THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JAN 08 2021

Mr. Henry J. Kerner
Special Counsel
1730 M Street, N.W., Suite 300
Washington, DC 20201

Dear Mr. Kerner:

This letter is in response to your referral of February 28, 2020, (OSC File No. DI-20-0372), requesting a review by the Department of Health and Human Services (HHS) of whistleblower allegations under 5 U.S.C. §1213, concerning the review of new tobacco product applications by U.S. Food and Drug Administration's (FDA's) Center for Tobacco Products (CTP), Office of Science (OS), Division of Nonclinical Science (DNCS).

On April 22, 2020, I referred the matter to the FDA to investigate and report on all of the allegations contained in the February 28, 2020 referral, specifically that DCNS had improperly relaxed its standards to speed its reviews, thus allowing potentially more harmful products to enter the market. This investigation and review was subsequently conducted by scientific and regulatory staff in FDA's Office of the Commissioner who were not involved in prior FDA decisions related to the substance of these allegations. Enclosed is the FDA report and transmittal letter from FDA's Chief Scientist, RADM Denise Hinton, which I have reviewed and am transmitting, pursuant to 5 U.S.C. § 1213(d).

Sincerely,

Alex M. Azar II

Enclosures

Review of Whistleblower Allegations

Office of the Commissioner

U.S. Department of Health and Human Services

U.S. Food and Drug Administration

December 16, 2020

Table of Acronyms

FDA: U.S. Food and Drug Administration

CTP: Center for Tobacco Products

CTP-IO: The immediate office of the Center Director

OS: Office of Science (within CTP)

DNCS: Division of Nonclinical Science (within OS)

HPHC: Harmful or potentially harmful constituent

NCM: Non-concur memo

OC: Office of the Commissioner

OSI: Office of Scientific Integrity (within OC)

SDR: Formal Scientific dispute resolution under either the SDR-SMG or SDR-ToPP

SDR-SMG: The agency-level Staff Manual Guide on scientific dispute resolution

SDR-ToPP: CTP's policy and procedures for resolving internal scientific disputes

SE: Substantial equivalence or substantially equivalent

QRA: Qualitative risk assessment

Review of Whistleblower Allegations

This review by the FDA's Office of the Commissioner, coordinated by the Office of Scientific Integrity, responds to a request from the Secretary to review certain whistleblower allegations described in a letter from the Office of Special Counsel (OSC referral) dated February 28, 2020 (OSC File No. DI-20-0372).[1] The allegations relate to the process adopted by FDA's Center for Tobacco Products for evaluating substantial equivalence applications for tobacco products, specifically the process for measuring and comparing harmful and potentially harmful constituents of tobacco products described in a memorandum issued on February 21, 2019 (the HPHC Memo).[2]

The OSC referral includes the following allegations:

1) The "qualitative or semi-[quantitative]" approach, as outlined in the HPHC Memorandum, is not based on the best available science.[3]

2) This "qualitative or semi-[quantitative]" approach can yield entirely different results than the quantitative approach, i.e., one approach might result in a product being approved for market while the other approach would not.

3) After several toxicology scientists, including the whistleblower, complained to CTP OS leadership about the issues outlined in this letter, DNCS leadership stopped sending those scientists SE product applications entirely.

4) DNCS's actions have effectively prevented those concerned toxicology scientists, including the whistleblower, from being able to invoke FDA's scientific integrity dispute process to raise, and possibly resolve, these issues internally.

To address the first two allegations, we convened an independent panel of experts to assess the relative merits of the two processes for evaluating and comparing HPHC levels in tobacco products and conducted a series of interviews with both managers and staff at CTP. Our review evaluates CTP management's rationale for the procedure outlined in the HPHC Memo in light of both the expert panel's assessment and CTP management's additional explanations for the revised approach. We also summarize the agency's plans to

[1] OSC Referral, Appendix 0.

[2] Appendix 1: "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" (February 21, 2019).

[3] Please note that the OSC referral uses the terminology "qualitative or semi-qualitative," but the HPHC Memo uses "qualitative or semi-quantitative" in describing the revised process for evaluating HPHCs. For the sake of simplicity and efficiency, this report refers to the process described in the HPHC memo—and thus the process challenged by the whistleblower—as "qualitative or semi-quantitative," notwithstanding the terminology in the OSC referral.

revise the HPHC Memo to clarify the criteria and stepwise process used to evaluate HPHCs when reviewing SE applications from both a regulatory and scientific perspective.

To evaluate the third and fourth allegations, we reviewed FDA and CTP policies and procedures related to resolving scientific disputes, reviewed relevant documents and communications between CTP personnel, and conducted a series of interviews with personnel at all levels involved in the underlying scientific disagreement to determine how CTP's approach to resolving the scientific disagreement in this matter worked in this case. This report describes our findings as well as steps the agency plans to take to improve and clarify the agency's methods for resolving scientific disagreements moving forward.

We have also considered, pursuant to the standard in 5 U.S.C. § 1213(d), whether the actions that form the basis of the allegations violate or appear to violate any law, regulation, or rule administered by FDA and failed to identify any such violations or the appearance thereof.

Summary of Findings

I. In response to the first allegation, we conclude that sound regulatory science supports the tiered approach described in the HPHC Memo for comparing HPHCs in SE applications but that revisions to the HPHC Memo are necessary to make the criteria and process for comparing HPHCs in the context of an SE application both more transparent and straightforward.

II. In response to the second allegation, we conclude that different regulatory decisions are possible when using the tiered approach described in the HPHC Memo, when compared to evaluation of a QRA, but that the tiered approach—as it was intended to operate and as we plan to revise the HPHC Memo to describe it—is more protective of public health in that it resolves uncertainty in favor of an NSE determination and thus represents the best available regulatory science to address SE applications in terms of both the regulatory standard at issue and agency resources.

III. In response to the third allegation, we find that OS/DNCS management did, in fact, postpone further review of certain SE applications implicated by the scientific dispute at issue and withheld assigning additional reviews to the toxicologists voicing scientific concerns, but we found no evidence that management took these actions for the purpose of preventing those toxicologists from elevating the underlying scientific disagreement within CTP.

IV. In response to the fourth allegation, we conclude that confusion stemming from ambiguity in CTP's written process for initiating the agency's process for formal scientific dispute resolution and a lack of experience in resolving scientific

disagreements of this type by CTP staff at all levels undermined CTP's efforts to resolve the scientific disagreement in this case in a timely and amicable manner, and we explain the actions FDA will take to improve and clarify the agency's approach to scientific disagreements moving forward.

I. Background

A. The HPHC Memo

On February 21, 2019, the Deputy Director for DNCS in CTP's Office of Science issued a memorandum setting forth a process to be used by toxicologists within that division for comparing harmful and potentially harmful constituents in two tobacco products to assist in evaluating whether one tobacco product is substantially equivalent to another.[4] As subsequently confirmed by the Director of CTP (CTP Director) in a decision described in more detail below, the principal intent of this memo was to assist the toxicologists in comparing HPHCs in a manner consistent with the definition of "substantially equivalent" or "substantial equivalence" at section 910(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (in relevant part):

> [T]he term 'substantially equivalent' or 'substantial equivalence' means, with respect to [a] tobacco product being compared to [a] predicate tobacco product, that the Secretary by order has found that the tobacco product (i) has the same characteristics as the predicate tobacco product or (ii) has different characteristics and the information submitted contains information . . . demonstrat[ing] that . . . the *product does not raise different questions of public health*.[5]

As directed by section 904(e) of the FD&C Act, FDA has issued a list of common chemicals or chemical compounds in tobacco products that cause harm or have the potential to cause direct or indirect harm in tobacco users or non-users.[6] In creating this list, FDA included:

> constituents that are toxicants, carcinogens, and addictive chemicals[;] . . . constituents that may increase the exposure to the harmful effects of a tobacco

[4] HPHC Memo.
[5] *See* Appendix 2, "CTP Response to Allegations in Whistleblower Complaint (OSC File No. DI-20-0372)" (Sep. 29, 2020) (CTP Director's Decision) at 4-5 (emphasis added).
[6] 77 Fed. Reg 20034, 20036 (April 3, 2012).

> product constituent by: (1) [p]otentially facilitating initiation of the use of tobacco products[,] (2) potentially impeding cessation of the use of tobacco products[,] or (3) potentially increasing the intensity of tobacco product use (e.g., frequency of use, amount consumed, depth of inhalation)[;] and "constituents that may enhance the harmful effects of a tobacco product.[7]

Section 910(a)(1) of the FD&C Act defines a new tobacco product as any tobacco product (including those products in test markets) that was not commercially marketed in the United States as of February 15, 2007 or any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the United States after February 15, 2007). One pathway for manufacturers to market a new product is to submit an application in accordance with section 905(j) of the FD&C Act (SE application) to seek an FDA determination of substantial equivalence to a predicate product. FDA has issued guidance recommending that applicants should include a list of all HPHCs and their levels in the new tobacco product and compare those levels to those in the predicate product.[8] FDA reviews the application and the accompanying report and supporting information in a manner:

> consistent with the requirements of sections 905(j) and 910 of the Act, i.e., to determine whether the new tobacco product is substantially equivalent to the predicate tobacco product. In addition to determining that the product is substantially equivalent, FDA must also determine that the new tobacco product is in compliance with the requirements of the Act before issuing an order under section 910(a)(2)(A)(i).[9]

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[7] *Id.* at 20034.

[8] "Guidance for Industry and FDA Staff: Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products," 8 (January 2011). FDA recommends manufacturers "report levels of all HPHC in tabular format, with a side-by-side comparison with the predicate tobacco product and, where applicable, to a grandfathered tobacco product. For tobacco products that are smoked (e.g., cigarettes), [the manufacturer] should report quantitative levels in smoke using both the International Organization for Standardization (ISO) and Canadian Intense smoking regimens. If an alternative to these regimens is used, [the manufacturer] should provide an explanation of why the alternative provides comparable results to the ISO and Canadian Intense regimens." *Id.* at 11.

[9] *Id.* at 6.

With respect to HPHCs in particular, the HPHC Memo explains:

> 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. . . . [The agency's published list of] HPHCs represent[s] 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.*[10]

The HPHC Memo sets out a process for staff to follow in comparing HPHCs in a new product to the HPHCs in a predicate product that includes using "a qualitative or semi-quantitative approach." The memo suggests—and our investigation confirmed—that the process described in the HPHC Memo replaced the typical process that DNCS toxicologists had used up until that point for comparing HPHCs in the two products: a full quantitative risk assessment or "QRA."[11] Based on our investigation, managers within both OS and DNCS (OS/DNCS managers or management) and the toxicologists asked to follow the process outlined in the HPHC Memo agree that a QRA is a peer-reviewed approach to comparing harmful substances in a complex mixture that would, in this context, involve accounting for the levels of all HPHCs in each of the two products, regardless of whether the HPHCs are deemed

[10] HPHC Memo at 1 (emphasis added).

[11] *See id.* at 2, citing 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; ATSDR (2004. Guidance Manual for the Assessment of Joint Action of Chemical Mixture. Agency for Toxic Substances and Disease Registry (May 2004). (http://www.atsdr.cdc.gov/interactionprofiles/ipga.html). As noted below, DNCS first started encouraging toxicologists to depart from a QRA in favor of a qualitative or semi-quantitative approach in late 2018.

analytically equivalent, and generating a report reflecting the relative toxicity of the two products.[12]

The HPHC Memo explains that part of the thinking behind it is to streamline SE assessments but clarifies that comparing HPHCs in tobacco products is an evolving discipline that requires innovation:

> 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.[13]

The HPHC Memo sets forth a stepwise process that walks toxicologists through the HPHC evaluation. The first step focuses the toxicologists on the "analytically non-equivalent HPHC increases and decreases," as identified by chemists based on whether the reported levels are analytically equivalent, and directs the toxicologists to evaluate whether "an HPHC increase

[12] As explained by the expert panel convened to assist the agency in evaluating the scientific disagreement in this matter, "[A] quantitative risk assessment approach relies on 4 steps: 1) hazardous chemical identification, 2) dose-response assessment, 3) exposure assessment, and 4) risk characterization. The quantitative risk assessment can provide an estimate of the risk of toxicity with the level of uncertainty for an exposure to a chemical or compound." Appendix 3, "RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP" (Jul. 31, 2020) (Expert Panel Report) at 2, citing, https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance, accessed 7/28/2020); *see also* Appendix 4, "Re: DNCS Memorandum: 'Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports'" (May 31, 2019) (May 2019 Appeal) at 4-5.

[13] HPHC Memo at 5.

[can] be offset by any HPHC decreases that also occur in the HPHC data set."[14] The first step also acknowledges:

> [I]n 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.[15]

The second step involves multiple directives, including:

- to evaluate "toxicity endpoints of the analytically non-equivalent HPHCs,"
- to consider carcinogenic endpoints as equivalent, regardless of the type of cancer risk (e.g. lung cancer risk considered the same as liver cancer risk);
- to offset non-carcinogenic endpoints only in comparison to the same type of non-carcinogenic (e.g. respiratory toxicants compared to other respiratory toxicants);
- to assess "[c]ancer slope or inhalation unit risk in the comparison of carcinogenic HPHC increases and decreases in concert with the magnitude of change";
- to consider groupings recommended by the International Agency for Research on Cancer not to be pivotal;
- to determine whether certain analytically non-equivalent HPHCs were measured through International Organization for Standardization smoking or the Canadian Intense smoking regimen and adjusting offsets accordingly; and
- to assess whether "the addition of a toxic ingredient to be offset by an HPHC decrease."[16]

[14] *Id.* at 3 (emphasis removed). As discussed in more detail below, in a decision ruling on a subsequent appeal by the concerned toxicologists, OS management acknowledged that the chemists referenced in the HPHC memo are also in OS but a different division: the Division of Product Science. *See* Appendix 5, "Concerns regarding DNCS's HPHC memo dated Feb. 21, 2019" (Dec. 13, 2019) (OS Appeal Decision) at 1.
[15] HPHC Memo at 3.
[16] *Id.* at 3-4.

The third step directs toxicologists to evaluate a QRA submitted by any applicant "if the qualitative evaluation of HPHC data indicates that there may be an increase in potential toxicity between the new and predicate products."[17] The HPHC Memo provides two exceptions to this general approach. The first is when the submission is "fatally flawed," i.e., when the submitted QRA includes only HPHC increases and "no 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.[18]

The other exception to conducting a QRA is an "[u]nnecessary QRA[]," i.e., when a qualitative or semi-quantitative approach is more appropriate because "the analytically non-equivalent HPHC decreases outweigh the analytically nonequivalent HPHC increases . . . , indicating that HPHC decreases outweigh modest increases in HPHCs of lesser potency or magnitude."[19]

B. The May 2019 Appeal

In a memorandum addressed to OS management and dated May 31, 2019 (the May 2019 Appeal), several of the toxicologists (the concerned toxicologists) challenged the HPHC Memo on several grounds.[20] In addition to arguing that DNCS managers had failed to adhere to good guidance practices at 21 CFR 10.115 in issuing the HPHC Memo, the May 2019 Appeal asserts

[17] *Id.* at 4. As further discussed below, CTP neither expects nor requires applicants to submit analysis reflecting a QRA, but many do. A key position of OS/DNCS managers is that applicants appear to do so in order to justify a finding of SE even when the basic HPHC levels might suggest that the new tobacco product is NSE.
[18] *Id.*
[19] *Id.*
[20] May 2019 Appeal. This report uses "the concerned toxicologists" to identify the employees within CTP's review staff in DNCS who individually or as a group challenged the methods contained in the HPHC Memo. Please note that, as we explain in more detail below, the May 2019 Appeal was not the first attempt by those concerned toxicologists to express disagreement with the qualitative or semi-quantitative approach.

that the concerned toxicologists do not find the "approach outlined in the HPHC Memorandum appropriate for the toxicology review of tobacco product application[s], and [that] thus [they] are not able to apply this memorandum to our toxicological evaluations."[21]

Citing scientific literature in support of its position, the appeal contends that the best scientific method for comparing the toxicity of two tobacco products is a QRA:

> The framework for cumulative human health risk assessments of complex mixtures, as first outlined in the 1983 NAS Report, provides a predictable scientific approach and consistency across regulatory agencies for evaluation of cumulative human health risk from chemical exposures. The standard QRA approach provides a systematic and transparent process to (1) determine the type of adverse effects that may be caused by a chemical (hazard identification), (2) determine the relationship between the magnitude of exposure to a hazard and the probability and severity of adverse effects (dose-response assessment), (3) determines the extent to which exposure actually occurs (exposure assessment), and (4) to combine the information from the preceding steps to reach a conclusion about the nature and potential magnitude of risk (risk characterization). Although this approach for evaluating potential human health risks from complex mixtures is not specific to any given type of exposure or regulated products, it has broad applicability and has been widely adopted by federal agencies, including FDA, to support a wide array of regulatory decision making.[22]

The May 2019 Appeal cites both a long-established precedent within DNCS—estimated as more than six years—for using a QRA and the discussions and consensus at a public meeting held by CTP, entitled "Risk Assessment of Tobacco Products: A Public Workshop."[23] The appeal further states, "The HPHC Memorandum does not mention any new information or scientific data to explain why the change in DNCS policy related to the use of QRA in the evaluation of HPHCs is supported by the best available science."[24] The appeal maintains that the HPHC

[21] *Id.* at 1. As further discussed below, our investigation disclosed that the concerned toxicologists opted to use 21 CFR 10.115(o) as a vehicle to elevate the scientific disagreement between them and DNCS managers to OS management for reasons related to their understanding of the channels available to them for such elevation.
[22] *Id.* at 4-5 (internal footnotes omitted).
[23] *Id.* at 5; *but see* CTP Director's Decision at 6 (stating that DNCS had used a QRA for eight years).
[24] May 2019 Appeal at 6. In support of its position that DNCS has long-conformed to principles consistent with a QRA, the appeal also cites a memorandum issued by DNCS in 2017 that outlines the process for evaluating

Memo does not rely on any scientific literature or other references—or indeed any meaningful scientific rationale—to support its position that the qualitative or semi-quantitative approach is an appropriate form of analysis for comparing two tobacco products to evaluate substantial equivalence.[25] Finally, the May 2019 Appeal challenges many specific aspects of the HPHC Memo, especially its directive to look at only the analytically non-equivalent HPHCs in evaluating toxicity, as opposed to assessing the totality of the submitted information with an emphasis on "health-based equivalence margins."[26]

On December 13, 2019, OS management issued a decision (the OS Appeal Decision) on the May 2019 Appeal by, among other things, upholding the approach for evaluating HPHCs outlined in the HPHC Memo.[27] In addition to rejecting the May 2019 Appeal's position that the HPHC Memo violated the agency's good guidance practices at 21 CFR 10.115, the OS Appeal Decision finds that the arguments raised in the appeal "are not supported":

> The fact that the QRA approach has been successfully used for other scientific purposes and even in some prior SE application reviews does not mean it is necessarily the only acceptable or the most appropriate method for use in review of SE reports. Also, it is not necessary for DNCS management to demonstrate the standard QRA approach is not scientifically appropriate prior to implementing a new, alternative review process.[28]

The decision characterizes the concerned scientists' position in the appeal—that DNCS should evaluate HPHCs using a comprehensive, validated methodology that has wide-ranging support among the scientific community—as a "viewpoint" that does not account for the full range of regulatory considerations within CTP and DNCS:

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carcinogenic HPHCs. See "SE Review: Evaluating Carcinogenic HPHC Increases and Assumption of Linearity for Low Dose Extrapolation" (Oct. 27, 2017) (https://www.fda.gov/media/124666/download). *Id.* at 3.

[25] *Id.* at 8.

[26] *Id.* at 8-11. The appeal also includes several appendices, including a chronology of how the scientific disagreement played out within DNCS. *See Id.* at 23-25, Appendix C.

[27] OS Appeal Decision

[28] *Id.* at 2-3

> Your viewpoint reflects a preference to perform the most comprehensive evaluation in all circumstances. Your viewpoint does not appear to reflect a consideration of how the data needed for regulatory review and comparison of the health risks between two tobacco products in an SE report is uniquely different than what is needed for a standard cumulative human health risk assessment of complex mixtures. This viewpoint also does not consider the Agency's need to manage programs and resources to best benefit our public health mission. Indeed, Agency leadership has a responsibility to manage regulatory programs that are based on sound science, the intent of the law, alternative approaches, and the efficient use of resources to effectively address regulatory issues and protect public health. It is proper for DNCS management to explore and determine whether a regulatory review decision can be adequately supported with less than the "comprehensive" data that is generally used for cumulative human health risk assessments of complex mixtures.[29]

The decision elaborates, "SE regulatory review does not require comprehensive, cumulative risk assessment of each tobacco product (e.g., over 7000 compounds in tobacco smoke), but rather comparison of selected HPHCs between two products (the predicate and new tobacco product) to address a specific regulatory standard."[30]

The OS Appeal Decision emphasizes that CTP has an established list of HPHCs and that it is now the responsibility of chemists in the Division of Product Science to determine whether HPHCs in the new and predicate product are "analytically equivalent."[31] The decision asserts that the HPHC Memo appropriately explains those key considerations by focusing on the need for "'a rapid assessment tool" that "focus[es] on HPHC increases and decreases that are analytically non-equivalent between the new and predicate products [and] an understanding that HPHC measurements that are considered equivalent are, in fact, accounted for in a risk evaluation.'"[32] The OS Appeal Decision asserts that "[i]nformation in [the May 2019 Appeal] dwells on concern with not using the QRA[] but *does not demonstrate the new approach is*

[29] *Id.*
[30] *Id.*
[31] *Id*.
[32] *Id*., quoting the HPHC Memo at 5.

inappropriate for the intended use."[33] The OS Appeal Decision concludes that the HPHC memo "is a well-considered and appropriate management directive that DNCS staff are expected to follow" and that the HPHC Memo helps DNCS conserve agency resources and "meet FDA performance goals," while at the same time protecting public health and supporting "sound and timely regulatory decisions."[34]

C. The OSC Referral

By letter dated February 28, 2020, and addressed to Secretary Alex M. Azar II, the U.S. Office of Special Counsel referred to the U.S. Department of Health and Human Services for investigation certain disclosures by a whistleblower with respect to a scientific disagreement within CTP. The disagreement described in the referral centers on the scientific disagreement between OS/DNCS managers and the concerned scientists as reflected in the HPHC Memo, the May 2019 Appeal, and the OS Appeal Decision—i.e., the appropriate approach to evaluating HPHCs in the context of determining whether a tobacco product intended for market is substantially equivalent to a predicate product currently on the market. By letter dated April 22, 2020, Secretary Azar delegated his authority in this matter to FDA to conduct a full and objective investigation of the allegations in the OSC referral. Although the OSC referral initially directed a response by April 28, 2020, FDA requested several 60-day extensions, resulting in a current response date of December 21, 2020.

