puff to the new tobacco product, then normalizing HPHC and other toxicant data to puff count may be an acceptable alternative to normalizing to nicotine yield (option 2).

Table 1. Summary of the normalization approaches for comparing products in ENDS PMTAs

Normalization	Ideal scenario for comparison	Limitations	Suitable comparison product
1. Product use	For comparing two products of different categories and characteristics	Typically not provided in PMTAs and data cannot be verified, validated, or lacks sufficient information	All product including other ENDS
2. Nicotine yield	When the two products have similar characteristics (e.g., same category, route of administration, unportioned and the same form of nicotine), but have different nicotine concentrations	May not be as accurate when the two products have different forms of nicotine since the different forms of nicotine may not be absorbed at the same rates	Best when comparing freebase nicotine ENDS products vs cigarettes. Less accurate when comparing ENDS vs smokeless or nicotine salt ENDS product vs cigarettes
3. Nicotine content	Alternative to nicotine yield	Less suitable option to nicotine yield as it does not represent the amount of nicotine delivered to users	
4. Puff count	Alternative to nicotine yield	The two products should have similar nicotine yields/puff	Better option when comparing nicotine salt ENDS product vs cigarettes