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Given the above, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents and webinars prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. This document does not bind FDA in its review of any tobacco product application and thus, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA.



MEMORANDUM

Date: February 21, 2019

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Subject: Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports

Introduction:

The modified risk tobacco product (MRTP), premarket tobacco product (PMT) and substantial equivalence (SE) product application pathways all rely on comparisons between tobacco products to inform regulatory decisions. Toxicologically, a comparison between two tobacco products is based on a comparison of the health risk posed to users by each of the two tobacco products. This is specifically relevant with SE Reports, as these are distinctly based on a decision on a comparison between two products, the new product and a predicate product.

The determination of whether a tobacco product presents more or less health risk than another tobacco product is a multifactorial process that takes into account (1) a comparison of the ingredients that make up each product and (2) the relative toxicant exposures to users and nonusers of the products, including route of administration and portal of entry effects in addition to simple differences in exposure magnitude. Section 904e of the Food, Drug, and Cosmetics Act requires FDA to establish and regularly define as appropriate a list of harmful and potentially harmful constituents (HPHCs) to health. These HPHCs represent FDA's current thinking on which chemicals out of the large number of constituents that are present in the consumable portion of a tobacco product are most representative of the health risk posed by these tobacco products. The current list of 93 chemicals published in 2012 includes constituents linked to the five serious health effects most commonly linked to tobacco use: cancer, cardiovascular disease, respiratory effects, reproductive problems, and addiction. Thus, the HPHC comparison between two tobacco products is critical in determining whether the two products present users and non-users to similar health risk or whether one of the two products present greater risk.

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This memorandum records the current approach to evaluating HPHC quantities between two tobacco products, sets out some key criteria by which HPHCs are to be compared, and lays out some important directions for further evaluation. DNCS plans to continue to evaluate this topic and, in time, develop more comprehensive thinking on this topic, including its applicability to pathways other than the SE pathway.

Discussion:

It is well-established that cigarette smoke is a complex mixture of over 7,000 compounds. Other types of tobacco products, such as oral tobacco, electronic nicotine delivery systems (ENDS), and hookah also expose users to complex chemical mixtures. While the cumulative human health risk of complex mixtures has been evaluated by organizations such as the EPA¹ and the ATSDR,² it is important to point out that none of these evaluations are (1) specific to tobacco products, (2) designed to rapidly assess relative risk between complex mixtures, or (3) designed to be compatible with the review of premarket product applications such as those reviewed by the FDA. Thus, the health risk evaluation of complex mixtures in the context of tobacco product review is a new and emergent field that is separate from previous approaches. Moreover, unlike previous approaches such as those used by the EPA and ATSDR, the health risk evaluation of tobacco products has the advantage of a set of defined key toxicants that are understood to drive the majority of human health risk posed by tobacco products: the HPHC list.

At this time, DNCS is continuing to develop increasingly more comprehensive approaches to (1) scientific evaluation of products and comparative health risks within tobacco product application reviews and (2) the management of tobacco product health risk as reflected in the criteria and approaches that are used to evaluate human health risk across all SE reviews. While this process will take into account previous approaches to risk assessment of complex mixtures, the majority of the work required in the continued development of a comprehensive approach for tobacco products will require framing the risk assessment thinking specific to the comparison of tobacco products. Specifically, the current approach requires:

1. A focus on HPHC increases and decreases that are analytically non-equivalent between the new and predicate products. Experience from tobacco product SE Report reviews has shown that the variation in an analytical method can produce apparent differences that are very likely to be spurious. It is critical that the determination of whether an HPHC increase or decrease is analytically non-equivalent be made by a chemistry reviewer from the Division of Product Science.
2. An understanding that HPHC measurements that are considered equivalent are, in fact, considered as part of a risk evaluation: they represent the component of health risk that does not change.
3. Use of qualitative or semi-quantitative analyses of HPHC data before quantitative risk assessments (QRAs) are evaluated.