As noted above, in evaluating the allegations in the OSC referral, FDA opted to bifurcate its investigation. For those allegations relating directly to the scientific disagreement between the concerned toxicologists and OS/DNCS managers (i.e., the first two allegations in OSC's referral), FDA convened a panel of independent scientific experts with experience in either or

[33] *Id*. (emphasis in original via underline).
[34] *Id*. at 4.

both toxicology and public health concerns related to tobacco products. The purpose of the Expert Panel was to provide written advice to the CTP Director, who would then render a decision for the Center on the scientific issues from a regulatory perspective. The Office of the Commissioner would also have access to the same written advice and the experts themselves in evaluating CTP Director's decision in generating OC's report.

The remaining allegations (i.e., the third and fourth allegations in the referral) relate to how CTP attempted to handle the scientific disagreement once the concerned toxicologists began to challenge OS/DNCS management's preferred approach to evaluating HPHCs in SE applications. To investigate those allegations, OSI staff: (1) interviewed CTP personnel who either were involved in the scientific disagreement or had knowledge of the events surrounding the disagreement, (2) reviewed key aspects of the administrative record for SE applications at issue, and (3) examined emails provided on request by the interviewees.

1. The Expert Panel

In convening the Expert Panel, OSI identified and selected independent experts who it believed could provide meaningful advice on the public health impact of the approach for assessing HPHCs at the center of the scientific disagreement. Taking into account two nominations from the CTP Director based on his experience working with scientific experts from outside FDA who were familiar with the public health effects of tobacco products, OSI initially selected five experts from outside CTP—(1) one toxicologist from FDA's National Center for Toxicological Research, (2) one toxicologist from the Office of the Commissioner, (3) two scientific experts from the Centers for Disease Control who had significant experience in evaluating the public health impact of tobacco products; and (4) and one scientific expert from the National Institutes of Health who had comparable experience to that of the CDC experts. In

the process of providing background materials to the panel, OSI asked the members to evaluate those materials to assess whether their background or previous collaborations might create an appearance of a conflict of interest—specifically any prior affiliations or experience that could cause a reasonable person to question his or her objectivity as a scientist providing advice to CTP in this matter. After the toxicologist from the Office of the Commissioner volunteered that she had worked directly with the whistleblower on toxicological standards related to the scientific disagreement at issue in this matter, OSI granted her request to recuse herself from the panel, thereby reducing the size of the panel from five members to four.

On June 5, 2020, via email, the OSI Director asked the Expert Panel to evaluate the first two allegations in the OSC referral and provided materials related to the scientific disagreement at CTP for purposes of that evaluation. The materials comprised the OSC Referral, the HPHC Memo, the May 2019 Appeal, and the OS Appeal Decision. The OSI Director explained the expectation that the panel would collaborate on reviewing the materials provided and any scientific literature deemed relevant and to work together—via phone calls, meetings, and emails—to generate a written memorandum reflecting the views and advice of the group on the two scientific issues, including dissenting or supplemental opinions. The email provided an initial deadline of July 6, 2020, for finalizing the written advice, but the OSI Director granted extensions requested by the Expert Panel, resulting in an ultimate deadline of July 31, 2020.

Over the course of close to two months, with the OSI Director functioning as a facilitator, the Expert Panel met multiple times and worked collaboratively, via email and access to a shared document platform, to evaluate the two scientific issues. In response to requests from the Expert Panel, the OSI Director provided additional materials to supplement those initially provided,

including:

- a link to FDA's list of HPHCs;[35]
- a link to CTP's reviewer guides;[36]
- three guidance documents issued by CTP concerning HPHCs and substantial equivalence; [37]
- CTP's proposed rule on "Content and Format of Substantial Equivalence Reports; Food and Drug Administration Actions on Substantial Equivalence Reports";[38] and
- portions of two sample SE applications, including reviews by DNCS toxicologists—one of which evaluated HPHCs using the qualitative or semi-quantitative approach and the other of which evaluated HPHCs using a QRA.

For the purposes of one meeting, the OSI Director also invited a guest speaker to participate in the meeting. The guest speaker was a senior toxicologist from FDA's Center for Food Safety and Applied Nutrition, and she provided insights on how her Center evaluates toxicity from a safety standpoint, along with fielding questions related to those evaluations and the exercise of professional judgment in such evaluations.

On July 31, 2020, the Expert Panel finalized its written advice and issued it via email to the OSI Director, who immediately forwarded it to the CTP Director.[39] The Expert Panel Report

[35] https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list.
[36] https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/reviewer-guides-and-scientific-policy-memoranda-about-fda-review-tobacco-product-applications.
[37] "Demonstrating the Substantial Equivalence of a New Tobacco Product: Responses to Frequently Asked Questions (Edition 3)" (December 2016), "Guidance: Section 905(j) Reports: Demonstrating Substantial Equivalence for Tobacco Products" (January 2011); "Guidance: "Harmful and Potentially Harmful Constituents" in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act" (August 2016).
[38] 84 Fed. Reg. 12740 (April 2, 2019).
[39] Expert Panel Report.

acknowledges "that traditional quantitative risk assessment methodologies were not developed for tobacco products, which possess distinct regulatory challenges" and "that there are potentially other scientific approaches to compare the risk of toxicity of two tobacco products in addition to [a QRA]."[40] But the report cautions, "[T]his does not mean that the 'qualitative or semi-quantitative approach' is necessarily the ideal one for FDA-CTP because additional methods can be needed to assess the risk of toxicity of the chemicals or compounds on the list of HPHCs."[41]

The Expert Panel Report observes that "management elected to modify the prior peer-reviewed quantitative risk assessment approach in favor of a unique and unfamiliar 'qualitative or semi-quantitative approach.'"[42] The report characterizes the qualitative or semi-quantitative approach as a "novel" three-step process:

> whereby reviewers focus specifically on 1) HPHC increases and decreases that are analytically non-equivalent between the new and predicate products, 2) whether the risk of toxicity from an identified increase in HPHC can be offset by a decrease in another HPHC, and 3) if there is evidence for an increase in potential toxicity from an HPHC, a [QRA] should be conducted.[43]

While qualifying that "the performance of the above approach in the assessment of HPHCs is unknown to us," the Expert Panel Report concedes, "[I]t also seems reasonable that there will be circumstances that do not need a quantitative assessment, such as the instance when an application is fatally flawed."[44] The report deems it "critical to consider that there can be differences between the conclusions drawn from quantitative and semi-quantitative approaches .

[40] *Id.* at 2.
[41] *Id.*, citing Leong, et al, 2013.
[42] *Id*.
[43] *Id.*
[44] *Id.* 2-3.

. . because these approaches can lead to varying decisions, depending on the chemical or compound under assessment."[45]

The Expert Panel Report emphasizes that one distinction between a QRA and the qualitative or semi-quantitative approach is that the former quantifies the difference between two tobacco products but that the latter is more binary in that it focuses on whether, in fact, there is a difference.[46] The report questions whether such a binary approach will produce consistent results, without additional, more transparent criteria:

> When a difference between two products is apparent, such as toxicity to the heart versus toxicity to the liver, the above approaches yield the same decision. However, when the difference between two products is not apparent because they are similar, such as carcinogens of different potency, the quantitative approach can provide information on the amount of "risk of cancer" for the two products. The difference in the "risk of cancer" between two products can be more (or less) than the expectation based on the qualitative assessment. It is important to specify the question about the chemical or compound under review.[47]

The Expert Panel Report notes that the qualitative or semi-quantitative approach "appears to rely solely on the judgement of the subject matter expert and impressions of FDA-CTP reviewers as opposed to quantifiable standards or criteria[,] even when these comparisons are complex, such as considering multiple and potentially offsetting HPHCs."[48] The report stresses that "more specific and transparent guidance to FDA-CTP reviewers is needed to ensure consistent and effective decisions that reduce population harm caused by the use of tobacco products."[49]

The Expert Panel Report concludes with a series of six recommendations to CTP.[50] The report opens the first of its recommendations with a statement that "[t]he qualitative or semi-

[45] *Id.* at 3 (internal citations omitted).
[46] *Id.* at 4.
[47] *Id.* at 3.
[48] *Id.*
[49] Id. at 3-4.
[50] *Id.* at 4.

quantitative approach . . . lacks sufficient detail and guidance to be enacted as a scientific methodology in its current form."[51] The report provides five specific examples:

a. Lack of methodology for assessing non-cancer chemical hazards
b. Lack of methodology for comparing cancer risks of different HPHCs using a quantitative analysis
c. Lack of methodology of how to examine HPHCs as a mixture
d. Lack of methodology for comparing risks of different organs
e. Failure to demonstrate a systematic review of risk analysis methodologies for application to HPHCs and the decision-making process.[52]

The first recommendation further cautions, "In the opinion of the panel, the process needs to have clear decision rules which guide the review and dictate the integration of the 'qualitative or semi-quantitative' evaluation with quantitative risk assessment. These decision rules should be added to the review process to ensure adequate protection of public health."[53] The third recommendation likewise suggests that CTP "develop and communicate standardized and objective criteria for deciding when a [QRA] should be conducted in a collaborative manner that includes CTP management and reviewers."[54] The remaining recommendations reflect additional suggestions from the Expert Panel regarding the development of procedures and other techniques, including training, to help ensure collaboration and consistency in scientific decision-making.[55]

2. CTP Director's Decision

On August 17, 2020, after receiving the Expert Panel Report from OSI, the CTP Director forwarded the report, along with four directed questions, to the OS Director to provide

[51] *Id.*
[52] *Id.* (all direct quotations).
[53] *Id*.
[54] *Id*.
[55] *Id*.

OS/DNCS management an opportunity for review and feedback.[56] On August 31, 2020, OS/DNCS management responded to the Expert Panel's written advice and six recommendations.[57] Of particular note, OS/DNCS management acknowledges in its response that the qualitative or semi-quantitative approach is not the ideal scientific process for comparing HPHCs in one product to those in another:

> From a purely scientific approach, I agree that a fully quantitative approach to evaluate HPHC differences between new and predicate products is ideal. However, as regulatory scientists, OS staff must consider practicality and public health impact of our decisions in context of a rigorous scientific standard. For the first eight years of the SE program, OS relied on a fully quantitative approach. However, over that time span, OS staff came to recognize the fully quantitative approach was unnecessarily burdensome to FDA and applicants and didn't impact public health in a meaningful way. Therefore, as the SE program evolved, OS staff gained a better understanding of HPHC data in SE Reports and recognized that the tiered approach in the memo allows a decision that aligns with our public health goal. FDA and other regulatory organizations (e.g., EPA) often use tiered approaches to scientifically evaluate products. Therefore, I believe the approach in the memo is scientifically sound.[58]

The response from OS management further notes that the HPHC Memo "does standardize the approach to assessing HPHC differences between new and predicate products" and that "the criteria in the memo are as objectives as possible based on our current experiences."[59]

On September 29, 2020, after reviewing the Expert Panel Report, the OS management's response, and other key documents, the CTP Director issued a decision on behalf of the Center.[60] The CTP Director's Decision concludes that the OS/DNCS management did not "err[] in

[56] CTP Director's Decision, at 64. The four questions were as follows: (1) "Are there relevant materials or information that the expert panel may not have been aware of, that should be considered?" *Id.* (2) "Has OS already implemented any policies or procedures that address recommendations made by the expert panel?" *Id.* (3) "What is the role of OS's experience with previous SE reviews in shaping how OS currently evaluates HPHCs?" *Id.* and (4) "Do you have any high-level recommendations with respect to how CTP should address the panel's recommendations both in the short- and long-term?" *Id.*

[57] *Id.* at 66.

[58] Appendix 6, "OS Response to the Scientific Panel Report" (OS Management Response) at 1.

[59] *Id.* at 2.

[60] CTP Director's Decision at 1-4.

changing the toxicological review process in 2019 to include a qualitative or semi-quantitative approach":

> I believe this new approach was informed by eight years of experience with the tobacco SE program, including reviewing over 7000 SE submissions, and uses the best available science for a regulatory science approach to "substantial equivalence" consistent with what is done across FDA. I also believe the Office of Science has implemented processes and procedures to ensure transparency and consistency across reviews and minimize the risk of error. Further, I believe the new approach makes the best use of limited resources while maintaining focus on protecting public health.[61]

With respect to the first allegation in the OSC referral regarding whether the qualitative or semi-quantitative approach described in the HPHC Memo constitutes the best available science, the CTP Director's Decision finds that the standard for "substantial equivalence" in section 905(j) of the FD&C Act does not require a more comprehensive scientific analysis.[62] In support of this finding, the CTP Director's Decision focuses on the statutory provision's language regarding whether the products "raise different questions of public health" and notes OS management's view that the "'data needed for regulatory review and comparison of the health risks between two tobacco products in an SE report is uniquely different than what is needed for a standard cumulative health risk assessment of complex measures.'"[63] The decision further states that "the differences include a defined list of toxicants of interest and the need for a relative comparison between two products."[64] In addition, the decision determines that the "best available science" does not always equate to the best regulatory science for product reviews at CTP:

> What constitutes the "best available science" in the unique SE regulatory setting for oversight of tobacco products, where the relative risk of a defined set of

[61] *Id.* at 4
[62] *Id.* at 4-5.
[63] *Id.* at 5, quoting OS Appeal Decision at 3.
[64] *Id*.

known toxicants is required, may be different than the "best available science" for calculating the cumulative human health risk of a complex mixture.[65]

The CTP Director's Decision elaborates on that principal conclusion in several key ways. First, it compares the experience of the OS leadership and the Expert Panel and points out that, in contrast to the panel, OS leadership has had eight years of experience in evaluating HPHCs and has learned through experience that "'OS staff were spending a lot of time doing fully quantitative assessments of HPHC data when it was obvious that the differences were not a public health concern.'"[66]

Second, the CTP Director's Decision notes that the Expert Panel did not have access to "materials and information . . . that contribute to transparency in the review process" and that eliminate the CTP Director's concerns in this regard.[67] The decision cites as examples "reviewer guides, weekly meetings involving all staff who work on SE reviews, and a recently-launched OS-wide SE training program [that] is recorded so staff can review again and to train new staff coming onboard."[68]

Third, the CTP Director's Decision maintains that there are additional processes in place within OS and CTP "to ensure that SE review decisions are aligned with the statutory standards."[69] The decision cites, *inter alia*, "[m]ultiple reviewer guides and other specific training materials designed for specific roles" and "[a] defined process for reviewer agreement that aligns with the process used across FDA" and that involves requiring reviewers to "document their conclusions, including any disagreements with conclusions made by subordinate

[65] *Id.*
[66] *Id.* at 6, quoting OS Management Response at 2.
[67] *Id.* at 7.
[68] *Id*.
[69] *Id.* at 8.

staff."[70] The CTP Director's Decision notes that the Expert Panel was "likely not aware" of many of these practices and processes.[71] The decision specifically concedes that no regulatory process can eliminate all inconsistencies or errors in rendering a regulatory decision such as whether two products are substantially equivalent.[72] It further notes, however, that there are agency channels available to applicants to challenge incorrect decisions and that the risk of allowing a more dangerous product on to the market is low and could result from other shortcomings in the regulatory process, such as permitting an applicant to choose the predicate on which it wishes to rely.[73]

Fourth, the CTP Director's Decision again observes that OS managers have a responsibility to ensure that agency resources are used efficiently in a manner consistent with science, public health, and the law:

> [OS leadership has] "a responsibility to manage regulatory programs that are based on sound science, the intent of the law, alternative approaches, and the efficient use of resources to effectively address regulatory issues and protect public health." * * * After years of experience with reviewing SE applications, DNCS leadership developed and implemented a new approach to reviewing HPHC data. Based on that experience, this new approach more efficiently uses reviewer time by providing[] * * * "a rapid assessment tool."[74]

The decision further stresses:

> "FDA senior leaders regularly look for opportunities to streamline processes and policies to improve efficiency, conserve resources, and develop alternative approaches that utilize the minimum amount of information necessary to adequately address the issue and render regulatory decisions within appropriate timeframes."[75]

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[70] *Id*.
[71] *Id*. As noted in the description of the Expert Panel's Review, OSI did make some, but not all, of those processes available to the Expert Panel and worked with the panel to help ensure it understood the nature of the toxicology review and its purpose in the larger scheme of the decision being made.
[72] *Id*.
[73] *Id*. at 8-9.
[74] *Id*. at 9, quoting OS Appeal Decision at 3 and HPHC Memo at 6, respectively.
[75] *Id*. at 9-10, quoting OS Appeal Decision at 4.

Finally, the CTP Director's Decision concludes by laying out the Director's plans moving forward with respect to ensuring both an appropriate pathway for resolving scientific disagreement within OS and transparency in the scientific and regulatory criteria that reviewers are expected to apply in reviewing SE applications:

> I will ask the OS Director to ensure that CTP's Ombudsman provide training at least twice a year to OS staff on FDA's scientific dispute resolution process to ensure CTP scientists know the process for raising scientific concerns related to review processes and decisions. I will also ask the OS Director to ensure that staff are aware of how to raise disputes that are not covered by the scientific dispute resolution process. * * * In addition, I will direct OS leadership to reinforce the importance of training, collaboration and transparency in decision-making to all supervisors and managers. I have also requested that OS leadership provide to me, twice a year, an update on any formal or informal scientific disputes and how they were resolved.[76]

3. The CTP Addendum

By email dated October 2, 2020, the Office of the Commissioner sought additional information from the CTP Director with respect to the scientific rationale underlying the qualitative or semi-quantitative approach described in the HPHC Memo. On October 13, 2020, the CTP Director responded with a memorandum (CTP Addendum) that provides some additional insights into the rationale underlying the qualitative or semi-quantitative approach and answers a series of questions posed in the email seeking the response.[77] The CTP Addendum frames the purpose of the memorandum as an effort "to provide additional information to explain how the evolution of the toxicology risk assessment to a qualitative or semi-quantitative approach remains protective of public health."[78]

[76] *Id*. at 10-11.
[77] Appendix 7, "Addendum to CTP Response to Allegations in Whistleblower Complaint (OSC File No. DI-20-0372)" (Oct. 13, 2020) (CTP Addendum).
[78] CTP Addendum at 1.

As to the underlying scientific rationale, the CTP Addendum states that the SE review process "ordinarily includes a scientific review by several disciplines, including engineering, toxicology, chemistry, and behavioral pharmacology to determine if the differences between the two products raise different questions of public health" but emphasizes, "The toxicology review portion of SE review is an important component because it helps determine if the new tobacco product presents more or less health risk than a predicate product."[79] The CTP Addendum relates that, based on "experience completing thousands of SE reviews and with input from staff," OS management issued the HPHC Memo to enable toxicologists "to come to a conclusion regarding the HPHCs without needing a quantitative approach" for many applications and thus to forgo evaluating applicants' efforts at a QRA submitted in support of such applications.[80] The CTP Addendum then provides some illustrative examples.[81]

The CTP Addendum also answers the series of specific questions posed by the Office of the Commissioner.[82] First, in response to a question about whether toxicologists are expected to

[79] *Id*.
[80] *Id*. at 1-2.
[81] *Id*. at 2-3.
[82] *Id*. at 3-4. The questions were as follows: "The HPHC memo acknowledges that, after application of the qualitative or semi-quantitative risk assessment, there are circumstances in which the a full QRA will be appropriate. Is a full QRA always appropriate if applying the qualitative or semi-quantitative risk assessment is inconclusive? If so, how are reviewers expected to determine inconclusiveness? Does inconclusiveness turn exclusively on whether the qualitative or semi-quantitative risk assessment demonstrates that substantial equivalence is a close call in the reviewer's judgment?"; "Is there a way of weighing or tiering the HPHCs in a manner consistent with the more qualitative approach that would enable a toxicologist to determine whether a full QRA is necessary when there are some increases and some decreases in analytically non-equivalent HPHCs? (In other words, are there certain HPHCs that CTP views as far more problematic than others, e.g. Formaldehyde?) If not, is it possible to provide additional criteria that would assist a toxicological reviewer in determining whether a full QRA is necessary beyond what is already in the HPHC memo? For example, is there a way to further explain how non-analytically equivalent HPHCs are offset in terms of carcinogenicity, toxicity, and organ affected or how they might be grouped for such a purpose?"; "Do you have any concern regarding the cumulative effect of the differences in analytically equivalent HPHCs when the value amounts are based on averages involving multiple smoke tests?"; and "Are there any additional materials provided to reviewers through training or otherwise that: (a) provide additional instruction with respect to how to apply the qualitative or semi-quantitative risk assessment or (b) shed light on how that assessment in combination with other disciplines and analysis adequately identifies products that raise different questions of public health?" *Id.*

exercise their own judgment in determining whether a QRA is necessary, the addendum clarifies that CTP reviewers are always expected to exercise their own judgment—even when evaluating a QRA—and that there are processes in place to ensure that the judgment rendered is consistent across a wide range of applications:

> CTP strives to have as much clarity and transparency in the product review process as possible[;] however, in all cases, toxicology reviews are based on the reviewers' judgment. This judgment is informed by training, experience, and collaboration with other subject matter experts. Even with the full QRA, toxicology reviewers still need to use their judgment in assessing the quality of the QRA and the outcomes. To date, CTP has not received any QRAs that would be considered complete and accurate. The QRA provides additional information to the reviewer if the reviewer feels the qualitative or semi-quantitative approach has not been conclusive, but the QRA does not provide a definitive answer.
>
> OS has instituted a system to help ensure the SE reviews are consistent, accurate, and comprehensive. This involves the review of each analysis by, at a minimum, the reviewer's Team Lead, the Branch Chief, and a member of OS's senior management. This process ensures that the toxicology reviews, as well as the other scientific discipline reviews, are not subject to one reviewer's judgment. There are also regular meetings of the toxicology reviewers to discuss issues that have arisen during reviews to ensure consistency across reviews.[83]

Second, in response to specific questions about how OS might further refine the criteria in the HPHC Memo, the CTP Addendum states:

> For SE reviews, toxicants identified as harmful or potentially harmful constituents (HPHCs) are categorized based on the outcome as either carcinogenic or non-carcinogenic. Within these categories, CTP does not see a scientific basis to rank toxicants as more or less "problematic." CTP does not group the toxicants based on the end organ effected because toxicants can impact more than one organ.[84]

Third, in response to a question regarding whether there is "any concern regarding the cumulative effect of the differences in analytically equivalent HPHCs when the value amounts are based on averages involving multiple smoke tests," the addendum answers "No," and explains that the averages are the best way to capture the variation in tobacco products:

[83] *Id*. at 3.
[84] *Id*. at 4.

> Because tobacco products are agricultural products, there can be natural variability within a specific product (for example, twenty cigarettes in a single pack can vary in toxicant levels). Increasing the number of measurements, and using the average value, is the best way to account for this variability in individual products.[85]

Finally, the CTP Addendum responds to a question about whether there are any supplementary materials providing additional instruction to reviewers on how to evaluate HPHCs or shedding light on how the HPHC Memo might function alone or in combination with other types of scientific evaluations within CTP.[86] The addendum declines to provide any specific examples and points in general to training given to reviewers and supervisors and the organizational structure within OS for rendering decisions on SE Applications:

> OS has established training on the qualitative or semi-quantitative approach for reviewers that is intended to provide clarity on the use of the qualitative or semi-quantitative approach, including when the approach is not sufficient and reviewers need to consider the QRA in their determination. OS provides this training on an ongoing basis, including when new staff are brought on board and when questions regarding the topic arise. Team Leads have also been trained so that they in turn can provide additional training to their team members, as needed.
>
> As described above, toxicology is one review discipline that is a part of the SE premarket review process. The toxicology reviewers decide on whether or not there are different questions of public health from a toxicological point of view. Every SE application has a Technical Project Lead (TPL), who is the OS staff member who looks at the outcomes of all of the scientific discipline reviews and determines whether the new product raises different questions of public health.[87]

4. Further Discussions with OS Managers

After receiving the CTP Addendum, the Office of the Commissioner reached out to the CTP Director to convey that the addendum had not cleared up several points of confusion for the investigative team—in light of what the team had learned through interviews with the concerned

[85] *Id*.
[86] *Id*.
[87] *Id*.

toxicologists and its review of the administrative record for this matter, including the HPHC Memo itself, the Expert Panel Report, and the CTP Director's Decision. With encouragement from the CTP Director, representatives from the Office of the Commissioner had a series of discussions with OS managers to gain a better understanding of their thinking for the HPHC Memo. During these discussions, we realized that the underlying scientific rationale and resulting implications for CTP's review of SE applicants and the outcomes for those applications differed from our initial interpretation of the HPHC Memo, as well as the Expert Panel's and concerned toxicologists' apparent understanding of that memo. The Office of the Commissioner then began collaborating with the OS managers to plan revisions to the HPHC Memo that would not only make the memo more consistent with the reasoning undergirding it but also more transparent and straightforward.

II. Allegations Related to the Substance of the Scientific Disagreement at CTP

This section responds to the first two bulleted allegations in the OSC referral, namely those allegations relating directly to the substance of the scientific disagreement between OS management and the concerned toxicologists. According to the OSC referral, the whistleblower alleged that "DNCS leadership has relaxed its standards in an effort to speed up reviews of new tobacco product applications and that "[a]s a result it has allowed potentially more harmful products to enter the market." [88] In response to that basic allegation and the more detailed allegations in support, OSC requested that Secretary Azar investigate, *inter alia*: (1) whether "[t]he qualitative or semi-qua[nt]itative' approach, as outlined in the HPHC [Memo], is not based on the best available science and (2) whether the qualitative or semi-quantitative approach

[88] OSC Referral at 1.

"can yield entirely different results than the quantitative approach, *i.e.*, one approach might result in a product being approved for market while the other approach would not." [89]

As further described in the OSC referral, the allegations from the whistleblower relate not only to the substance of the scientific disagreement but also to the thinking behind altering CTP's approach to evaluating HPHCs in the context of reviewing SE applications. In addition to alleging that the change in approach was motivated by "an effort to speed up reviews," as noted above, the whistleblower alleged to OSC that, in late 2018, "DNCS management became concerned about an anticipated increase in e-cigarette premarket authorization applications" and that, as a result, "DNCS management . . . began pushing scientists to adopt a faster, and less rigorous, 'qualitative or semi-qua[nt]itative' approach to reviewing SE applications."[90]

The whistleblower characterized this new approach as "more akin to 'eyeballing it.'" [91] He explained that, in contrast, the approach used by CTP before adopting the qualitative or semi-quantitative approach in 2018, toxicologists would focus on a quantitative analysis in comparing HPHCs between the new product and the predicate:

> Scientists used a quantitative approach to measure [HPHCs] when comparing tobacco products on SE applications and that . . . the reviewing scientist quantified the specific concentration and toxicity level of each HPHC, like formaldehyde or acetaldehyde, for example, using mathematical equations to evaluate cancer risks and noncancer hazards, like respiratory illness, for both the new and predicate tobacco product. [92]

The whistleblower elaborated that this previous mathematical approach "is based on the best available science and consistent with other federal regulatory agencies', [and] other [FDA] components[']. . . , approach to measuring [] human health risks created by . . . the chemical

[89] *Id*. at 1-2.
[90] *Id*.
[91] *Id*. at 2.
[92] *Id*. at 3.

compounds found [in tobacco products]." [93] As set forth in the OSC referral, the whistleblower's allegations also indicated that the outcome of this this quantitative approach—otherwise referred to as a QRA—would suggest a definitive determination from a toxicological perspective with respect to whether the new product should be deemed SE or NSE based on the HPHCs under the applicable regulatory standard. [94]

The whistleblower further alleged that, once he and the other concerned toxicologists began to voice concerns about the qualitative or semi-quantitative approach advocated by DNCS management in the context of their reviewing individual applications, management issued the HPHC Memo—which memorialized the approach to which those concerned toxicologists objected—and directed toxicologists in DNCS to follow that memo in evaluating HPHC differences in SE applications.[95] The whistleblower pointed out that "the HPHC Memorandum cites no scientific sources or bases for using [the new] approach, in contrast to the established and scientifically supported quantitative approach." [96] The whistleblower also explained that he and the other concerned toxicologists used the approach described in the HPHC Memo to evaluate several SE applications and "found that the two approaches yielded different results for the same application":

> One new product, for example, was found to be SE using the qualitative approach—meaning it was safe enough to go to market—but was found to be *NSE* using the quantitative approach. Another product, when tested with both approaches, resulted in the inverse. [97]

A. Interviews and Discussions with the Concerned Scientists and OS/DNCS managers

[93] *Id*. at 3.
[94] *Id*.
[95] *Id*. Please note that the allegations related to the concerned scientist's efforts to challenge and elevate the approach outlined in the HPHC Memo are discussion below.
[96] *Id*.
[97] *Id*. at 3.

In the investigative team's interviews with the whistleblower and the other concerned toxicologists, they echoed the reservations about the qualitative or semi-quantitative approach voiced by the whistleblower in his allegations to OSC. Indeed, all of the concerned toxicologists expressed their view that DNCS management's decision to transition from evaluating HPHCs using a quantitative methodology to the new approach in the context of an SE application was motivated at least in large part by a desire to conserve resources by increasing expedience and that, in doing so, DNCS management had not adequately considered whether sound science supported the new approach.[98] The concerned scientists further explained that they understood the HPHC Memo—both in terms of how they interpreted the memo and how DNCS managers applied it in practice—to require them to justify supplementing or departing from the qualitative or semi-quantitative approach before conducting a full QRA. The interviews with the concerned toxicologists left a distinct impression that they believed DNCS management was purposely disregarding the potential effect on public heath if the qualitative or semi-quantitative approach were used in lieu of a more robust quantitative assessment and that the new approach could be used to resolve uncertainty in close cases in favor of an SE determination.

Of note, based on our subsequent interviews with OS/DNCS managers, the concerned scientists uniformly did not distinguish between SE applications containing a submitted QRA prepared by the applicant and those that did not. In fact, consistent with their broader understanding of how and when they might apply a quantitative analysis to an SE application, several of the concerned toxicologists described to us their efforts to begin creating an algorithm to be used when evaluating relative HPHs increases and decreases in an SE application. As

[98] Reviewing the HPHC Memo itself discloses statements supporting a read that DNCS issued and implemented the memo to promote expedience. *See* HPHC Memo at 2 (the quantitative methods used by other agencies are not "designed to *rapidly* assess relative risk between complex mixtures" (italics added, underline in original)) and at 5 ("This approach will require a *rapid* assessment tool" (emphasis added)).

explained by the concerned toxicologists, they envisioned the algorithm as a tool that could be used by entering the relative HPHCs reported by applicants into a computer program that would include established criteria for each HPHC—including, e.g., assumptions regarding toxicity magnitude, carcinogenicity, and exposure—based on CTP's conclusions drawn from scientific research and experience, as well as a formula for multiplying and adding the resulting quantities for a numerical output on the risks of the new product relative to the predicate.[99] Several of the concerned toxicologists expressed confusion with respect to why developing an algorithm along the lines of what they envisioned would not create a far more rapid assessment tool than the approach reflected in the HPHC Memo.

Finally, in line with the arguments made in the May 2019 Appeal, the concerned toxicologists criticized the HPHC Memo's approach of disregarding "analytically equivalent" HPHCs "per the Chemistry discipline."[100] The toxicologists emphasized that disregarding such HPHCs is inconsistent with a scientifically rigorous approach to assessing the relative toxicity of complex mixtures. They felt that any relative increase or decrease in HPHCs was relevant even if "analytically equivalent" because such slight differences could affect the outcome of a comprehensive toxicological review using a quantitative method.

In the investigative team's initial interviews with DNCS/OS managers, those managers painted a very different picture of their intentions and the thinking behind the HPHC Memo—though the specifics of their views did not become apparent until discussions that began after the CTP Director had issued a decision and they had assisted on providing an addendum to that

[99] See *supra* at page 5, for discussion of how agency guidance encourages applicants to list HPHC levels for both the new and predicate products in tabular format.
[100] HPHC Memo at 3.

decision, as noted above and discussed in more detail below.[101] The managers universally expressed surprise that the concerned toxicologists objected so strongly to the qualitative or semi-quantitative approach described in the memo. They conveyed that, in their minds, the new approach was intended to memorialize a simpler, more straightforward approach to evaluating relative HPHC increases and decreases in an SE application and to permit toxicology reviewers to focus on any key differences between the two products without having to conduct a comprehensive evaluation of a QRA submitted by an applicant when such an evaluation is not likely to resolve uncertainty with respect to the relative public health risk. Critical to this line of thinking—and in contrast to the way the concerned toxicologists framed the issue for themselves and us, as noted above—the OS/DNCS managers made a clear distinction between SE applications containing a QRA and those that did not.[102] Indeed, the OS managers hinted that the reason for adopting the qualitative or semi-quantitative approach stemmed from a distrust of

[101] Given how FDA structured this investigation, as noted above, the principal purpose of these initial interviews was to investigate the manner in which CTP had handled the scientific disagreement at issue in this matter—*i.e.*, the third and fourth allegations in the OSC referral, as discussed further below—but some of their views on the scientific disagreement became clear during the course of those discussions. As our analysis below suggests, the discrepancies between the concerned toxicologists' understanding of the HPHC Memo and DNCS/OS management's rationale for that memo may be the product of a lack of clarity in the memo itself, the manner in which management issued that memo, and shortcomings in the involved parties' understanding of how to resolve scientific disagreements under both agency-wide and CTP-specific policies and procedures for such disagreements.

[102] The HPHC Memo itself makes this distinction, as well. In describing when a toxicologist should conduct a quantitative analysis, the memo directs reviewers to a submitted QRA:

> 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 (HPHC Memo at 5) (emphasis added).

See also HPHC Memo at 4 ("QRAs *submitted* to address situations where there are HPHC increases and no HPHC decreases that could be possibly offsetting." and "Although relatively rare, DNCS *has also received* QRAs where a QRA is not warranted to address the changes between the two tobacco products." (emphases added)).

QRAs submitted by applicants for a variety of reasons, including how complicated they could be and how they could be used to skew the analysis and data in a misleading fashion.

Perhaps most significantly, the OS Director stated that, when he would review SE applications in rendering a formal decision for CTP regarding substantial equivalence, he would zero in on the types of increases and decreases described in the HPHC Memo because his experience both as a former reviewer and as a manager was that a submitted QRA—even when accompanied by a toxicologist's written evaluation—seldom, if ever, illuminated or affected his view of the application under the applicable regulatory standard. In his view, therefore, he thought that the toxicology reviewers would appreciate being provided a stepwise process for evaluating SE applications in a manner that aligned with his own approach as a means of saving them unnecessary work.

In our preliminary interviews with OS/DNCS managers, some of those managers also stressed in various ways that they disagreed with the concerned toxicologists' view that disregarding "analytically equivalent" HPHCs in assessing the differences between a new product and the predicate in an SE application is problematic. The DNCS Deputy Director in particular made a point of explaining how, in his view, giving any weight whatsoever to differences that were not at least "analytically non-equivalent" would introduce error into the evaluation. He elaborated that agricultural variation would almost always occur for tobacco products and that, even when averages are used by applicants to specify a precise level of a particular HPHC, those averages are themselves the product of analytical limitations from a chemistry perspective and thus not sufficiently reliable to establish such fine differences.

These preliminary interviews with OS/DNCS managers did not enable the investigative team for the Office of the Commissioner to reconcile OS/DNCS management's view of the

HPHC Memo with the concerned toxicologists'. The plan at the time was to evaluate the substance of scientific disagreement at issue in the OSC referral once the Expert Panel provided advice to the CTP Director and he rendered a decision for the Center. However, as noted above, the Office of Commissioner continued to have questions about CTP's rationale for issuing and implementing the HPHC Memo even once the CTP Director rendered his decision, as supplemented by the CTP Addendum. Therefore, the Office of the Commissioner then engaged two OS/DNCS managers in a series of discussions focused on further clarifying the thinking behind the HPHC Memo.

During those discussions, the OS/DNCS managers framed how they expected the analysis reflected in the HPHC Memo to work in a manner that enabled the Office of the Commissioner to understand how and why management's view of the HPHC Memo diverged so significantly from the concerned toxicologists'. As clarified by the OS/DNCS managers during these later discussions, they intended the HPHC Memo to function as a three-tiered process turning on: (1) whether the application presents a clear-cut case for an SE or NSE determination because there are all HPHC increases or decreases relative to the predicate product (Tier One); (2) whether there is only one or two relative HPHC increases for the new product that can reasonably be offset by relative HPHC decreases using the qualitative or semi-quantitative approach (Tier Two); and (3) whether the new product has more than one or two HPHC increases as compared to the predicate product (Tier Three). The OS/DNCS managers indicated that they intended the qualitative or semi-quantitative approach to apply only to applications falling into Tier One or Tier Two.

The OS/DNCS managers also further clarified that the decision to issue and implement the HPHC Memo flowed from an increasing distrust of QRAs submitted by applicants. As noted

by OS managers during our preliminary interviews with them, part of this skepticism regarding QRAs resulted from their experience that QRAs submitted by applicants usually frame the analysis and the underlying data in a skewed or inaccurate way—relying on inaccurate or unreliable assumptions or calculations with respect to toxicity—unless the new product presented a clear-cut case for an SE determination in Tier One or would effectively reach the same SE determination that would result if using the qualitative or semi-quantitative approach in Tier 2. Indeed, according to the OS/DNCS managers, submitted QRAs are almost always inadequate to overcome an obvious determination for Tier One applications that the new product poses greater (or lesser) risks to the users. Likewise, as explained by OS management, submitted QRAs seldom, if ever, resolve any remaining uncertainty with respect to the relative risks posed by the new product after either using the qualitative or semi-quantitative approach for one or two HPHC increases (i.e., Tier Two) or concluding that the qualitative or semi-quantitative approach is inapplicable (i.e., Tier Three).

In OS/DNCS management's view, applications for new tobacco products that fall into Tier Three (i.e., applications with more than one or two relative HPHC increases) create too much uncertainty with respect to whether the new product poses a greater risk to the user than the predicate product. Key to this line of thinking was the managers' view that, when there are more than one or two relative HPHC increases in the context of comparing tobacco products, it is difficult—and usually impossible—to deduce with an adequate degree of confidence from a scientific perspective what effect on human health those increases might have when, for example, a user is deliberately inhaling on a regular basis the smoke at issue for many tobacco products. Put another way, the OS/DNCS managers felt that, from a scientific perspective, it was difficult to know how more than two HPHC increases might interact and combine—

synergistically, antagonistically, and cumulatively—to create additional risk for a consumer deliberatively inhaling, or otherwise consuming, the mixture. Indeed, the OS/DNCS managers were not comfortable adopting the quantitative methodology (i.e., a QRA) used by the Environmental Protection Agency, for example, because the methodology had been designed for environmental exposure over a defined period of time, not deliberate consumption on a regular basis. In their view, therefore, an application for a tobacco product that has more than one or two HPHC increases should usually result in an NSE determination under the statutory standard for substantial equivalence—which requires the applicant to "demonstrate that . . . the product does not raise different questions of public health"—even if an applicant submits a QRA attempting to show otherwise.[103] In fact, the uncertainty itself raises "different questions of public health."[104]

As a result, in contrast to how the concerned toxicologists and the Expert Panel appear to have read the HPHC Memo—and, in fact, as initially interpreted by the Office of the Commissioner—the OS/DNCS managers intended the tiered process that they envisioned in issuing the memo to be more protective of public health than the previous approach while conserving agency resources at the same time. The OS/DNCS managers clarified to the Office of the Commissioner that they adopted the qualitative or semi-quantitative approach not only as a means of increasing efficiency but also as an effort to capture those circumstances in which a full QRA would otherwise be likely to demonstrate substantial equivalence to an adequate degree of certainty in their minds. To the extent that the OS/DNCS managers considered resources, they only sought to limit a more extensive review of a submitted QRA to those cases where it was necessary or appropriate from a scientific and regulatory perspective. In their view, those cases

[103] *See* section 910(a)(3)(A) of the FD&C Act.
[104] *See id*.

would only include: (1) Tier 2 applications for which the assigned toxicologists believe evaluating a full QRA would shed additional light on the findings achieved through the qualitative or semi-quantitative approach in Tier Two and (2) Tier Three applications for which the only path to an SE determination is—at this point in time—the rare compelling QRA that can resolve uncertainty regarding the relative risks associated with the new product because there are more than two relative HPHC increases.*B. Analysis*

Once the Office of the Commissioner gained a fuller understanding of both how OS/DNCS managers intended the HPHC to function and why they felt it was important to limit reliance on evaluating QRAs submitted in support of an SE application—or otherwise conducting a quantitative analysis—we became convinced that the tiered process in the HPHC Memo is appropriate from a scientific perspective when viewed in light of the regulatory standard for "substantial equivalence" in section 910(a)(3)(A) of the FD&C Act. The purpose of the HPHC Memo is to resolve uncertainty with respect to the risks presented by a new tobacco product by preventing that product from reaching the market through the SE application pathway. Although the concerns expressed by the whistleblower merit remedial action by the agency—in the form of revisions to the HPHC Memo to make it both more consistent with the thinking behind the memo and more transparent—we find that the tiered approach in the HPHC Memo is protective of public health and represents an appropriate exercise of the agency's statutory authority in addressing SE applications.

As noted above, the HPHC Memo sets forth a process for toxicology reviewers to follow when evaluating HPHCs in the context of SE applications, submitted in accordance with section 905(j) of the FD&C Act, to seek an FDA determination of substantial equivalence between a new tobacco product and a predicate product. There are two potential outcomes to such

applications: "not substantially equivalent," which would result in a denial of the application, and "substantially equivalent" which would result in a grant of the application. But the definition of "substantial equivalence" applicable to such applications under the FD&C Act makes clear both (1) that the burden for establishing a new product satisfies the contemplated standard for such applications falls squarely on the applicant's shoulders and (2) that CTP's authority to grant or deny such applications turns on an expansive discretionary standard:

> [T]he term 'substantially equivalent' or 'substantial equivalence' means, with respect to [a] tobacco product being compared to [a] predicate tobacco product, that the Secretary by order has found that the tobacco product (i) has the same characteristics as the predicate tobacco product or (ii) has different characteristics and the information submitted contains information . . . *demonstrat[ing]* that . . . the *product does not raise different questions of public health*.[105]

This statutory standard clearly permits CTP to deny SE applications if the applicant has not established that the new tobacco product is substantially equivalent to the predicate product by resolving uncertainty—given the current state of the science—with respect to how those many HPHC increases relative to the predicate might affect health risks when consumed, based on interactions those many HPHC increases might have, including any potential synergistic or antagonistic effect.