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Application of a qualitative or semi-quantitative approach that focuses on HPHC increases and decreases can allow DNCS reviewers to come to a conclusion regarding the HPHCs without needing a quantitative approach in many cases.

Currently, DNCS review practice for HPHC comparisons between two tobacco products is as follows:

1. Reviewers should evaluate submitted HPHC data sets using a qualitative or semi-quantitative approach that does the following:
 - a. **Asks the question: can an HPHC increase be offset by any HPHC decreases that also occur in the HPHC data set?**
 - b. Considers both analytically non-equivalent HPHC increases and decreases.
 - c. Considers HPHCs that are analytically non-equivalent to contribute to bulk of the difference in cancer risk or non-cancer hazard between the two compared products.
 - d. Considers HPHC measurements that are analytically equivalent per the Chemistry discipline as equivalent for purposes of toxicological comparison between the two compared products. That is, the HPHC measurements are considered unchanged between the two compared products if the Chemistry discipline indicates that analytical HPHC measurements are equivalent.
 - e. Acknowledges that in HPHC comparison scenarios where there are only HPHC increases and no concomitant HPHC decreases, there is no way that a qualitative or quantitative risk analysis approach based on the same analytical data could succeed in establishing that the cancer risk or non-cancer hazard due to the HPHC changes is equivalent between the two compared products. Toxicology reviews of product applications should be direct about this fact.

2. In evaluating whether an HPHC decrease or several HPHC decreases can offset an HPHC increase (or several increases), the following considerations have emerged:
 - a. The toxicity endpoints of the analytically non-equivalent HPHCs are central to the toxicological comparison between two tobacco products. An HPHC decrease that has an endpoint different from that of an HPHC that is increased cannot offset the HPHC increase.
 - b. At this time, carcinogenic endpoints are considered equivalent. For example, an HPHC increase that evidence indicates raises liver cancer risk can be offset by a decrease in an HPHC that evidence indicates increases lung cancer risk. This approach will continue to evolve as risk assessment methods evolve and as DNCS continues to gain experience with other review pathways, tobacco products, and industry-conducted QRAs.
 - c. The analysis of non-cancer endpoints is more complicated than that of cancer endpoints. For example, the respiratory irritation of formaldehyde, cannot be offset by a decrease in an HPHC that is not a respiratory toxicant., For example, benzene might

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offset formaldehyde in terms of carcinogenicity, but as it is not also a respiratory toxicant, it cannot offset the respiratory effects of formaldehyde.

- d. Cancer slope or inhalation unit risk should be considered in the comparison of carcinogenic HPHC increases and decreases in concert with the magnitude of change. An increase in a carcinogenic HPHC that has a steep cancer slope may not be offset by a decrease in another HPHC that has a shallower cancer slope. However, the difference in cancer slope might be overcome by a difference in magnitude.
 - e. At this time, the IARC group of an HPHC versus another HPHC (e.g., group 1 versus group 2B) should not be pivotal to the evaluation of an HPHC comparison. FDA has evaluated the evidence of harm and potential harm for each of the HPHCs on the list prior to establishing the HPHC list; FDA continues to evaluate this evidence.
 - f. Because the CI smoking regimen yields are lower than the mouth level exposure of 86 – 97% of smokers,³ decreases of HPHCs measured under CI can offset increases in HPHCs as measured under the ISO smoking regimen; decreases in HPHC levels as measured by the ISO regimen cannot offset HPHC increases measured under the CI regimen.
 - g. It may be possible for the addition of a toxic ingredient to be offset by an HPHC decrease. For example, the addition of a small amount of carcinogenic defoamer might be offset by a decrease in a carcinogenic HPHC. In this case, the toxic ingredient is neither an HPHC nor an ingredient that is known to lead to an increase in one or more HPHCs and therefore cannot be evaluated by HPHC measurements.
3. If the qualitative evaluation of HPHC data indicates that there may be an increase in potential toxicity between the new and predicate products, then a QRA, if provided by the applicant, should be fully evaluated. The exceptions when a QRA should not be fully evaluated are as follows:
- a. Fatally flawed HPHC comparison: QRAs submitted to address situations where there are HPHC increases and no HPHC decreases that could be possibly offsetting. In this situation, any well-conducted QRA would simply reflect an elevated non-cancer hazard or cancer risk associated with the HPHC increases. The most common scenario occurs when a new product has HPHC increases in several high-potency HPHCs without any offsetting decreases in other HPHCs. Another scenario could be where there are several HPHCs increased and several decreased, however the increased HPHCs are primarily carcinogens and the decreased HPHCs are not on the HPHC list due to carcinogenicity. These decreased HPHCs are unlikely to decrease the cancer risk of the product.
 - b. Unnecessary QRAs: Although relatively rare, DNCS has also received QRAs where a QRA is not warranted to address the changes between the two tobacco products. In these situations, analytically non-equivalent HPHC decreases outweigh the analytically non-equivalent HPHC increases and a qualitative or semi-quantitative approach, indicating that HPHC decreases outweigh modest increases in HPHCs of lesser potency or magnitude, is more appropriate.