An applicant may opt to submit a QRA in an effort to demonstrate "substantial equivalence," but OS/DNCS management's view is that, in many cases, those efforts should fail. For Tier One applications in which the application shows only increases for non-analytically equivalent HPHCs, there is ample reason to conclude that the applicant has failed to establish that "the [new] product does not present different issues of public health."[106] For Tier Two applications for which the qualitative or semi-quantitative approach is inadequate to eliminate

[105] *Id*. (in relevant part, emphases added).
[106] *Id*. Please see above for a more detailed discussion of Tier One applications.

uncertainty regarding the potential health effects of one or two HPHC increases, reviewing a submitted QRA may be helpful but is seldom sufficiently illuminating to make a difference.[107] For Tier Three applications (i.e., when there are more than two relative HPHC increases), a submitted QRA not only typically presents data in support of the analysis in a skewed and misleading way, based on inaccurate assumptions regarding toxicity magnitude, etc., but—in the words of the OS/DNCS managers themselves—"the science is not there" to account for the complicated nature of how those increases might affect human health risks. [108] Indeed, in the view of the OS/DNCS managers with respect to Tier Two and Tier Three applications, creating an algorithm—or otherwise establishing definitive criteria for a quantitative assessment, as apparently envisioned by the concerned toxicologists, to assess relative toxicity between two tobacco products, with or without a submitted QRA—would be problematic because there is no existing scientific research to support such a precise quantitative approach in this area.

On the other hand, OS/DNCS managers' skepticism with respect to more precise measurements and calculations than current science permits in the context of an SE application compels a different conclusion with respect to their distinction between "analytically equivalent" and "non-analytically equivalent" HPHCs for the purposes of comparing two tobacco products. As noted above, OS/DNCS management believes that including relative HPHC increases that do not exceed the typically small scope of analytical equivalence in any toxicity comparison merely introduces additional error into the evaluation process because even averages of HPHC levels depend on limits in the underlying chemistry in terms of precision. And, given that agricultural variation for tobacco products makes such pinpoint calculations less useful, the OS/DNCS managers feel comfortable disregarding analytically equivalent HPHC increases as part of the

[107] *Id*. Please see above for a more detailed discussion of Tier Two applications.
[108] *Id*. Please see above for a more detailed discussion of Tier Three applications.

simplified approach to assessing whether a small number of HPHC increases can be offset using the qualitative or semi-quantitative approach. The Office of the Commissioner has likewise concluded that adopting this approach is consistent with the standard for substantial equivalence in the FD&C Act.

CTP's overall approach to assessing whether an SE application establishes substantial equivalence aligns, in fact, with how other FDA Centers must handle uncertainty in their premarket reviews. For example, in evaluating new drug applications, FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) focus, in part, on whether the application demonstrates safety "upon the basis of the information submitted . . . as part of the application, or upon the basis of any other information . . . with respect to such drug, [FDA] has insufficient information to determine whether such drug is safe for use under [the] conditions [of use]."[109] Those same Centers must also consider, when evaluating the effectiveness of the drug under review, whether "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[110] The standard for "substantial evidence" turns, in part, on whether "it could fairly and responsibly be concluded by [] experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed."[111] It almost goes without saying that FDA places the burden on the applicant to show safety and effectiveness under those standards because the question is whether the submitted data and information are sufficient (or "insufficient") to meet that statutory standard. In exercising agency discretion under that statutory authority, CDER and

[109]Section 505(d)(4) of the FD&C Act.
[110] Section 505(d)(5) of the FD&C Act.
[111] Section 505(d) of the FD&C Act.

CBER must necessarily consider whether the information provided by the applicant resolves uncertainty with respect to safety and effectiveness.

An even more apt analogue is Center for Devices and Radiological Health's (CDRH's) approach to evaluating "substantial equivalence" when conducting a premarket review of a new device pursuant to section 510(k) of the FD&C Act. Section 513(i) requires FDA to evaluate for such notifications whether a new device is "as safe and effective" as a predicate device before clearing the device for market. Under section 513(i)(1)(A)(ii)(1), if the new device:

has different technological characteristics . . . the information submitted . . . [must] contain[] information, including appropriate clinical or scientific data if deemed necessary by [FDA] that demonstrates that the device is as safe and effective as a legally marketed device[] and . . . does not raise different questions of safety and effectiveness than the predicate device.

The parallels between CTP's approach to HPHC increases when comparing a new tobacco product to a predicate could not be clearer.

CTP's process for evaluating relative HPHC increases and decreases for SE applications outlined in the HPHC Memo, as further explained and clarified by the OS/DNCS managers, also diminishes any concerns expressed by the Expert Panel about the qualitative or semi-quantitative approach and its use within the memo's framework. As noted above, in its report the Expert Panel specifically framed the qualitative or semi-quantitative approach as supportable when viewed as part of a binary decision-making process and stated that one distinction between a full QRA and the qualitative or semi-quantitative approach is that the former quantifies the difference between two tobacco products but that the latter is more binary in that it focuses on whether, in fact, there is a difference. [112] According the OS/DNCS management, the HPHC

[112] Expert Panel Report at 4.

Memo is intended to function in precisely that way. Indeed, CTP is not attempting to quantify the differences in toxicity or risks between the new and predicate products. The question for CTP is whether the applicant has met its burden by showing that the new product does not present any additional risk for the consumer and resolves any uncertainty with respect to whether the new tobacco product poses additional risks to the public. The HPHC Memo, as it was intended to function, answers those questions through a tiered process, as set forth above.

In light of the foregoing analysis, the Office of the Commissioner has concluded that the first two allegations in the referral letter relating to CTP's underlying scientific rationale for the HPHC Memo and the resulting potential outcomes for SE applications (i.e., "[t]he qualitative or semi-qua[nt]itative' approach, as outlined in the HPHC [Memo], is not based on the best available science" and (2) the qualitative or semi-quantitative approach "can yield entirely different results than the quantitative approach") reflect valid concerns regarding the clarity of the HPHC Memo itself but not regarding the underlying thinking of the tiered approach outlined in that memo. From both a scientific and regulatory perspective, it makes sense to evaluate HPHC increases in a new tobacco product relative to a predicate product by focusing on the number and types of HPHCs at issue in determining whether a QRA evaluation is necessary or worthwhile based on the current state of the science and the potential complications resulting from more than two HPHC increases.

The Office of the Commissioner also agrees with CTP that resolving substantial uncertainty through reliance on a submitted QRA—or through any other quantitative analysis—without accounting for the potential synergistic or antagonistic effect of more than two HPHC increases would be less protective of public health. Accordingly, we find that the qualitative or semi-quantitative approach, when implemented as part of the tiered process contemplated by

CTP, does represent the appropriate application of the "best available science" for evaluating HPHCs in a SE application given the statutory standard. We also find that any potential differences in outcome are also justified from the perspective of regulatory science under that statutory standard in that CTP resolves uncertainty in favor of an NSE determination. We nonetheless conclude that revisions to the HPHC Memo, as set forth in the next section, are appropriate to align the reasoning and intended effects to be consistent across a full range of applications and to be as clear and as transparent as possible.

B. Remedial Actions

After the OS/DNCS managers illuminated their thinking and the scientific rationale for issuing and implementing the HPHC Memo, the Office of the Commissioner began discussing with them ways that they might revise the HPHC Memo to square with our discussions regarding its intended effect. After several discussions along those lines, the Office of the Commissioner and CTP agreed that OS/DNCS management should refine and clarify the stepwise, tiered process outlined in the HPHC Memo and otherwise revise the framing to better enable both toxicologists and other CTP staff to implement the memo in a more straightforward and consistent manner. FDA now plans to make the following changes to the HPHC Memo and believes that they will help effectuate the thinking behind it:

1. Revise the HPHC Memo:

    a. to establish in the first few pages that, for purposes of the contemplated process, SE applications are grouped into the three tiers reflected in the analysis above (i.e., (Tier One) all relative HPHC increases or all relative HPHC decreases; (Tier Two) one or two relative HPHC increases that are appropriate for qualitative or semi-quantitative offsetting with relative HPHC decreases; and (Tier Three) more than two HPHC increases);

    b. to incorporate the tiered process more explicitly into the methods for evaluating applications in the different tiers, including by revising the HPHC Memo to

clarify the criteria used to place SE applications in Tier 2, such as criteria focused on the number of relative HPHC increases and specific examples to illustrate how the types of HPHC increases and decreases at issue might affect that analysis;

c. to clarify how CTP will resolve scientific uncertainty with respect to SE and NSE determination for SE applications falling into Tiers Two and Three, including: (i) the manner in which any submitted QRAs may be used in evaluating those applications and (ii) additional sub-tiers hinging on whether any provided analysis in submitted QRAs contains problematic reference values, excludes consideration of critical HPHC increases, or relies on HPHC measurements whose methods cannot be verified by the chemistry reviewer.

2. Clarify in the HPHC Memo that toxicology reviewers have the discretion to evaluate a QRA submitted in support of any application and to supplement their analysis under the tiered approach with such an evaluation but acknowledge that any analysis in a QRA departing from the typical outcomes for Tiers One through Three is unlikely to produce a different outcome, absent very compelling arguments grounded in science, because QRAs are often insufficient to resolve elements of scientific uncertainty related to tobacco products, which are complex mixtures (e.g., the synergistic or antagonistic effects or interactions of more than two HPHC increases).

3. Develop a decision tree (to be included as an appendix to the HPHC Memo) that sets forth how SE applications are assigned to each tier and how a decision at each stage leading to an SE/NSE determination is made.

4. Continue (on an ongoing basis) to evaluate and revise the tiered process and the criteria for the qualitative or semi-quantitative approach to reflect any advancements in science and CTP's experiences in conducting such reviews and, as appropriate, to make existing criteria more transparent and straightforward as a means of ensuring consistency across applications.

FDA views plans to finalize the first two of these remedial actions in the next one to three months but views the third remedial action as a longer-term goal—i.e., four to nine months. As stated, the fourth remedial action is a commitment to evaluate and revise the HPHC Memo, as appropriate, on an ongoing basis.

The planned revisions are consistent with the Expert Panel's recommendations and advice. As noted above, the Expert Panel concluded that the tiered approach "needs to have

clear decision rules which guide the review and dictate the integration of the 'qualitative or semi-quantitative' evaluation and that these "decision rules should be added to the review process to ensure adequate protection of public health."[113] The Expert Panel also recommended that CTP "develop and communicate standardized and objective criteria for deciding when a [QRA] should be conducted in a collaborative manner."[114] In adopting our remedial measures, FDA intends to make precisely those types of changes to the HPHC Memo.

III. Allegations Related to CTP's Efforts to Resolve the Scientific Disagreement

A. Existing Procedures and Policies for Resolving Scientific Disagreements at FDA and CTP

On January 13, 2009, FDA's Office of the Commissioner issued a staff manual guide on the resolution of internal scientific disputes at the agency.[115] The stated purpose of this SMG-SDR is "to improve the process of internal scientific dispute resolution[] and to encourage open communication throughout the agency."[116] The SDR-SMG "encourages the resolution of scientific disputes at the working level in the organization, starting with the frontline employees and their immediate supervisors or team leaders" and cautions that the "agency's appeals process for scientific disputes is not a replacement for robust and fair Center-level processes."[117] The SDR-SMG provides for submission of SDR appeals to the Office of the Commissioner and outlines the process and standards for evaluating such appeals.[118] Under the SDR-SMG, the SDR Board evaluates whether "the processes followed in the Center fully considered all relevant

[113] *Id*.
[114] *Id*.
[115] See Appendix 8, Staff Manual Guide 9010.1, "Scientific Dispute Resolution at FDA" (SDR-SMG).
[116] *Id*. at 1.
[117] *Id.* at 2.
[118] *Id.* at 11-13

evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director."[119]

In addition to outlining the process for elevating scientific disputes to the Office of the Commissioner, the SDR-SMG details the agency's "requirements for the minimum standards for scientific dispute resolution processes in the Centers" and provides a collection of non-mandatory "best practice[s]" for such dispute resolution.[120] The SDR-SMG's requirements for resolving scientific disputes at the Center-level begin with an obligation on the part of Center management to ensure open scientific debate on controversial issues:

> Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization.[121]

The SDR-SMG then proceeds to require the Centers to have in place written standard operating procedures for formally resolving scientific disputes in the event that such informal attempts at resolution are unsuccessful.[122] In contrast to the procedural review contemplated by the SDR-SMG, Center-level procedures should provide for substantive review of the scientific disputes at issue within the Center.[123]

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[119] *Id*. at 12.
[120] *Id*. at 2-3.
[121] *Id*. at 6.
[122] *Id*. To be clear, this report often uses the term "SDR" to indicate the process for formal resolution of a scientific dispute.
[123] *See id*.

On September 2, 2011, CTP issued Center-level policies and procedures for internal scientific disagreements.[124] By its own terms, the SDR-ToPP:

> covers all CTP employees involved in scientific regulatory decision making, including, but not limited to, those responsible for writing or reviewing scientific and technical documents and making recommendations to their supervisor or team leader. The recommendations may subsequently be reviewed by a supervisor, Division Director, Office Director, and sometimes the Center Director, for final approval and action.
>
> In order for a dispute to be eligible for resolution under this [SDR-]ToPP, it must be consequential to a decision. A dispute is consequential to a decision if taking one position on an issue would lead to a different decision than taking another position, for example, whether a tobacco product is, or is not, substantially equivalent. Also, the difference in the decision may have a significant negative impact on public health.[125]

The SDR-ToPP excludes from its application "disputes that challenge an established CTP, Agency or Department policy."[126]

In line with the SDR-SMG, the SDR-ToPP encourages CTP managers to "create an atmosphere in which consultation and open discussion on evolving scientific findings (e.g. draft reviews) and controversial issues are encouraged."[127] Likewise, consistent with the SDR-SMG, the SDR-ToPP contemplates that Center personnel may resolve many scientific disagreements informally without resort to the formal SDR process set forth later in the document:

> It is inevitable, indeed intended and encouraged, that employees, supervisors, and managers bring different perspectives and concerns to their respective analyses of data and information. FDA has a long history of valuing scientific exchange, openness and transparency to facilitate reaching optimal and fully considered public health decisions. Thus, it is necessary for everyone to work together informally to discuss evolving scientific findings and to resolve differences when they occur so that an institutional decision may be reached. The basic approach to accomplishing this is to attempt consensus development and agreement through discussion among participants as the work proceeds. In cases where an employee

[124] See Appendix 9, "ToPP: Internal Scientific Dispute Resolution (SDR) in Regulatory Decision Making" (SDR-ToPP).
[125] *Id*. at 2.
[126] *Id*.
[127] *Id.* at 3.

> disagrees and cannot accept a planned regulatory decision/action, resolution of differences may need to be achieved by using the formal dispute resolution process described in this [SDR-]ToPP.[128]

In describing the process for initiating the formal SDR process if informal attempts to resolve a scientific disagreement fail, the SDR-ToPP indicates that the first step for the individual who is dissatisfied with the resolution is to "write an initiation memorandum to the next highest supervisor/manager above the initiator's immediate supervisor or team leader, with copies to that supervisor/team leader, others involved in the dispute, and the CTP Ombudsman."[129] The CTP Ombudsman then evaluates the initiation memorandum for completeness and eligibility for the SDR process and then notifies all appropriate parties of his determinations in writing.[130] The SDR process then moves up the chain of command within CTP

until resolution is achieved:

> Dispute resolution will be addressed successively higher supervisor/manager levels up the chain until resolution is achieved; i.e. all parties agree with, or at least accept, a decision by a particular level in the chain of command. This means that issues that cannot be resolved at one level may be taken to the next highest level, e.g. Division Director, Office Director, Center Director.[131]

The SDR-ToPP directs supervisors in the management chain to address all issues raised as part of the SDR process and to provide a basis for each decision made on those issues, including the scientific evidence on which those decisions turn.[132] It further encourages "supervisors and managers at each successively higher level" to consult "relevant scientific, technical or other

[128] *Id.*
[129] *Id.* at 5.
[130] *Id.*
[131] *Id.*
[132] *Id*. at 6.

resources on the matter at issue to gain a better understanding of the issues in dispute and to aid in addressing them."[133]

The SDR-ToPP provides explicit timeframes for decisions at each level of the process and requires that supervisors and managers (including the Center Director) memorialize their decisions in writing and ensure that those decisions are made a part of the administrative record.[134] If the employee remains dissatisfied with the CTP's resolution of the scientific dispute after the Center Director has rendered his decision, the employee may then elevate the matter to the Office of the Commissioner for review under the procedures outlined in the SDR-SMG.[135]

B. Response to the Third Allegation

In response to the third allegation, we confirmed that DNCS management did put some SE reviews implicated by this scientific dispute on hold and withheld assigning additional reviews to the concerned toxicologists, but we found no evidence that these reviews were halted or withheld from particular personnel for the purpose of preventing them from pursuing this scientific dispute.

During the course of our investigation, OS/DNCS managers consistently explained that they developed the qualitative or semi-quantitative approach in the HPHC Memo in response to several programmatic concerns highlighted above. By late 2018 and early 2019, as this tiered approach was being developed and as DNCS managers were encouraging staff toxicologists to implement such a tiered approach in specific SE application reviews, the concerned toxicologists began to object to management's application of the tiered approach in discussions with DNCS

[133] *Id.* at 5.
[134] *Id.* at 5-6.
[135] *Id.* at 7.

managers about particular SE application reviews. Initially, consistent with the both the SDR-SMG and SDR-ToPP, the concerned toxicologists first attempted to raise their scientific issues with the tiered approach informally with DNCS management, beginning in late 2018.[136]

Interviews and a review of email communications demonstrate that the concerned toxicologists expected that DNCS management would write non-concur memos and add them to the administrative file for the implicated applications and that those NCMs would explain management's disagreement with the conclusions of the toxicologists. The concerned toxicologists believed that, at that point, they would have a "decision" that they intended to challenge and elevate, along with their scientific concerns with the tiered approach, under the process contemplated by the SDR-ToPP. As a result, the concerned toxicologists requested that DNCS management provide NCMs for specific applications that they then intended to challenge.

Our investigation determined that, during the same period, DNCS management—in collaboration with the OS Director—began to formalize the tiered approach by developing the HPHC Memo, which ultimately issued on February 21, 2019, to clarify OS/DNCS's evolving approach to HPHC evaluation. Rather than engaging in the application-by-application discussions with the concerned toxicologists for each application that involved the challenged approach, OS/DNCS managers intended the HPHC Memo as a global resolution to the critical scientific disagreement that had cropped up and would, in their minds, continue to arise in application-specific discussions. During interviews, OS/DNCS managers consistently maintained that the HPHC Memo was intended to help explain and clarify management's position on the tiered approach that had been evolving through application-specific discussions and that they hoped it would provide a framework for SE reviews going forward. Management

[136] SDR-SMG at 6 and SDR-ToPP at 3.

reported, and our interviews confirmed, that at least one toxicologist—who was not a member of the concerned toxicologists—had requested that a memo be issued to provide such clarification and guidance on management's expectations to inform his SE application review using the tiered approach.

On May 31, 2019, as previously described in this report, the concerned toxicologists elevated the scientific disagreement surrounding the HPHC Memo via their May 2019 Appeal. In response to this appeal, OS management informed both DNCS management and the concerned toxicologists that OS management would evaluate the appeal and issue a decision at that level. Our investigation confirmed that, while this OS appeal was pending, DNCS management did place several reviews of SE applications on hold and withheld assigning additional SE applications containing QRA data to the concerned toxicologists. Although the concerned toxicologists viewed DNCS management's decision to halt certain implicated reviews and to withhold assigning to them incoming reviews that presented similar issues as an effort to stymie their scientific concerns, DNCS managers credibly represented during our investigation that the consideration of those scientific concerns itself was the motivation for halting and withholding implicated reviews while the May 2019 Appeal was pending.

As explained during interviews, DNCS management concluded that, until OS management issued a decision on the May 2019 Appeal by upholding, modifying, or rejecting the tiered approach at issue in the HPHC Memo, finalizing the reviews in which the scientific disagreement had first arisen or assigning incoming SE applications with similar issues to the concerned toxicologists would have been counter-productive. Our investigation found no evidence that DNCS management halted or withheld these reviews for the purpose of preventing the concerned toxicologists from initiating the process under the SDR-ToPP. Rather, DNCS

managers appear to have acted out of a desire to limit the number of SE applications that might have to be reworked using the tiered approach following OS management's decision regarding the May 2019 Appeal, which set forth the substance of the concerned toxicologists' views on the underlying scientific disagreement.[137] In sum, our review of management communications and interviews with relevant staff provided no evidence that DNCS management halted certain reviews or withheld assigning others to the concerned toxicologists for the purpose of preventing those toxicologists from initiating process under the SDR-ToPP, as suggested by this allegation.

As the next section describes in more detail, it is critical to note that halting and withholding these reviews during this time period—even if it had been done for the purpose the concerned toxicologists allege—could not and should not have prevented these concerned toxicologists from initiating the SDR process and elevating their dispute through that process, had that process otherwise functioned as intended. The next section describes how confusion concerning the SDR process itself at CTP, rather than the routing of reviews, undercut the successful elevation and potential resolution of this dispute.

B. Response to the Fourth Allegation

In response to the fourth allegation, we concluded that a lack of experience in resolving scientific disagreements of this type by CTP staff undermined efforts within the Center to resolve the scientific disagreement in this case in a timely and amicable manner. Our investigation determined, however, that the primary obstacle to the initiation of the SDR process and elevation

[137] When the OS management issued its decision on the appeal in December 2019, review of these applications could have continued, but DNCS took no further action on those reviews in early 2020 before CTP became aware of OSC's referral of the current allegations. As described in the previous sections, the status of these individual application reviews remains pending at this time, until the updated processes described in the previous sections are implemented.

of this dispute within that process was confusion concerning the applicable scope of the SDR-ToPP by CTP staff at all levels.

As described in the section on the SDR-SMG and SDR-ToPP, the policies and procedures at both the agency and CTP level define two primary pathways for attempting to resolve scientific disputes. When a scientific disagreement occurs, the SDR-ToPP encourages the staff involved to first attempt to resolve the disagreement directly through open and informal discussion. For scientific disagreements that cannot be resolved informally, the SDR-ToPP provides a clear pathway to initiate the formal SDR process, which provides a formal dispute resolution process with significant safeguards and avenues for appeal for initiators. Under the SDR-ToPP, "[i]f . . . an employee cannot accept a science-based regulatory decision because he/she believes it would result in significant harm to the public health, that employee may choose to become the initiator of the formal SDR process."[138] The SDR-ToPP then provides instructions, beginning with the filing of an initiation memorandum with the CTP Ombudsman and the employee's first line supervisor, that together initiate the SDR process.[139] At that point, the procedures described in the SDR-ToPP and SDR-SMG would immediately attach, including appeals to the Center Director and then to the Commissioner.[140]

Our investigation determined that, beginning in early 2019, the concerned toxicologists encouraged DNCS management to write non-concur memos to particular application files because these toxicologists believed they needed a management "decision" that they could challenge under the SDR-ToPP. Anticipating an NCM that they believed they could challenge under the SDR-ToPP, the concerned toxicologists viewed the issuance of the HPHC Memo as an

[138] SDR ToPP at 4.
[139] *Id*.
[140] *Id.* at 3.

effort to suppress their disagreement with the underlying scientific approach. Our investigation determined that the concerned toxicologists did not believe they could challenge the HPHC Memo under the existing SDR-ToPP without an NCM. The concerned toxicologists viewed the HPHC Memo, once issued, as an "established CTP policy" falling outside of the scope of the SDR-ToPP.[141]

In our view, the concerned toxicologists' understanding of the purpose and scope of the SDR-ToPP as written at the time of this dispute was likely narrower than intended. However, as discussed more fully below with respect to the remedial actions the agency plans to take to improve the process for resolving scientific disagreements at CTP, clarifying the scope of the SDR-ToPP is a key remedial step to preventing such confusion in the future. The agency believes that the scientific disagreement at issue in this matter—one that hinges on a new scientific approach, developed internally, for evaluating a category of applications or other regulatory submissions—falls squarely within the types of scientific disagreements contemplated by the SDR-SMG and, indeed, is a type disagreement that the agency SDR process is designed to assist in resolving in a robust, orderly, and transparent fashion.

Our investigation determined that the concerned toxicologists nonetheless did not believe they could initiate CTP's SDR process after the HPHC Memo was issued. Although discussions between the concerned scientists and the CTP Ombudsman earlier in this dispute had covered the option of initiating the SDR process, the concerned toxicologists concluded for themselves that the HPHC Memo foreclosed that option because, in their view, the memo established a CTP policy and established policies are explicitly exempt from the scope of the SDR-ToPP.[142] Interviews with the concerned toxicologists attempted to determine where this interpretation of

[141] *See id*. at 2.
[142] *Id.* at 2.

the SDR-ToPP originated, and it appears to have resulted primarily from the ambiguity of the terms in the SDR-ToPP itself and the efforts of the concerned toxicologists to interpret these terms for themselves to the best of their ability.

Although none of the concerned toxicologists conveyed that anyone in DNCS or OS management discouraged them from initiating the SDR process under the SDR-ToPP, the concerned toxicologists did state that they believed that issuing the HPHC Memo was an effort by DNCS management to prevent them from elevating the scientific disagreement via that process. As a result, rather than attempting to initiate the SDR process, the concerned toxicologists elected to focus on their view that the process used to develop the HPHC Memo itself was improper and to frame their May 2019 Appeal to OS management as an effort to elevate a dispute regarding the agency's "good guidance practices" in 21 CFR 10.115.

In 21 CFR 10.115, the agency sets out its process for developing and issuing "documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue."[143] That definition does not include, among other things, "[d]ocuments relating to internal FDA procedures."[144] Under 21 CFR 10.115(o), anyone who believes that "someone at the agency" has not complied with "good guidance practices" may elevate that concern to that person's supervisor.

Our investigation disclosed that, in addressing the May 2019 Appeal, OS management checked with FDA's Office of the Chief Counsel about good guidance practices in the context of internal memos used to document a scientific approach. While not specific to the HPHC memo, they learned that legal counsel had evaluated internal scientific memos similar to the HPHC Memo in the past and provided legal advice to the effect that following the process outlined in 21

[143] 21 CFR 10.115(b)(1).
[144] 21 CFR 10.115(b)(3).

CFR 10.115 did not generally apply to these types of internal scientific memos. In this context, from OS/DNCS management's perspective, the concerned toxicologists were now challenging a widely used practice at CTP for disseminating internal information to its staff that was consistent with legal advice from agency counsel.

It was clear from our interviews with both the concerned toxicologists and OS/DNCS managers that no one involved in the ongoing scientific disagreement believed that the May 2019 Appeal was an attempt to initiate the process under the SDR-ToPP. Indeed, our investigation determined that, by selecting 21 CFR 10.115(o) as a vehicle to elevate their dispute, the concerned toxicologists unknowingly undermined rather than aided their efforts to resolve the scientific disagreement. In particular, CTP's OS Deputy Director of Regulatory Management (OS Deputy), charged with responding to the toxicologists' May 2019 Appeal, viewed this challenge to routine CTP practice as a non-starter and felt that OS could and possibly should have dismissed the challenge summarily. From the perspective of the concerned toxicologists, they were elevating their dispute in the only manner they perceived to be available to them, but their choice of pathway significantly undermined their case in the view of OS management, particularly in the view of the OS Deputy assigned to respond to their concerns.

At the same time, DNCS management had become increasingly frustrated and disappointed by what it perceived as the unwillingness of the concerned toxicologists to attempt to implement the qualitative or semi-quantitative approach described in the HPHC Memo. In management's view, assessing a QRA remained an option that would be appropriate in some cases, but management began to insist that toxicologists start their SE reviews by explaining why using the qualitative or semi-quantitative approach was not appropriate for a particular application before moving to the QRA.

During our investigation, the concerned toxicologists explained that, in their view, they remained unwilling to adopt an approach they viewed as lacking a scientific basis. Rather than explain why the tiered approach—specifically the qualitative or semi-quantitative approach described therein—did not suffice for a particular SE application, the concerned toxicologists saw no alternative than to continue to oppose the tiered approach as a categorical matter. This opposition eventually took the form of the addition of an "Appendix" that the concerned scientists added to the administrative files of several SE applications. This "Appendix" took issue with the tiered approach from the HPHC Memo, essentially explaining not why the qualitative or semi-quantitative approach was inadequate for a specific application as the HPHC Memo directed, but how that approach would be inadequate for evaluating HPHCs in *any* SE application. [145]

Our investigation disclosed that the concerned toxicologists thought the HPHC Memo's description of the qualitative or semi-quantitative approach was so scientifically baseless and practically confusing as to defy implementation and that their efforts to avoid doing so entirely only further frustrated DNCS management, given management's view that the qualitative or semi-quantitative approach was scientifically acceptable. An early example of this evolving dynamic was a meeting in April of 2019, during which—according to several of the concerned toxicologists we interviewed—DNCS managers framed as a directive staff were expected to follow. From the DNCS manager's perspective, they were asking their staff to implement an acceptable approach, and the staff were flatly refusing to do so. From the perspective of the concerned toxicologists, management's directive was not one they could follow, due both to a

[145] As noted in the previous section, the waging of this global scientific dispute in particular SE application files in this manner contributed to the decision by DNCS management to halt these reviews and to withhold additional reviews until the OS decision on the method dispute could be reached.

fundamental disagreement with the lack of a scientific foundation for the qualitative or semi-quantitative approach and to a lack of understanding as to how they could even adopt that approach in evaluating particular SE applications. As a result, from April 2019 moving forward, the two sides appeared to entrench rather than attempt to work on refining the approach being applied, with management insisting on the tiered process that should begin with the qualitative or semi-quantitative approach and the concerned toxicologists unwilling or unable to begin their evaluation of any application through use of that approach.

Throughout the course of this scientific disagreement, individuals from DNCS and OS management and the concerned toxicologists had periodic discussions with the CTP Ombudsman. Although the Ombudsman discussed the SDR-SMG and SDR-ToPP with the concerned toxicologists and the OS/DNCS managers who contacted him, the Ombudsman acknowledged during interviews that he had limited to no experience in implementing the SDR process at CTP or FDA because there had been no scientific disagreements of this magnitude during his tenure. By all accounts, the Ombudsman attempted to help the involved parties to understand their options for moving forward to the best of his ability. The Ombudsman reported that, early on, he spoke to the concerned toxicologists about both the informal discussion options and the option to initiate the SDR process. As the scientific disagreement evolved, however, and the informal discussions appeared to all parties to be faltering, neither the Ombudsman nor any of the OS/DNCS managers suggested to the concerned toxicologists that they consider initiating the process under the SDR-ToPP—even once the concerned toxicologists had opted instead to initiate a process outside of that contemplated by the SDR-ToPP by framing their May 2019 Appeal under 21 CFR 10.115(o). This investigation determined that, although the SDR-ToPP directs employees wishing to initiate the SDR process to do so on their own by submitting a

memorandum to the appropriate supervisor and the Ombudsman, both the Ombudsman and the managers in OS/DNCS were in a position to encourage the concerned toxicologists to consider initiating the SDR process described in the SDR-ToPP, particularly when it became clear to all parties that the informal efforts to resolve the dispute at the DNCS level had failed. The OS Director, the DNCS managers, and the Ombudsman acknowledged that, in hindsight, an effort to route this dispute into the SDR process at the early stages of the scientific disagreement would have provided a better framework to address that disagreement compared to the manner in which the efforts to do so played out.

In December 2019, the OS Deputy issued his decision on the May 2019 Appeal filed by the concerned scientists and upheld the qualitative or semi-quantitative approach in HPHC Memo as a "well-considered and appropriate management directive that DNCS staff are expected to follow."[146] The concerned scientists viewed the decision as conclusory and largely non-responsive to their scientific concerns, observing that it cites not a single scientific article or publication. The OS Appeal Decision also provides no instructions for next steps for the concerned toxicologists to further elevate their dispute within CTP and the agency, even though several pathways for such an elevation remained available, including the initiation of the SDR process under the SDR-ToPP and a general process to challenge such a decision under 21 CFR 10.75.[147] The OS Deputy stated, both in his decision and during interviews, that he believed the concerned toxicologists attempt to challenge the HPHC Memo via 21 CFR 10.115(o) must fail because, based on his understanding of legal counsel's advice, the process under 21 CFR 10.115

[146] OS Appeal Decision at 4.

[147] Under 21 CFR 10.75(a), "[a] decision of an FDA employee, other than the Commissioner, on a matter, is subject to review by the employee's supervisor * * * (1) At the request of the employee." The SDR-DMG reflects the agency's judgment with respect to how it wishes to implement 21 CFR 10.75(a)(1) with respect to internal scientific disagreements.

did not apply to the HPHC memo as a legal matter. The OS Deputy did not think that, once he resolved the legal issue, there was any need to reach the substance of the scientific disagreement to determine the outcome and did so only as an effort to assist in the resolution of the ongoing scientific disagreement within DNCS.

When asked why they did not further elevate the scientific disagreement within CTP during interviews, the concerned toxicologists explained that their efforts for more than a year had not resulted in what they viewed as a full and fair hearing on the scientific issue. Pointing to emails about the scientific disagreement sent by both them and the Ombudsman to the CTP Director and others in his immediate office, they also conveyed during interviews that they believed the OS Appeal Decision was CTP's final decision on the matter. In contrast, had the concerned toxicologists opted to initiate the process under the SDR-ToPP rather than challenge the HPHC Memo via 21 CFR 10.115(o), there would have been a clear pathway for elevating decisions from one supervisor to the next, including to the Center Director and the Office of the Commissioner.[148] The concerned scientists further explained that, because so much time had been invested in an effort to resolve the scientific disagreement through either informal means or the May 2019 Appeal, they were no longer interested in pursuing the matter within CTP or the agency.

C. Remedial Actions.

Based on our investigation, the agency plans to eliminate the ambiguity in the SDR-ToPP by clarifying the circumstances under which CTP staff may initiate the SDR process, creating an institutionally knowledgeable point of contact for SDR issues at the agency level, and providing substantial education and training to CTP staff involved in scientific decision-making.

[148] SDR ToPP at 6-7.

As described in the previous sections, much of the confusion concerning whether the formal SDR process described in the SDR-ToPP stemmed from an ambiguity in the SDR-ToPP that caused the concerned toxicologists to conclude that the SDR process was unavailable to them. The resulting decision by the concerned toxicologists not to initiate the SDR process gave rise to several subsequent obstacles to successful and transparent resolution of this scientific disagreement. FDA has concluded that the probability of successfully resolving the scientific disagreement would have been higher had this disagreement been routed into the SDR process already established by the SDR-ToPP at the early stages of that disagreement. Many of the issues described in the previous two sections appear to have resulted directly from efforts to elevate this dispute through other means that were less likely to effectively address a scientific disagreement than the SDR process designed precisely for that purpose. Indeed, had the OS/DNCS managers received clearer guidance from either the SDR-ToPP itself or the CTP Ombudsman on whether the scientific disagreement surrounding the HPHC Memo was appropriate for resolution through the SDR process, they could have played a role in directing the concerned toxicologists to that process once the scientific disagreement proved to be intractable.

Correcting the ambiguity in the SDR-ToPP to make clear that disputes of this type qualify for resolution under the formal SDR process will go a long way toward preventing confusion of the type that hampered successful resolution in this case. However, this investigation also concludes that revising the ambiguous language is not sufficient by itself to ensure that similarly situated staff in the future do not misread a set of policies and procedures that should be understood and construed in the context of their purpose. As discussed in more detail in the SDR policies and procedures section, the general purpose of the SDR process is to

ensure that scientific disagreements that affect FDA regulatory decisions are fully and fairly evaluated from all perspectives through a robust, orderly, and transparent process so that the agency's ultimate regulatory decisions are based on sound science.

Our investigation determined that confusion about the applicability and scope of the SDR-ToPP was not limited to the concerned toxicologists. Discussions with all involved CTP managers and the CTP Ombudsman resulted in acknowledgements across the board that these personnel were not sufficiently familiar with the scope and purpose of the SDR process described in the SDR-ToPP and SDR-SMG. Most of these personnel appear to have struggled with good intentions to attempt to understand these policies and implement them, but their lack of familiarity with them and the lack of an available resource specifically designated to provide insight and guidance under these circumstances left staff at all levels of this dispute unclear at various points what procedures were available and how to best navigate them toward successful resolution.

Because scientific disagreements that are good candidates for the SDR process are infrequent at FDA generally, the agency also intends to establish an agency-wide point of contact in the Office of the Commissioner to act as an institutional resource for all FDA personnel when questions arise concerning the scope and purpose of the SDR-SMG and relevant Center's implementing policies and procedures. Such a point of contact will be a valuable resource in future disputes because that contact will be in a better position than those closer to the scientific disagreement to provide advice to staff at all levels concerning the pathways available to them. This point of contact could coordinate with appropriate Center personnel to help route scientific disagreements appropriately and suggest at different points in a disagreement which pathway seems to be the most likely to reach a fair and equitable resolution. In this dispute, for example,

this point of contact could have urged earlier initiation of the SDR process and clarified that any ambiguity in the scope of the SDR-ToPP at issue should be read consistent with the purpose of the agency-level SDR-SMG.

As the last paragraphs suggest, the lack of information and education at CTP concerning the SDR-ToPP and SDR-SMG, as well as their purpose, also represents an area where the agency can improve. All CTP personnel with roles that involve them in scientific decision-making need to be aware of the applicable SDR policies and procedures before they encounter a situation that might give rise to a scientific disagreement suitable for resolution under the formal SDR process. To that end, the agency will provide training to agency employees at all levels that includes a thorough education on the SDR-SMG and their own Centers' policies and procedures regarding the resolution of scientific disagreement and informs them of the pathways available to them for resolving such scientific disagreements.

In sum, because this investigation concludes that confusion regarding whether the formal SDR process was available in this case was largely attributable to ambiguous language within the SDR-ToPP, which was compounded by a lack of familiarity with the existing procedures by CTP staff and a lack of an identified and appropriately knowledgeable resource to provide assistance, the agency intends to:

- revise the SDR-ToPP to remove any ambiguity concerning the coverage of that policy and the SDR process to clearly reflect that SDR is available for disputes of this type;
- create an easily-identifiable agency-level point of contact, who is available to staff at all levels who will provide impartial guidance on the options available to staff under the SDR-SMG and each Center's implementing policies and procedures in order to encourage effective and efficient resolution of scientific disagreements; and

- provide training and education to all CTP staff engaged in scientific decision-making, to include the clarified applicability of the SDR-ToPP, the SDR-SMG, and the availability of the institutional point of contact at the agency level to assist staff in the event of a potential SDR dispute.

We believe that, collectively, these remedial actions will address the ambiguity in the SDR-ToPP that significantly impeded dispute resolution in this case and will provide an improved resource to aid staff in navigating their options for elevating and resolving scientific disagreements at FDA.

IV. Conclusion

For the reasons stated above, FDA's Office of the Commissioner has conducted a full and impartial investigation of the allegations in the OSC referral letter. Although we have concluded that the concerns expressed by the whistleblower warrant remedial action, we have found that the allegations regarding the intent of CTP managers lack merit. Our investigation found that those managers issued the HPHC for reasons consistent with appropriate regulatory science aligning with the applicable statutory standard and did not assign reviews to other toxicology reviewers for the purpose of limiting agency review of the scientific disagreement at issue. We have also considered, pursuant to the standard in 5 U.S.C. § 1213(d), whether the actions that form the basis of the allegations violate or appear to violate any law, regulation, or rule administered by FDA and failed to identify any such violations or the appearance thereof.

Appendix Table

Appendix 0: OSC Referral Letter. Office of Special Counsel Referral letter, "Re: OSC File No. DI-20-0372," dated February 28, 2020.

Appendix 1: HPHC Memo. "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" (February 21, 2019).

Appendix 2: CTP Director's Decision. "CTP Response to Allegations in Whistleblower Complaint (OSC File No. DI-20-0372)" (Sep. 29, 2020).

Appendix 3: Expert Panel Report. "RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP" (Jul. 31, 2020).

Appendix 4: May 2019 Appeal. "Re: DNCS Memorandum: 'Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports'" (May 31, 2019).

Appendix 5: OS Appeal Decision. "Concerns regarding DNCS's HPHC memo dated Feb. 21, 2019" (Dec. 13, 2019).

Appendix 6: OS Management Response. "OS Response to the Scientific Panel Report," appended to the CTP Director's Decision (our Appendix 2) at Appendix G.

Appendix 7: CTP Addendum. "Addendum to CTP Response to Allegations in Whistleblower Complaint (OSC File No. DI-20-0372)" (Oct. 13, 2020).

Appendix 8: SDR-SMG. Staff Manual Guide 9010.1, "Scientific Dispute Resolution at FDA."

Appendix 9: SDR-ToPP. "ToPP: Internal Scientific Dispute Resolution (SDR) in Regulatory Decision Making."

Appendix 0

OSC Referral Letter

U.S. OFFICE OF SPECIAL COUNSEL
1730 M Street, N.W., Suite 300
Washington, D.C. 20036-4505

The Special Counsel

February 28, 2020

The Honorable Alex M. Azar II
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

VIA ELECTRONIC MAIL

Re: OSC File No. DI-20-0372

Dear Secretary Azar:

Pursuant to my responsibilities as Special Counsel, I am referring to you for investigation whistleblower disclosures regarding the Food and Drug Administration (FDA) Center for Tobacco Products (CTP) Office of Science (OS) Division of Nonclinical Science (DNCS). I have determined that there is a substantial likelihood that the allegations disclose a substantial and specific danger to public health and safety, as well as a potential abuse of authority and violation of law, rule, or regulation. A report of your investigation, including any remedial actions, if warranted, is due to the U.S. Office of Special Counsel (OSC) by April 28, 2020.

The whistleblower, [redacted] alleges that DNCS leadership has relaxed its standards in an effort to speed up reviews of new tobacco product applications. As a result it has allowed potentially more harmful products to enter the market. Specifically, according to the whistleblower, in early 2019, DNCS directed its toxicology reviewers—the scientists who are responsible for calculating the health risks posed by new tobacco products—to use a "qualitative or semi-qualitative" approach, rather than the more scientifically appropriate and rigorous quantitative one, when measuring and comparing harmful and potentially harmful chemical compounds in new versus old tobacco products (substantial equivalence (SE) product applications).[2] This approach, according to the whistleblower, is not based on the best available science and can result in arbitrary decisions on SE tobacco product applications, including allowing more harmful products to enter the market. Allegations to be investigated include:

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[1] [redacted] consented to the release of [redacted]name.

[2] *See* Memorandum from [redacted] Deputy Director, OS DNCS, to file, through [redacted], PhD, Director, OS DNCS, dated February 21, 2019, "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalent [SE] report" ("HPHC Memorandum").