Conclusion:

The MRTP, PMT and SE application pathways all rely on comparisons between tobacco products to inform regulatory decisions. However, currently, this memorandum applies only to review of tobacco products through the SE pathway. This scope is due to (1) the extensive experience that DNCS has with product evaluations in the SE pathway and (2) the fact that the SE pathway is defined as a comparison of the new product to a distinct predicate product and whether the differences between the two cause the new product to raise different questions of public health. The applicability of this memorandum to MRTPAs and PMTAs will continue to be evaluated as DNCS gains additional experience with these application pathways.

The HPHC comparisons between two tobacco products are critical in determining whether the two products present users and non-users to similar health risk or whether one of the two products presents greater risk. This memorandum records recent changes in DNCS thinking on how to evaluate HPHC comparisons between two tobacco products, sets out some key criteria by which HPHCs are to be compared, and lays out some important directions for further evaluation. This process is evolving, with DNCS continuing to develop more comprehensive approaches to (1) scientific evaluation within tobacco product reviews of the health risks of a tobacco product and comparison of the health risks between tobacco products and (2) the management of tobacco product health risk as reflected in the criteria and approaches that are used to evaluate human health risk across toxicology reviews of SE Reports. While this process takes into account previous approaches to risk assessment of complex mixtures, the majority of the work required to develop a new comprehensive approach for tobacco products requires new thinking that is specific to the comparison of tobacco products and not necessarily applicable beyond this use. This approach will require a rapid assessment tool; a focus on HPHC increases and decreases that are analytically non-equivalent between the new and predicate products; an understanding that HPHC measurements that are considered equivalent are, in fact, accounted for in a risk evaluation; and use of qualitative or semi-quantitative analyses of HPHC data before quantitative risk assessments (QRAs) are evaluated. DNCS reviewers should apply a qualitative approach first in evaluating HPHC comparisons between tobacco products and only review quantitative risk information if a qualitative approach cannot be applied. In such cases, DNCS staff should review a submitted QRA to determine if it addresses the HPHC changes. However, if an applicant has provided a QRA to address HPHC changes between two tobacco products, and a DNCS reviewer conducted a qualitative evaluation of the submitted HPHCs that determines either that the QRA cannot address the HPHC changes or QRA is unnecessary for the evaluation of the HPHC changes, then the DNCS reviewer should use the qualitative analysis as a basis for their review conclusions and not focus on the QRA.

¹ EPA (U.S. Environmental Protection Agency). 2003. Framework for Cumulative Risk Assessment. EPA/600/P-02/001F. National Center for Environmental Assessment, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC

² ATSDR (2004). Guidance Manual for the Assessment of Joint Action of Chemical Mixture. Agency for Toxic Substances and Disease Registry. May 2004. Available at: <http://www.atsdr.cdc.gov/interactionprofiles/ipga.html>.

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³ Jackson et al, Tob Regul Sci. 2016 Jan 1; 2(1): 3–8. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4811367/>