- The "qualitative or semi-qualitative" approach, as outlined in the HPHC Memorandum, is not based on the best available science.
- This "qualitative or semi-qualitative" approach can yield entirely different results than the quantitative approach, *i.e.*, one approach might result in a product being approved for market while the other approach would not.
- After several toxicology scientists, including the whistleblower, complained to CTP OS leadership about the issues outlined in this letter, DNCS leadership stopped sending those scientists SE product applications entirely.
- DNCS's actions have effectively prevented those concerned toxicology scientists, including the whistleblower, from being able to invoke FDA's scientific integrity dispute process to raise, and possibly resolve, these issues internally.

The Federal Food, Drug and Cosmetic Act (FD&C) requires new or modified tobacco products to obtain premarket authorization from the FDA before going to market.[3] To be approved, a new proposed tobacco product essentially must not be *more* harmful to public health than a product already on the market (*i.e.*, there must be SE).[4] Nearly all the premarket tobacco product applications that the FDA reviews are SE Reports by applicants seeking to demonstrate that their new product is SE to a predicate product.[5] If the applicant meets its burden, the FDA issues an SE order allowing that product to go to market.[6] If the applicant fails, or does not otherwise qualify for an exemption, FDA issues a 'not substantially equivalent' or NSE order making it illegal to sell, distribute, or import the product in the United States.[7]

In late 2018, the whistleblower alleges that DNCS management became concerned about an anticipated increase in e-cigarette premarket authorization applications. As a result, DNCS management allegedly began pushing scientists to adopt a faster, and less rigorous, 'qualitative or semi-qualitative' approach to reviewing SE applications. Under this approach, generally speaking, according to the whistleblower, scientists ask whether a certain HPHC increase in a new product can be offset by another HPHC decrease in that product and, if it can, then that product can be determined SE without assessing additional quantitative data. This approach to review, according to the whistleblower, is more akin to 'eyeballing it.'

The whistleblower reviewed these tobacco premarket authorization applications and, from 2013 to early 2020, oversaw a team of toxicology reviewer scientists who did

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[3] Section 910(a)(2), as modified by The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), Pub. L. No. 111-31 (2009).
[4] https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/substantial-equivalence.
[5] https://www.federalregister.gov/documents/2019/04/02/2019-05787/content-and-format-of-substantial-equivalence-reports-food-and-drug-administration-actions-on.
[6] *Id.*, https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/substantial-equivalence.
[7] *Id.*

the same. According to the whistleblower, prior to the late 2018 change in procedures, these scientists used a quantitative approach to measure the harmful and potentially harmful constituents (HPHCs), or chemical compounds, when comparing tobacco products on SE applications. Under this approach, according to the whistleblower, the reviewing scientist quantified the specific concentration and toxicity level of each HPHC, like formaldehyde or acetaldehyde, for example, using mathematical equations to evaluate cancer risks and noncancer hazards, like respiratory illness, for both the new and predicate tobacco product. This approach, the whistleblower explains, is based on the best available science and consistent with other federal regulatory agencies', including other components within the FDA's, approach to measuring the human health risks created by tobacco products and the chemical compounds found therein. Using this information, the agency decided whether the new and predicate products were SE or NSE.

Following the change of the late 2018 review procedures, several toxicology review scientists raised concerns to DNCS management about using this qualitative approach on SE applications, and some asked to write 'non-concur' opinions when they did not feel the approach was appropriate. DCNS management declined these requests and, on February 21, 2019, issued the HPHC Memorandum, essentially directing reviewers to use the qualitative or semi-qualitative approach whenever possible in lieu of the quantitative approach.

The whistleblower notes that the HPHC Memorandum cites no scientific sources or bases for using this approach, in contrast to the established and scientifically supported quantitative approach. The whistleblower also explained that he and several other scientists tested the quantitative and qualitative (as outlined in the HPHC Memorandum) approaches on several SE applications and found that the two approaches yielded different results for the same application. One new product, for example, was found to be SE using the qualitative approach—meaning it was safe enough to go to market—but was found to be *NSE* using the quantitative approach. Another product, when tested with both approaches, resulted in the inverse.

The whistleblower alleges that, after the whistleblower and several other toxicology reviewer scientists raised concerns directly to DNCS management and to CTP OS leadership about the new approach and the manner in which the agency effectuated the new approach,[8] management stopped routing any SE evaluations requiring risk assessments to the whistleblower and the other concerned scientists entirely. This, the whistleblower explained, functionally prevented the whistleblower and his colleagues from being able to dispute management's decision to use the qualitative approach on any

[8] The scientists alleged that the HPHC Memorandum equates to a guidance document that was not developed in accordance with the FD&C Act and FDA's Good Guidance Practices

specific reviews, thereby preventing them from invoking the FDA's internal scientific dispute processes.[9]

Pursuant to my authority under 5 U.S.C. § 1213(c), I have concluded that there is a substantial likelihood that the information provided to OSC discloses a substantial and specific danger to public health and safety and possibly abuse of authority and violation of law, rule, or regulation. Please note that specific allegations and references to specific violations of law, rule, or regulation, or other enumerated wrongdoing, are not intended to be exclusive. If, in the course of your investigation, you discover additional violations, please include your findings on these additional matters in the report to OSC. As previously noted, FDA must investigate these matters and produce a report, which must be reviewed and signed by you. Per statutory requirements, I will review the report for sufficiency and reasonableness before sending copies of the report, along with the whistleblower's comments and any comments or recommendations I may have, to the President and congressional oversight committees, and making these documents publicly available.

Additional important requirements and guidance on the agency report are included in the Appendix. If your investigators have questions regarding the statutory process or the report required under section 1213, please contact Elizabeth McMurray, Chief of the Retaliation and Disclosure Unit, at (202) 804-7089 for assistance. I am also available for any questions you may have.

As discussed above, your investigative report, including any remedial actions, if warranted, is due to OSC by April 28, 2020.

Sincerely,

Henry J. Kerner
Special Counsel

Enclosure

cc: Christi A. Grimm, Principal Deputy Inspector General, U.S. Department of Health and Human Services

[9] The whistleblower states he and his colleagues attempted to work with the agency's Ombudsman but were ultimately informed, for the reasons outlined above, they did not have standing to invoke the FDA's internal scientific dispute process.

APPENDIX
AGENCY REPORTS UNDER 5 U.S.C. § 1213

GUIDANCE ON 1213 REPORT

- OSC requires that your investigators interview the whistleblower at the beginning of the agency investigation when the whistleblower consents to the disclosure of his or her name.
- Should the agency head delegate the authority to review and sign the report, the delegation must be specifically stated and include the authority to take the actions necessary under 5 U.S.C. § 1213(d)(5).
- OSC will consider extension requests in 60-day increments when an agency evidences that it is conducting a good faith investigation that will require more time to complete.
- Identify agency employees by position title in the report and attach a key identifying the employees by both name and position. The key identifying employees will be used by OSC in its review and evaluation of the report. OSC will place the report without the employee identification key in its public file.
- Do not include in the report personally identifiable information, such as social security numbers, home addresses and telephone numbers, personal e-mails, dates and places of birth, and personal financial information.
- Include information about actual or projected financial savings as a result of the investigation as well as any policy changes related to the financial savings.
- Reports previously provided to OSC may be reviewed through OSC's public file, which is available here: https://osc.gov/PublicFiles. Please refer to our file number in any correspondence on this matter.

RETALIATION AGAINST WHISTLEBLOWERS

In some cases, whistleblowers who have made disclosures to OSC that are referred for investigation pursuant to 5 U.S.C. § 1213 also allege retaliation for whistleblowing once the agency is on notice of their allegations. The Special Counsel strongly recommends the agency take all appropriate measures to protect individuals from retaliation and other prohibited personnel practices.

EXCEPTIONS TO PUBLIC FILE REQUIREMENT

OSC will place a copy of the agency report in its public file unless it is classified or prohibited from release by law or by Executive Order requiring that information be kept secret in the interest of national defense or the conduct of foreign affairs. 5 U.S.C. § 1219(a).

EVIDENCE OF CRIMINAL CONDUCT

If the agency discovers evidence of a criminal violation during the course of its investigation and refers the evidence to the Attorney General, the agency must notify the Office of Personnel Management and the Office of Management and Budget. 5 U.S.C. § 1213(f). In such cases, the agency must still submit its report to OSC, but OSC must not share the report with the whistleblower or make it publicly available. See 5 U.S.C. §§ 1213(f), 1219(a)(1).

Appendix 1

HPHC Memo

The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

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.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

Date: February 21, 2019

From: [redacted]
Deputy Director
Division of Nonclinical Science
Office of Science

[redacted] 2019.02.21 14:42:34 -05'00'

Through: [redacted]
Director
Division of Nonclinical Science
Office of Science

Digitally signed by [redacted]
Date: 2019.02.21 14:45:50 -05'00'

To: File

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.

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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 EPA[1] 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.

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 <u>different</u> from that of an HPHC that is increased <u>cannot</u> 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

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 off-setting 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.

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[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.

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

Appendix 2

CTP Director’s Decision

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

Date: September 29, 2020

To: [redacted], Supervisory Regulatory Counsel, FDA, Office of the Chief Scientist, Office of Scientific Integrity

From: Mitchell Zeller, Director, FDA, Center for Tobacco Products

Mitchell Zeller -S
Digitally signed by Mitchell Zeller -S
Date: 2020.09.29 09:10:54 -04'00'

Re: CTP Response to Allegations in Whistleblower Complaint (OSC File No. DI-20-0372)

This review by the Office of the Center Director (OCD), Center for Tobacco Products (CTP), FDA, responds to certain whistleblower allegations described in a letter from the Office of the Special Counsel dated February 28, 2020 (OSC File No. DI-20-0372). The allegations related to changes in the toxicological review process for Substantial Equivalence Reports.

I. Background

On February 21, 2019, the Office of Science (OS), Division of Nonclinical Science (DNCS), Deputy Director, [redacted], issued a memorandum entitled "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" (hereinafter: HPHC Memorandum).[1] This memorandum "sets out some key criteria by which HPHCs are to be compared, and lays out some important directions for further evaluation."[2] This memorandum instructs reviewers to "evaluate submitted HPHC data sets using a qualitative or semi-quantitative approach," first, potentially negating the need to review a quantitative risk assessment (QRA) submitted by the applicant.[3]

On May 31, 2019, an OS Toxicology Reviewer and the OS Branch 3 Toxicology Team Lead sent a memorandum to OS leadership expressing their belief that the approach outlined in the HPHC Memorandum was not "appropriate for the toxicology review of tobacco product application," and that they were "not able to apply this memorandum to our toxicological evaluations" (hereinafter Toxicology Reviewer Memorandum).[4] Another Toxicology Reviewer and the Toxicology Branch 3 Chief concurred with the memo. In the Toxicology Reviewer Memorandum, the authors state that the HPHC Memorandum is "not supported by the best

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[1] HPHC Memorandum (Appendix A).
[2] *Id.*, page 2.
[3] *Id.*, pages 3-4.
[4] Toxicology Reviewer Memorandum, page 1 (Appendix B).

available science," and that "the rationale in the HPHC Memorandum for why standard QRA approach is not to be used to evaluate HPHCs in SE applications is not supported by the best available science."[5] The authors of the memo (hereinafter toxicology reviewers) also cite one case where the qualitative or semi-quantitative approach would lead to a finding of Not Substantially Equivalent (NSE), when evaluation of the QRA would lead to a finding of Substantially Equivalent (SE).[6]

On July 3, 2019, [redacted], Deputy Director of Regulatory Management, Office of Science, met with the toxicology reviewers to listen and discuss the concerns raised in the memo.

On December 13, 2019, [redacted] sent a response to the toxicology reviewers addressing concerns raised in the Toxicology Reviewer Memorandum and at the in-person meeting (hereinafter OS Response to Toxicology Reviewers).[7] The OS Response to the toxicology reviewers found that the Toxicology Reviewer Memorandum "dwells on concern with not using the QRA, but **does not demonstrate the new approach is inappropriate for the intended use**."[8] The OS Response to Toxicology Reviewers further found that:

> DNCS management provided adequate justification for developing an alternative, less burdensome, approach for comparison of HPHCs between new and predicate tobacco products. The new (current) DNCS approach is based on sound science and is properly tailored to address the unique regulatory requirements for decisions within the SE program while minimizing the amount of information and resources needed.[9]

On February 28, 2020, the U.S. Office of Special Counsel sent a letter to the Secretary, U.S. Department of Health and Human Services[10] referring a whistleblower complaint that alleges:

- The "qualitative or semi-qualitative [sic]" approach, as outlined in the HPHC Memorandum, is not based on the best available science.
- This "qualitative or semi-qualitative [sic]" approach can yield entirely different results than the quantitative approach, *i.e.*, one approach might result in a product being approved for market while the other approach would not.

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[5] *Id.*, pages 4, 6.
[6] *Id.*, page 12.
[7] OS Response to Toxicology Reviewers (Appendix C).
[8] *Id.*, page 3 (emphasis in original)
[9] *Id.*, page 4.
[10] *Letter from Henry J. Kerner, Special Counsel, to the Honorable Alex M. Azar II, Secretary, U.S. Department of Health and Human Services*, re: OSC File No. DI-20-0372, dated February 28, 2020 (hereinafter Special Counsel Letter, Appendix D).

- After several toxicology scientists, including the whistleblower, complained to CTP OS leadership about the issues outlined in this letter, DNCS leadership stopped sending those scientists SE product applications entirely.
- DNCS's actions have effectively prevented those concerned toxicology scientists, including the whistleblower, from being able to invoke FDA's scientific integrity dispute process to raise, and possibly resolve, these issues internally.[11]

In my capacity as Center Director, I have been asked to examine the first two allegations and make a decision on behalf of the Center. I take the allegations seriously, so I worked closely with FDA's Office of Scientific Integrity (OSI) to develop an approach to review these allegations that was fair, objective, and based in part on similar reviews conducted in other parts of the Agency. To help inform my decision, OSI convened a panel of toxicologists from outside CTP, including some from other agencies, to develop a report[12] (hereinafter Expert Panel Report) providing their opinion on the following statements:

- The "qualitative or semi-quantitative" approach, as outlined in the relevant reviewer guide, is not based on the best available science.
- This "qualitative or semi-quantitative" approach can yield entirely different results than the quantitative approach, i.e., one approach might result in a product being approved for market while the other approach would not.[13]

The Expert Panel Report found that "more specific and transparent guidance to FDA-CTP reviewers are needed to ensure consistent and effective decisions that reduce population harm caused by the use of tobacco products" and provided six recommendations.[14] After consulting with OSI, I provided the Expert Panel Report to the OS Director, along with four other questions, to allow OS leadership an opportunity to review and provide feedback on the recommendations.[15] Obtaining the perspective of the OS leadership provided additional context to inform my review of these issues. The OS Director provided their responses on August 31, 2020.[16]

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[11] *Id.*, page 2. (Note that the approach put forward by DNCS is a "qualitative or semi-quantitative" approach, not a "qualitative or semi-qualitative" approach as referenced by the Special Counsel.)
[12] *Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP*, July 31, 2020 (hereinafter Expert Panel Report, Appendix E)
[13] *Id.*, page 2.
[14] *Id.*, page 4
[15] *Email from Mitch Zeller, CTP Center Director, to* [redacted] *Director, Office of Science*, August 17, 2020 (Appendix F).
[16] *OS Response to the Scientific Panel Report*, August 31, 2020 (hereinafter OS Response to Panel Report, Appendix G).

I have reviewed all documents and present my findings below.

II. The Office of Science did not err in changing the toxicological review process to include a qualitative or semi-quantitative approach.

For the reasons laid out below, and after reviewing all of the available and relevant information, I do not believe the Office of Science erred in changing the toxicological review process in 2019 to include a qualitative or semi-quantitative approach. I believe this new approach was informed by eight years of experience with the tobacco SE program, including reviewing over 7000 SE submissions, and uses the best available science for a regulatory science approach to "substantial equivalence" consistent with what is done across FDA. I also believe the Office of Science has implemented processes and procedures to ensure transparency and consistency across reviews and minimize the risk of error. Further, I believe the new approach makes the best use of limited resources while maintaining focus on protecting public health.

A. The "best available science" standard is subjective and in a regulatory environment may differ from the "best available science" standard in another setting.

The definition of "substantial equivalence" is defined in section 910(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act. The Act states:

> In General. In this section and section 905(j), the term 'substantially equivalent' or 'substantial equivalence' means, with respect to the tobacco product being compared to the predicate tobacco product, that the Secretary by order has found that the tobacco product
>
> i. has the same characteristics as the predicate tobacco product; or
> ii. has different characteristics and the information submitted contains information, including clinical data if deemed necessary by the Secretary, that demonstrates that it is not appropriate to regulate the product under this section because the product does not raise different questions of public health.[17]

The SE application review process requires comparison between two tobacco products (the new tobacco product and a predicate tobacco product) to determine if the products have the same

[17] Section 910(a)(3)(A) of the Federal Food, Drug, and Cosmetic Act, as modified by The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), Pub. L. No. 11-31 (2009).

characteristics, and if not, do the differences in characteristics "raise different questions of public health."[18] The phrase "different questions of public health" is not defined in the Tobacco Control Act, leaving it to the Agency's interpretation.[19]

In evaluating whether there are "different questions of public health," OS leadership believes:

> [T]he data needed for regulatory review and comparison of the health risks between two tobacco products in an SE report is uniquely different than what is need for a standard cumulative health risk assessment of complex measures.[20]

These differences include a defined list of toxicants of interest and the need for a relative comparison between two products.

In 2012, FDA established a list of harmful and potentially harmful constituents (HPHCs) that includes 93 of the greater than 7000 compounds known to be in tobacco smoke, which are linked to the five most common tobacco-associated diseases.[21] This defined list of key toxicants drives the majority of human health risk from tobacco products, and the need to compare relative risk between two products as part of the SE application review. It created a new scientific field unique to the regulatory considerations related to FDA review of SE applications for tobacco products.[22]

While approaches have been developed by the Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) to calculate the cumulative human health risk of complex mixtures (*e.g.*, the quantitative risk assessment approach at issue in this case), these approaches were not designed for relative risk evaluation of tobacco products under the Tobacco Control Act.[23]

Therefore, what constitutes the "best available science" in the unique SE regulatory setting for oversight of tobacco products, where the relative risk of a defined set of known toxicants is required, may be different than the "best available science" for calculating the cumulative human health risk of a complex mixture.

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[18] *Id.*
[19] *See* Chevron U.S.A. v. Natural Resources Defense Council, 467 U.S. 837 (1984).
[20] OS Response to Toxicology Reviewers, page 3.
[21] *See* HPHC Memorandum, page 1-2.
[22] *See Id.*, page 2.
[23] *See Id.*

1. The Office of Science's experience with SE reviews supports the change in toxicological review process.

The Substantial Equivalence (SE) review process has evolved significantly since the beginning of the program. For the first eight years of the SE program, OS relied on a fully quantitative approach.[24] Over that time period, OS staff gained a better understanding of HPHC data in the thousands of SE reports it reviewed.[25] After multiple discussions with many OS toxicologists and OS leadership, OS leadership recognized that the "fully quantitative approach was unnecessarily burdensome to FDA and applicants and didn't impact public health in a meaningful way."[26]

This occurred because OS staff responsible for overseeing the scientific review programs to identify areas for continuous improvement identified that "OS staff were spending a lot of time doing fully quantitative assessments of HPHC data when it was obvious that the differences were not a public health concern."[27] The result of this continuous learning process was the HPHC Memorandum.[28]

2. The Toxicology Expert Panel's review was not informed by the Office of Science's years of experience in SE reviews.

The Expert Panel's Report does not actually directly address the question of whether the HPHC Memorandum uses the "best available science." The report does note concerns about the "qualitative or semi-quantitative" approach. They felt the new approach:

> [A]ppears to rely solely on the judgement of the subject matter expert and impressions of FDA-CTP reviewers as opposed to quantifiable standards or criteria; even when these comparisons are complex, such as considering multiple and potentially offsetting HPHCs. Given the environment in which FDA-CTP operates, the above situation can be a significant limitation of the semi-quantitative approach as presently described. For these reasons, we believe that

[24] OS Response to Panel Report, page 1.
[25] *Id*.
[26] *Id.*, pages 1-2.
[27] *Id.*, page 2.
[28] *See* HPHC Memorandum, page 5 (noting "This memorandum records recent changes in DNCS thinking on how to evaluate HPHC comparisons between tobacco products," and "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 evaluation in the SE pathway…".

> the semi-quantitative approach would substantially benefit from increased transparency.[29]

The panel then made six recommendations, two of which related to the qualitative or semi-quantitative approach.[30] The other four recommendations related to Office of Science workflow and review processes to ensure consistency.[31]

Office of Science leadership agree that "a fully quantitative approach to evaluat[ing] HPHC differences between new and predicate products is ideal."[32] They note that they need to consider practicality and the public health impact of their decisions in relation to the rigorous scientific standard.[33] They also state that over the first eight years of the SE program while using only the quantitative approach, "OS staff came to recognize the fully quantitative approach was unnecessarily burdensome to FDA and applicants and didn't impact public health in a meaningful way."[34]

Furthermore, OS identified materials and information that were not available to the expert panel, but that contribute to transparency in the review process, such as reviewer guides,[35] weekly meetings involving all staff who work on SE reviews,[36] and a recently-launched OS-wide SE training program which is recorded so staff can review again and to train new staff coming onboard.[37] OS also notes that – consistent with other FDA regulatory programs – that as the Agency gains knowledge and experience from reviewing tobacco products, the criteria in the HPHC Memorandum reflect a more objective approach than what was previously used.[38]

For these reasons, I do not have concerns with the transparency of the new qualitative or semi-quantitative approach.

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[29] Expert Panel Report, page 3.
[30] *Id.*, page 4 (See recommendations 1 and 3).
[31] *Id*.
[32] OS Response to Panel Report, page 1.
[33] *Id*.
[34] *Id*.
[35] *See* Reviewer Guides and Scientific Policy Memoranda about FDA Review of Tobacco Product Applications, available at: https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/reviewer-guides-and-scientific-policy-memoranda-about-fda-review-tobacco-product-applications (listing 15 Chemistry/Toxicology Reviewer Guides). Accessed September 24, 2020.
[36] OS Response to Panel Report, page 3.
[37] *Id.*, pages 3-4.
[38] *Id.*, page 2.

3. The Office of Science has appropriate systems in place to protect public health during the SE review process.

Both the toxicology reviewers who raised concerns with the qualitative or semi-quantitative approach and the expert panel note that the new approach could lead to different regulatory outcomes compared with using a fully quantitative approach.[39] They suggest that this could lead to products which raise different questions of public health compared to their predicate entering the marketplace, and products that do not raise different questions of public health could be kept from entering the marketplace by receiving a Not Substantially Equivalent (NSE) finding.[40]

OS has many processes and procedures in place that the expert panel was likely not aware of to ensure that SE review decisions are aligned with the statutory standards. These include:

- Multiple reviewer guides and other specific training materials designed for specific roles.[41]
- Quality control review by OS staff of every SE order.[42]
- Routine review across review programs to identify areas for improving the review process and decision-making.[43]
- A defined process for reviewer agreement that aligns with the process used across FDA. All staff involved in a review are required to document their conclusions, including any disagreements with conclusions made by subordinate staff. The Technical Project Lead then evaluates these conclusions and documents their final decision.[44]
- An OS-wide SE training program which is recorded so staff can review materials again and to train new staff coming onboard.[45]

While these processes and procedures can minimize the risk of inconsistencies or errors, they cannot eliminate them entirely. The risk that a product inadvertently receives a finding of Not Substantially Equivalent, despite not raising different questions of public health, has no impact on public health because the result is an inherently harmful product remains off the market or, in

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[39] Toxicology Reviewer Memorandum, page 12. Expert Panel Report, page 3.
[40] Toxicology Reviewer Memorandum, page 12.
[41] *See* Reviewer Guides and Scientific Policy Memoranda about FDA Review of Tobacco Product Applications, available at: https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/reviewer-guides-and-scientific-policy-memoranda-about-fda-review-tobacco-product-applications. Accessed September 24, 2020. OS Response to Panel Report, page 3.
[42] OS Response to Panel Report, page 2.
[43] *Id.*
[44] *Id.*, pages 2-3.
[45] *Id.*, pages 3-4.

the case of provisional SE products, is removed from the market. If the applicant believes the Agency erred in its decision, they could file an appeal under 21 C.F.R. §10.75 for reevaluation.

The risk of a product which raises different questions of public health (compared to an individual predicate) inadvertently receiving a finding of substantial equivalence could impact public health by allowing a "more dangerous" product onto the market. But the risk of this happening is low given all the processes in place that are described above. There is also the reality that under the SE process, the new tobacco product is compared to a predicate tobacco product of the applicant's choosing. Had the manufacturer chosen a "more dangerous" predicate tobacco product, the new product could have been correctly found to be SE.

B. The Office of Science's management team has a responsibility to use resources efficiently.

As noted by OS leadership, they have:

> a responsibility to manage regulatory programs that are based on sound science, the intent of the law, alternative approaches, and the efficient use of resources to effectively address regulatory issues and protect public health.[46]

After years of experience with reviewing SE applications, DNCS leadership developed and implemented a new approach to reviewing HPHC data.[47] Based on that experience, this new approach more efficiently uses reviewer time by providing 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.[48]

As noted by OS leadership:

> FDA senior leaders regularly look for opportunities to streamline processes and policies to improve efficiency, conserve resources, and develop alternative approaches that utilize the minimum amount of information necessary to

[46] OS Response to Toxicology Reviewers Memorandum, page 3.
[47] HPHC Memorandum.
[48] *Id.*, page 6.

> adequately address the issue and render regulatory decisions within appropriate timeframes.[49]

I agree with this approach and believe that is what motivated OS leadership to make the changes to the SE review process at issue here.

III. Conclusion and Next Steps

In summary, after carefully reviewing the toxicology reviewers' concerns, reviewing the report of the expert panel, reviewing the additional context and responses to my questions provided by OS leadership, and reading all related documents, I support the decision of OS management. The OS management decision reflected input from experienced OS staff to change the SE review process proposed in the HPHC Memorandum. I believe this change is based on OS's years of experience with thousands of SE reviews and that OS provided adequate justification for that change, both from a regulatory-science perspective and from management's responsibility to use resource efficiently.

I agree with OS leadership's conclusion that the Toxicology Review Memorandum "reflects a preference to perform the most comprehensive evaluation in all circumstances," but does not consider the unique regulatory requirements at issue in SE reviews.[50] The Review Memorandum "does not demonstrate the new approach is inappropriate for the intended use."[51] While the expert panel expressed concerns with the qualitative or semi-quantitative approach related to details and transparency, the expert panel did not state that the new approach was inappropriate, and in fact made recommendations to better implement the new approach (many of which OS had in place already).[52]

For all the reasons stated above, I find that OS leadership appropriately changed the SE review process related to review of HPHC information.

Going forward, I will ask the OS Director to ensure that CTP's Ombudsman provide training at least twice a year to OS staff on FDA's scientific dispute resolution process to ensure CTP scientists know the process for raising scientific concerns related to review processes and decisions. I will also ask the OS Director to ensure that staff are aware of how to raise disputes that are not covered by the scientific dispute resolution process.

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[49] OS Response to Toxicology Reviewers Memorandum, page 4.
[50] *Id.*, page 3.
[51] *Id.*, (emphasis omitted).
[52] *See* Expert Panel Report.

In addition, I will direct OS leadership to reinforce the importance of training, collaboration and transparency in decision-making to all supervisors and managers. I have also requested that OS leadership provide to me, twice a year, an update on any formal or informal scientific disputes and how they were resolved.

Appendix A

HPHC Memorandum

The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

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.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

Date: February 21, 2019

From: [redacted]
Deputy Director
Division of Nonclinical Science
Office of Science

[redacted]

Through: [redacted]
Director
Division of Nonclinical Science
Office of Science

Digitally signed by [redacted]
Date: 2019.02.21 14:45:50 -05'00'

To: File

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.

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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 EPA[1] 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.

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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 <u>different</u> from that of an HPHC that is increased <u>cannot</u> 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

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 off-setting 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.

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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.

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[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.

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

Appendix B

Toxicology Reviewer Memorandum

May 31, 2019

To: [redacted]
Director, CTP/OS

[redacted]
Deputy Director of Regulatory Management, CTP/OS

[redacted]
Deputy Director of Regulatory Science, CTP/OS

From: [redacted]
Toxicology [redacted], CTP/OS/DNCS

Digitally signed by [redacted] -S
Date: 2019.05.31 12:03:21 -04'00'

[redacted] Toxicology [redacted], CTP/OS/DNCS

Digitally signed by [redacted] -S
Date: 2019.05.31 12:20:05 -04'00'

Concurring: [redacted]
Toxicology [redacted], CTP/OS/DNCS

Digitally signed by [redacted] -S
Date: 2019.05.31 12:30:31 -04'00'

[redacted]
Toxicology [redacted], CTP/OS/DNCS

Digitally signed by [redacted] -S
Date: 2019.05.31 12:33:06 -04'00'

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

We submit this letter to seek resolution[1] on matters related to the memorandum "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" signed by Food and Drug Administration's (FDA's) Center for Tobacco Products (CTP) Office of Science (OS) Division of Nonclinical Science (DNCS) on February 21, 2019 (the HPHC Memorandum)[2].

First, we find that in issuing the HPHC Memorandum, DNCS issued a guidance document that set forth new Agency policy and provides DNCS staff guidance on a new approach for review of SE product applications but was not developed in accordance with the FD&C Act and FDA's regulations for good guidance practice (GGP)[3]. *Second*, we find that the HPHC Memorandum is a guidance document that is not supported by the best available science as required by FDA policies related to preservation and promotion of scientific integrity[4]. For these reasons, we do not find the qualitative (or semi-qualitative) approach outlined in the HPHC Memorandum appropriate for the toxicology review of tobacco product application, and thus are not able to apply this memorandum to our toxicological evaluations. The

[1] 21C.F.R.§10.115 states: "*If you believe that someone at FDA did not follow the procedures in this section* [GGP] *or that someone at FDA treated a guidance document as a binding requirement, you should contact that person's supervisor in the center or office that issued the guidance document*" (see Appendix A).
[2] See Appendix B
[3] FDA's Good Guidance Practices, 21 C.F.R. § 10.115(b); FDA 2011, Food and Drug Administration Report on Good Guidance Practice. Improving Efficiency and Transparency
[4] SMG 9001.1 FDA staff manual guides, volume iv – agency program directives

discussion below, includes, but is not limited to all issues with the February 21, 2019 memo. We respectfully request an in-person meeting so that we may have the opportunity to discuss these issues directly and receive concurrence that the reviewers do not need to apply the February 21, 2019 memo to tobacco product application review.

Introduction:

On Feb 22, 2019 DNCS staff were issued the memorandum entitled "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports", signed February 21, 2019. The HPHC 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*". The document sets forth the implementation of a "*new approach toward HPHC comparisons in SE reviews*"[5] for use by DNCS reviewers instead of the standard QRA framework and approach, used by DNCS in SE reviews since 2013, and indicates that the previously used approach is not "*designed to be compatible with the review of premarket product applications such as those reviewed by the FDA.*" The HPHC Memorandum does not provide scientific data and reasonable explanation for, nor does it mention how, the new approach to evaluating HPHCs is more appropriate than the established QRA approach previously used and considered appropriate by DNCS. We find the HPHC Memorandum to be a guidance document that is problematic in multiple respects:

First, the HPHC Memorandum, which was developed to inform DNCS staff of a new CTP policy and provide guidance on application of a new approach for evaluating SE product applications, was not developed in accordance with the FD&C Act and FDA's regulations for GGP[6]. The FD&C Act and FDA's GGP policies require any such substantial change in agency policies or those related to complex scientific issues to be made through notice and comment procedures; this is necessary to ensure adequate scientific deliberation, review and public input.

Second, we find that the HPHC Memorandum is a guidance document that is not supported by the best available science as required by FDA policies related to preservation and promotion of scientific integrity (SMG 9001.1); these FDA policies "*seek to strengthen the scientific quality, integrity and credibility of scientific reviews and decision-making at the agency.*" GGP procedures are also designed to allow adequate scientific deliberation, review and public input to ensure FDA guidance documents are of high quality. Also, the HPHC Memorandum does not provide a reasonable explanation or even mention how the new approach to evaluating HPHCs is more appropriate than the standard QRA approach which has been considered appropriate by DNCS in SE reviews since 2013[7], and has previously been used in regulatory decisions made by CTP. For example, DNCS has previously determined that the standard QRA approach was appropriate to make conclusions in findings of SE as NSE orders for tobacco product applications and was used to inform the development of the NNN product standard for

[5] 2/22/2019 Email from Dr. [redacted] to CTP-OS-DNCS on "New Memorandum on HPHC comparisons in toxicology SE reviews"

[6] FDA's Good Guidance Practices, 21 C.F.R. § 10.115(b); FDA 2011, Food and Drug Administration Report on Good Guidance Practice. Improving Efficiency and Transparency

[7] Toxicology Review of 905(j)(1)(A)(i) Report Second-Cycle Review of Additional Information for SE0003730; SE0003731; signed 06-03-2013

smokeless tobacco products[8]. In addition, there is a current DNCS Memorandum on "SE Review: Evaluating carcinogenic HPHC increases and assumptions of linearity for low-dose extrapolation", signed October 27, 2017[9], that continues to indicate that the standard QRA approach is appropriate for evaluating HPHCs in SE applications. Although scientific or policy conclusions can change based on new information or scientific data, such information should be provided and discussed to address prior findings and decisions, and to explain *why* the change in policy or conclusions is supported by the relevant data or references. Without such information, changes in policy or regulatory conclusions could be perceived as arbitrary and capricious[10].

Discussion:

1. <u>The HPHC Memorandum is not in accordance with GGP</u>

The HPHC Memorandum meets the definition of Guidance:

We find that the HPHC Memorandum issued to DNCS staff is a "*guidance document*" or its functional equivalent[11] within the meaning of the FD&C Act[12] and FDA's regulations and policies for GGP[13] because it is a document "*prepared for FDA staff*" to describe Agency policies that relate to "*the processing, content, and evaluation or approval of submissions.*" By informing staff of the new "*DNCS review practice for HPHC comparisons between two tobacco products*[14]", the HPHC Memorandum has broad applicability and future effect on CTP regulatory decisions related to tobacco product SE applications.

Prior to the 2019 HPHC Memorandum, DNCS used the standard QRA paradigm to support regulatory decisions related to tobacco product SE applications since 2013, to develop the draft NNN product standard for smokeless tobacco products[15], and in communications with stakeholders related to using the QRA approach for evaluating HPHCs in the context of SE product applications[16]; stakeholder input on the applicability of the standard QRA approach in the context of evaluating HPHCs in SE

[8] See FDA-2016-N-2527 Smokeless NNN PRIA

[9] DNCS Memoranda: SE Review: Evaluating carcinogenic HPHC increases and assumptions of linearity for low-dose extrapolation", signed October 27, 2017

[10] *W. Deptford Energy, LLC v. FERC,* 766 F.3d 10, 20 (D.C. Cir. 2014) ("an agency must 'provide a reasoned explanation for departing from precedent or treating similar situations differently")

[11] Policies and procedures for the development, issuance, and use of significant guidance documents by agencies are further refined in the Office of Management and Budget (OMB) Bulletin entitled, "Agency Good Guidance Practices" published January 18, 2007.

[12] FDA's Good Guidance Practices, 21 C.F.R. § 10.115(b): "*What is a guidance document? (1) Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue. (2) Guidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies*.

[13] FDA 2011, Food and Drug Administration Report on Good Guidance Practice. Improving Efficiency and Transparency

[14] HPHC Memorandum, p3: "*Currently, DNCS review practice for HPHC comparisons between two tobacco products is as follows*:"

[15] See FDA-2016-N-2527 Smokeless NNN PRIA

[16] Feedback on the use of QRA in SE applications has been provided to applicants as part of SE deficiencies. In addition, FDA has indicated that the QRA approach is appropriate for a comparison between two tobacco products in SE applications during meetings with applicants; as an example, see the August 17, 2016 Meeting Minutes for (b) (4) ; during the meeting, FDA noted that "*If* (b) (4) *does not provide a study with a complete datasets in its SE Reports, then other evidence might be useful, such as a quantitative risk assessment (QRA)*"

applications has been received by CTP not only in product applications, but also during the CTP Risk Assessment public workshop. As noted in the HPHC Memorandum, "… *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*." Given CTP's prior use and findings that the standard QRA approach in regulatory decision-making is appropriate, previous communications to stakeholders and public input regarding this approach, the HPHC Memorandum set forth policy changes that are more than minor in nature. In addition, the HPHC Memorandum relates to scientific principles and approaches used to evaluate risks to human health from HPHC exposures in tobacco products or tobacco smoke; these are complex scientific issues.

Guidance documents "*that set forth … changes in interpretation or policy that are of more than a minor nature; include complex scientific issues*" are within the definition of Level 1 Guidance under the FD&C act and FDA GGP policies procedures; these require public comment prior to implementation (21 C.F.R. § 10.115). However, not only was the HPHC Memorandum issued for implementation without public feedback, the guidance document was developed without addressing or considering relevant scientific data and rationale[17] provided by DNCS staff with expertise in human health risk assessment; although not yet established, a "*task force focusing on the toxicology risk assessment process and applicant-submitted QRAs*" was proposed by DNCS on March 5, 2019[18], after the HPHC Memorandum was signed and issued for implementation.

To ensure that the guidance document is "*developed with appropriate review and public participation, accessible and transparent to the public, of high quality*" (OMB 2007), we believe that FDA GGP should have been followed in the development, and prior to the issuance and implementation of this guidance document on how DNCS reviewers should evaluate HPHCs in the context of tobacco product SE application review.

2. The HPHC Memorandum is not supported by the best available science[19]

The standard QRA approach is a systematic and transparent process to evaluate human health risk from chemical exposures:

The framework for cumulative human health risk assessments of complex mixtures, as first outlined in the 1983 NAS Report, provides a predictable scientific approach and consistency across regulatory agencies for evaluation of cumulative human health risk from chemical exposures. The standard QRA approach provides a systematic and transparent process to (1) determine the type of adverse effects that may be caused by a chemical (hazard identification), (2) determine the relationship between the magnitude of exposure to a hazard and the probability and severity of adverse effects (dose-response assessment), (3) determines the extent to which exposure actually occurs (exposure assessment), and (4) to combine the information from the preceding steps to reach a conclusion about

[17] See Appendix C for a timeline and information related to the scientific concerns previously communicated by reviewers to the DNCS Deputy Director on the use the qualitative approach in the context of SE review.

[18] The Proposal for DNCS Internal Group Formation for a "Toxicology SE Reviewer Guide Task Force" was made by the DNCS IO and dated 5/13/2019

[19] This section highlights some of the main points of scientific disagreement the reviewers have with the HPHC Memorandum; it is not intended to list all the issues identified.

the nature and potential magnitude of risk (risk characterization)[20]. Although this approach for evaluating potential human health risks from complex mixtures is not specific to any given type of exposure or regulated products, it has broad applicability and has been widely adopted by federal agencies, including FDA, to support a wide array of regulatory decision making[21].

The standard QRA approach has been considered appropriate for over 30 years to evaluate human health risk from tobacco:

The standard QRA approach has been used for more than 30 years to evaluate human health risks from tobacco products. Some notable scientific publications that include a discussion of the applicability and use of the QRA approach in the context of tobacco products, include: the NAS 1986 report- Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects; the EPA 1993 Report- Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders; the NAS 2001 Report- Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction; the OEHHA 2005 Report- Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant; and several other publications[22,23,24,25, 26,27].

The standard QRA approach has been considered appropriate in CTP regulatory decisions (including in the context of SE applications) for over 6 years:

The applicability of the standard QRA approach in the context of tobacco product applications, was discussed at the public meeting held by CTP "Risk Assessment of Tobacco Products: A Public Workshop". The workshop focused specifically on the use of the standard QRA in the review of premarket tobacco product applications; during this meeting, CTP received information and feedback from a wide array of stakeholders in academia, industry, non-profit as well as other regulatory agencies. Although there are aspects relevant to tobacco product risk assessment that are developing, the general compatibility of the standard QRA approach with review of premarket tobacco product applications, including SE applications, was not an issue of dispute during the Public Workshop. Based on the available scientific information, including feedback CTP previously received from stakeholders during the

[20] GAO 2001. Report to Congressional Requests; Chemical Risk Assessment- Selected Federal Agencies' Procedures, Assumptions and Policies.

[21] GAO 2001 Report to Congressional Requests; Chemical Risk Assessment- Selected Federal Agencies' Procedures, Assumptions and Policies.

[22] Fowles and Dybing, 2003. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tob Control*, vol 12: 424-430.

[23] Fowles, Bates, and Dybing, 2000. The chemical constituents n cigarettes and cigarette smoke: Priorities for harm reduction. A report to the New England Ministry of Health.

[24] Cunningham, Fiekelkorn, Johnson, and Meredith, 2011. A novel application of the margin of exposure approach: Segregation of tobacco smoke toxicants. *Food and Chemical Toxicology*, vol. 49: 2921-2933.

[25] Haussmann, 2012, Use of hazard indices for a theoretical evaluation of cigarette smoke composition. Vol. 25(4):794-810.

[26] Xie et al. 2011. A probabilistic risk assessment approach used to prioritize chemical constituents in mainstream smoke of cigarettes sold in China. *Regulatory Toxicology and Pharmacology*, vol. 62: 355-362.

[27] Marano et al, 2012. Quantitative risk assessment of tobacco burning and tobacco-heating cigarettes. 66th Annual Tobacco Science Research Conference, Quantitative Risk Assessment: A Path Forward. Recent Advances in Tobacco Science, Vol. 38: 3-20.

Public Workshop[28], the standard QRA approach is applicable and appropriate to evaluate relative human health risks from tobacco products in SE applications.

The rationale in the HPHC Memorandum for why standard QRA approach is not to be used to evaluate HPHCs in SE applications is not supported by the best available science:

The HPHC Memorandum does not mention any new information or scientific data to explain why the change in DNCS policy related to the use of QRA in the evaluation of HPHCs is supported by the best available science. Rather, the HPHC Memorandum provides the following lines of justification (without any supportive references) as for why the new approach was developed and should be used for the evaluation of HPHCs in SE applications instead of the standard QRA approach and methods:

- The cumulative human health risk of complex "*mixtures evaluated by organizations such as the EPA and the ATSDR, are (1) not specific to tobacco products, (2) not designed to rapidly assess relative risk between complex mixtures, or (3) not designed to be compatible with the review of premarket product applications such as those reviewed by the FDA*." and
- "*…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*."

<u>This justification does not provide a reasoned rationale consistent with the best available science:</u>

1. The statement that "*the cumulative human health risk of complex mixtures evaluated by organizations such as the EPA and the ATSDR are not specific to tobacco products*" is not accurate; Federal agencies such as the EPA has used the QRA approach to evaluate cumulative human health risk from tobacco products. A notable example is the EPA 1993 report "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders", which used a risk assessment framework to classify secondhand smoke as a Group A carcinogen. However, whether agencies such as EPA and ATSDR evaluate health risk of complex mixtures specific to tobacco products, or if the QRA approach outlined by NAS (and built upon by EPA, FDA and ATSDR among others) was (or was not) developed to be specific for tobacco products has no bearing on whether this approach is applicable and appropriate for the evaluation of human health risks from HPHCs in tobacco products[29,30,31]. The appropriateness of using the standard QRA approach in the evaluation of HPHC exposures from tobacco products and tobacco smoke is evidenced in the multitude for regulatory decisions, including SE and NSE marketing orders

[28] Feedback received from industry regarding the use of QRA to compare relative risks between tobacco products was summarized in the publication by Marano et al, 2018 "Quantitative risk assessment of tobacco products: A potentially useful component of substantial equivalence evaluations" (*Regulatory Toxicology and Pharmacology*, vol. 95:371-384). While the paper has limitations, it synthesizes much of the workshop discussion, and shows how the established risk assessment paradigm can be used to inform tobacco product review.

[29] See footnotes 18 to 24 above, and see also NAS, EPA, and OEHHA references noted previously.

[30] NAS, 1983. Risk assessment in the federal government: Managing the process. National Research Council. "Risk assessment is the use of factual base to define health effects of exposure to individuals or populations to hazardous materials and situations."

[31] NAS, 2009. Science and Decisions: Advancing Risk Assessment. National Research Council. "[R]isk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk"; "[R]isk assessment remains the most appropriate available method for measuring the relative benefits of many possible interventions available to improve human health"

issued by CTP that have considered the standard QRA approach appropriate to evaluate human health risks from HPHCs in tobacco products. In addition, evaluation of HPHC data using the standard QRA approach has been provided by CTP as an option for applicants to address HPHC increases in new tobacco products as compared to corresponding predicate product(s)[32]; CTP also granted deficiency response extensions to allow reasonable time for applicants to conduct a QRA addressing deficiencies in product applications[33].

2. The HPHC Memorandum indicates that the standard QRA approach is not appropriate in the context of tobacco product review because it is "*not designed to rapidly assess relative risk between complex mixtures.*" The toxicology reviewer evaluates the appropriateness of a QRA (or assessment of relative risk between two complex mixtures) that has already been conducted and submitted by applicants to support tobacco product SE applications. Whether or not the QRA approach was specifically "*designed to rapidly*" evaluate the relative risks of complex mixtures, does not provide information relevant to why an HPHC evaluation (provided by applicants) that uses the standard QRA approach is not scientifically appropriate to evaluate relative human health risks in the context of SE product applications. Therefore, this statement does not provide a scientific rationale for why the new approach was developed and should be used for the evaluation of HPHCs in SE applications instead of the standard QRA approach.
3. The statement that the standard QRA paradigm is "*not designed to be compatible with the review of premarket product applications such as those reviewed by the FDA*" is not accurate. The risk assessment paradigm provides a framework for a systematic and consistent approach to evaluate human health risks (cancer and non-cancer) from chemical exposures. The standard QRA approach for evaluation of cumulative human health risk of complex mixtures has been widely adopted federal regulatory agencies including the FDA[34,35]; the standard QRA approach is compatible with, and has been used by the FDA to inform the evaluation of premarket applications for various regulated products, including foods[36], drugs and devices[37] as well as tobacco product applications[38].
4. The statement that "*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*

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[32] See August 17, 2016 Meeting Minutes for (b) (4) ; during the meeting, FDA noted that "*If* (b) (4) *does not provide a study with complete datasets in its SE Reports, then other evidence might be useful, such as a quantitative risk assessment (QRA*)"

[33] The FDA A/I Extension Granted letter dated November 30, 2018 (SE0014989) states "*we do believe that the extension granted is a reasonable amount of time which would enable you to provide a complete response through the combined approach of a quantitative risk assessment (QRA*)"

[34] GAO 2001. Report to Congressional Requests; Chemical Risk Assessment- Selected Federal Agencies' Procedures, Assumptions and Policies. Agencies (including FDA) generally following a transparent four-step risk assessment process recommended by the NAS in the context of the given diverse assessments for the agency, though the procedures used have many common basic assumptions; "Risk assessment is an important, but extraordinarily complex, element in federal agencies' regulation of potential risks associated with chemicals."

[35] Gaylor et al, 1997. Health risk assessment practices in the U.S. Food and Drug Administration. *Regulatory Toxicology and Pharmacology*, vol. 26: 307-321.

[36] March 2002. Report by the CFSAN Risk Analysis Working Group (accessed at https://www.fda.gov/food/cfsan-risk-safety-assessments/initiation-and-conduct-all-major-risk-assessments-within-risk-analysis-framework); Dickey, RW (2102) FDA Risk Assessment of Seafood Contamination after the BP Oil Spill; Environ Health Perspect.120(2)

[37] FDA 2005. Premarketing Risk Assessment Guidance for Industry

[38] See footnotes 18 to 24 above, and see also NAS, EPA, and OEHHA references noted previously.

tobacco products: the HPHC list", is not accurate and counter to FDA's final HPHC guidance for industry and FDA staff[39] and the April 2011 FR Notice[40]:

- The definition of HPHC does not limit the HPHC established list to the chemicals "*understood to drive the majority of human health risk posed by tobacco products.*" As defined in the HPHC Guidance document, the phrase "harmful and potentially harmful constituent" includes any chemical or chemical compound in a tobacco product or in tobacco smoke that: a) is, or potentially is, inhaled, ingested, or absorbed into the body, including as an aerosol (vapor) or any other emission; and b) causes or has the potential to cause direct or indirect harm to users or non-users of tobacco products.
- Consistent with the HPHC definition, as published in the April 2011 FR Notice, the HPHC established list was developed using a hazard-based approach that identified chemicals or chemical compounds in a tobacco product or in tobacco smoke that cause or have the potential to cause direct or indirect harm; this approach is different from the risk-based approach that would be necessary to determine (and limit) the HPHC established list to chemicals "*understood to drive the majority of human health risk posed by tobacco products.*"
- Furthermore, the Supplementary Information of the April 2012 FR Notice[41] specifies that the established HPHC list may not be comprehensive and is restricted by the scope and criteria used for its development.

However, even if this statement was accurate, it does not provide information relevant to why the standard QRA approach is not scientifically appropriate to evaluate relative human health risks in the context of SE product applications.

The "*qualitative or semi-quantitative approach*" outlined in the HPHC Memorandum is not supported by the best available science:

The HPHC Memorandum sets forth implementation of a "*qualitative or semi-quantitative approach"* for HPHC evaluations in SE reviews, without providing any scientific references or rationale explaining why this approach is supported by the best available science. Broadly, the HPHC Memorandum informs DNCS staff that when an applicant provides a QRA, "...*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*

[39] FDA 2016. Guidance for Industry and FDA Staff: "Harmful and Potentially Harmful Constituents' in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act" (Revised).
[40] FDA 2011. Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments. 76 FR 50226.
[41] FDA. 2012. Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List. 77 FR 20034

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."*

We find that application of a "*qualitative or semi-quantitative approach"* that meets the above criteria is not supported by the best available science and does not consider all data and information provided by an applicant in an SE application that contains a QRA:

1. A risk assessment approach that meets criteria a-c[42] and considers only HPHCs identified as "*analytically non-equivalent HPHC increases or decreases"* would not consider the totality of information provided in a QRA submitted by applicants in the context of SE applications. This could result in the loss of important risk information that is relevant to the toxicology evaluation of relative cancer risk and noncancer hazard (EPA 2002) between the new and predicate products. The results of the statistical or analytical equivalence evaluation depend on several factors such as the decision criteria for equivalence (e.g., value considered a meaningful analytical difference) and data quality among others. In the context of risk assessment, such evaluations are generally conducted as screening level assessments only[43]; this gives an indication that either 1) all constituents (e.g., HPHC) are below the pre-set health based criteria used to conduct the equivalence test and identify constituents of potential concerns and thus a risk assessment is not warranted or 2) there are constituents above the set criteria of concern (e.g., HPHC increases above the equivalence margin), and a risk assessment is informative. When a screening level assessment identifies constituents above a set level or criteria predetermined to be of concern (which in the case of the HPHC analysis is the equivalence margin), a baseline risk assessment is conducted to characterize the current and potential human health risks from exposures to the hazardous substances. Based on established risk assessment principles and available guidance it is accepted practice to include all constituents (with data of sufficient quality) in the risk or hazard calculations when evaluating human health risk from chemical mixtures[44,45,46,47].

[42] Criteria a-c are discussed together because they provided repeated instructions on which HPHCs submitted in SE applications that should be considered in the toxicology evaluation when the applicant submits a QRA.

[43] EPA 2002. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites

[44] IGHRC 2009. Chemical Mixtures: A Framework for Assessing Risk to Human Health (CR14). Institute of Environment and Health, Cranfield University, UK.

[45] EPA 1989. Risk Assessment Guidance for Superfund. Volume I. Human Health Evaluation Manual (Part A). EPA/540/1-89/002. Office of Emergency Response;

[46] EPA 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures Published on September 24, 1986, Federal Register 51(185):34014-34025. Risk Assessment Forum U.S. Environmental Protection Agency Washington

[47] EPA 2002. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. *"EPA cautioned that eliminating COPCs based on background (either because concentrations are below background levels or attributable to background sources) could result in the loss of important risk information for those potentially exposed, even though cleanup may or may not eliminate a source of risks caused by background levels*"

HPHC data provided in SE applications are intended to provide a comparison of the HPHC levels and potential user exposures from differences in product characteristics. A risk assessment approach that only considers compounds identified as "*analytically non-equivalent HPHC increases or decreases*" does not consider the totality of information provided and could result in the loss of important risk information that is relevant to the evaluation of relative cancer risk and noncancer hazard between the new and predicate products. A risk assessment approach that includes all measured HPHCs can provide a more comprehensive hazard identification; this is more representative of the relative cumulative cancer risk and noncancer hazards and thus is more appropriate for a comparison between tobacco products in SE applications.

2. The statement *"Considers HPHC measurements that are analytically equivalent per the Chemistry discipline as equivalent for purposes of toxicological comparison between the two compared products"* is not accurate. The equivalence margins used in the HPHC evaluation are set based on analytical methods and analytical variability, not health-based equivalence margins. Because the evaluation does not use health-based equivalence margins, it cannot be concluded that HPHC increases or decreases found by Chemistry as analytically equivalent are also "*equivalent for purposes of toxicological comparison*" in terms of human health risks especially given the differences in potency for the different HPHCs.
3. The statement 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"* is not accurate and inconsistent with previous CTP regulatory decisions**.** As mentioned above, the results of the analytical equivalence evaluation depend on several factors, such as the decision criteria for equivalence (e.g., value considered a meaningful analytical difference). For this reason, several scenarios exist where while there are only non-equivalent HPHC increases (i.e., without non-equivalent decreases), the totality of data and information submitted by an applicant could be adequate to demonstrate that the differences between two products are unlikely to raise different questions of public health. Although CTP does not have an established criterion or threshold for a *de minimis* risk in the context of SE applications, there could be specific scenarios for which the HPHC increase (and associated increase in risk) is unlikely to raise different questions of public health. For example, the Memoranda written by Dr. [redacted] for SE0006198, SE0006199, SE0006211 (signed May 3rd, 2018)[48] and for SE0000603 (signed July 27th, 2018)[49] provide two specific HPHC comparison scenarios where (without mention of offsetting HPHC decreases), Dr. [redacted] concluded that based on the totality of information, "*the increases in formaldehyde do not cause the new products to raise different questions of public health."* In addition, an HPHC comparison scenario where the equivalence test identified a non-equivalent HPHC increase (without concomitant non-equivalent decreases) but the standard QRA approach (i.e., using on all measured HPHCs) shows that there is no increase in the overall

[48] From Dr. [redacted] (OS Director) to File; R.J. Reynolds Tobacco Company SE Reports: SE0006198, SE0006199, SE0006211; signed 05-03-2018.
[49] From Dr. [redacted] (OS Director) to File Philip Morris USA SE Report: SE0000603; signed 07-27-2018.

risk or hazard from the new product would be adequate to demonstrate that the non-equivalent HPHC increase does not raise different questions of public health from a toxicology perspective.

Taken together, the use of this "*qualitative or semi-quantitative approach"* in the toxicology evaluation of HPHCs and associated QRAs could result in product review conclusions (and issuance of marketing orders) that are made without consideration of all relevant toxicology information submitted in the tobacco product SE applications. To be consistent with the Administrative Procedure Act (APA)[50] and FDA policies that govern the scientific integrity of the product review process, we believe that all relevant information should be considered, and the Toxicology review conclusions should "rely on the best available science"[51].

Summary:

As discussed in detail above, we find application of the HPHC Memorandum to our Toxicology reviews of SE applications problematic for several reasons, including:

- Although the HPHC Memorandum signed February 21, 2019 meets the definition of Guidance, the process outlined by FDA GGP does not appear to have been followed in the development, prior to its issuance and implementation, of this guidance document by DNCS. Following the process for FDA GGP is needed to ensure guidance is "*developed with appropriate review and public participation, accessible and transparent to the public, of high quality*" (OMB 2007).
- Also, we find that the HPHC Memorandum is a guidance document that is not supported by the best available science. The standard QRA approach is a systematic and transparent process to evaluate human health risk from chemical exposures, has been considered appropriate to evaluate human health risk from tobacco products in general, and has also been identified as appropriate and informative specifically for the toxicology review of tobacco product SE applications for over six years. As discussed previously in this document, the rationale provided in the HPHC Memorandum for why the standard QRA approach is not appropriate to evaluate HPHCs in SE applications is not supported by the available science. In addition, the HPHC Memorandum set forth implementation of a "*qualitative or semi-quantitative approach*" for HPHC evaluations in SE reviews, without providing a reasonable explanation, scientific references, or even mentioning how the new approach to evaluating HPHCs is more appropriate than the standard QRA approach used by DNCS since 2013[52], especially considering previous recommendations to industry in the context of SE applications, previous regulatory decisions DNCS has made, as well as other CTP memoranda currently implemented by DNCS for SE application reviews. Moreover, the available information indicates that the "*qualitative or semi-*

[50] *See,* 5 U.S.C. § 55

[51] Under 21 CFR Part 10, Administrative Practices and Procedures, 21 CFR 10.70 states "*FDA employees responsible for handling a matter are responsible for insuring the completeness of the administrative file relating to it. The file must contain appropriate documentation of the basis for the decision…" also,*
FDA SMG9001.1 FDA Staff Manual Guides, Volume IV- Agency Program Directives/ General or Multidiscipline/Scientific Integrity states "*FDA must rely on the best available science to make difficult decisions with respect to those products. In making those decisions, an unbiased presentation and full evaluation and analysis of the data, including its uncertainties, is absolutely critic*al".

[52] Toxicology Review of 905(j)(1)(A)(i) Report Second-Cycle Review of Additional Information for SE0003730; SE0003731; signed 06-03-2013

quantitative approach" outlined in the HPHC Memorandum is not grounded in the best available science and use of this approach in the toxicology evaluation of HPHCs and associated QRAs could result in product review conclusions (and issuance of marketing orders) that are made without consideration of all relevant toxicology information submitted in the tobacco product SE applications.

Possible Impacts on CTP Regulatory Decisions:

Applying the February 21, 2019 HPHC Memorandum to our current evaluations of SE Reports would result in toxicology review conclusions, and consequently tobacco product marketing orders, that do not consider all relevant information are not adequately supported by the available science. For example, in (b) (4) (new product vs. predicate product 1) the equivalence test identified analytically important (non-equivalent) increases in two carcinogens, with no concomitant analytically important (non-equivalent) decreases in carcinogens; based on the HPHC Memorandum the toxicology review, without full consideration of all relevant information provided, would have to conclude that the new product is NSE to predicate product 1. However, results from the applicant's submitted QRA, which included smoke yields for 17 measured HPHCs, indicate that there is no increase in the cumulative estimated cancer risk for the new product relative to predicate product 1; if the reviewer conducts the evaluation based on the totality of relevant information provided by the applicant, the tentative conclusion is that the new product as compared to predicate product 1 is unlikely to raise different questions of public health, and thus is SE to predicate product 1. CTP's own website states that "*decisions made by the FDA in the regulation of tobacco products are grounded in science*[53]"; regulatory decisions that would be made by CTP made without consideration of all relevant information and that are not supported by the available science could be incorrect and may be overturned if challenged.

The HPHC Memorandum could also have negative consequences that reach far beyond those related to specific product review applications. Because the February 21, 2019 HPHC Memorandum 1) was not developed and issued following the process for FDA GGP to ensure appropriate review, public participation, and transparency; 2) provides information inconsistent with other current CTP Guidance and FR Notices[54] related to HPHCs as well as other current documents related to HPHC evaluations in SE applications[55]; and 3) it is not grounded in, and conflicts with the best available science, the HPHC memorandum could have a negative impact on the extent to which CTP and the Agency are perceived as trustworthy, competent, and credible. Consequently, this can have a negative impact on the effectiveness with which CTP and FDA carry out the mission to protect public health.

[53] https://www.fda.gov/tobacco-products/products-guidance-regulations (last accessed 05/30/2019)

[54] FDA 2016. Guidance for Industry and FDA Staff "Harmful and Potentially Harmful Constituents" in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry and FDA Staff"; "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List," 77 FR 20034 (April 3, 2012); "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments," 76 FR 50226 (August 12, 2011.

[55] DNCS Memoranda: SE Review: Evaluating carcinogenic HPHC increases and assumptions of linearity for low-dose extrapolation", signed October 27, 2017

Appendix A

CFR - Code of Federal Regulations Title 21

The information on this page is current as of April 1 2018.

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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 10 -- ADMINISTRATIVE PRACTICES AND PROCEDURES

Subpart B--General Administrative Procedures

Sec. 10.115 Good guidance practices.

(a) *What are good guidance practices?* Good guidance practices (GGP's) are FDA's policies and procedures for developing, issuing, and using guidance documents.

(b) *What is a guidance document?* (1) Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue.

(2) Guidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies.

(3) Guidance documents do not include: Documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms.

(c) *What other terms have a special meaning?* (1) "Level 1 guidance documents" include guidance documents that:

(i) Set forth initial interpretations of statutory or regulatory requirements;

(ii) Set forth changes in interpretation or policy that are of more than a minor nature;

(iii) Include complex scientific issues; or

(iv) Cover highly controversial issues.

(2) "Level 2 guidance documents" are guidance documents that set forth existing practices or minor changes in interpretation or policy. Level 2 guidance documents include all guidance documents that are not classified as Level 1.

(3) "You" refers to all affected parties outside of FDA.

(d) *Are you or FDA required to follow a guidance document?* (1) No. Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.

(2) You may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations. FDA is willing to discuss an alternative approach with you to ensure that it complies with the relevant statutes and regulations.

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(3) Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.

(e) *Can FDA use means other than a guidance document to communicate new agency policy or a new regulatory approach to a broad public audience?* The agency may not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time. These GGP's must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.

(f) *How can you participate in the development and issuance of guidance documents?* (1) You can provide input on guidance documents that FDA is developing under the procedures described in paragraph (g) of this section.

(2) You can suggest areas for guidance document development. Your suggestions should address why a guidance document is necessary.

(3) You can submit drafts of proposed guidance documents for FDA to consider. When you do so, you should mark the document "Guidance Document Submission" and submit it to Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. If you wish to submit the draft of a proposed guidance document electronically, submit it through *https://www.regulations.gov* at Docket No. FDA-2013-S-0610. It is only necessary to submit one copy.

(4) You can, at any time, suggest that FDA revise or withdraw an already existing guidance document. Your suggestion should address why the guidance document should be revised or withdrawn and, if applicable, how it should be revised.

(5) Once a year, FDA will publish, both in the Federal Register and on the Internet, a list of possible topics for future guidance document development or revision during the next year. You can comment on this list (e.g., by suggesting alternatives or making recommendations on the topics that FDA is considering).

(6) To participate in the development and issuance of guidance documents through one of the mechanisms described in paragraphs (f)(1), (f)(2), or (f)(4) of this section, you should contact the center or office that is responsible for the regulatory activity covered by the guidance document.

(7) If FDA agrees to draft or revise a guidance document, under a suggestion made under paragraphs (f)(1), (f)(2), (f)(3) or (f)(4) of this section, you can participate in the development of that guidance document under the procedures described in paragraph (g) of this section.

(g) *What are FDA's procedures for developing and issuing guidance documents?* (1) FDA's procedures for the development and issuance of Level 1 guidance documents are as follows:

(i) Before FDA prepares a draft of a Level 1 guidance document, FDA can seek or accept early input from individuals or groups outside the agency. For example, FDA can do this by participating in or holding public meetings and workshops.

(ii) After FDA prepares a draft of a Level 1 guidance document, FDA will:

(A) Publish a notice in the Federal Register announcing that the draft guidance document is available;

(B) Post the draft guidance document on the Internet and make it available in hard copy; and

(C) Invite your comment on the draft guidance document. Paragraph (h) of this section tells you how to submit your comments.

(iii) After FDA prepares a draft of a Level 1 guidance document, FDA also can:

(A) Hold public meetings or workshops; or

(B) Present the draft guidance document to an advisory committee for review.

(iv) After providing an opportunity for public comment on a Level 1 guidance document, FDA will:

(A) Review any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate;

(B) Publish a notice in the Federal Register announcing that the guidance

Appendix A

document is available;

(C) Post the guidance document on the Internet and make it available in hard copy; and

(D) Implement the guidance document.

(v) After providing an opportunity for comment, FDA may decide that it should issue another draft of the guidance document. In this case, FDA will follow the steps in paragraphs (g)(1)(ii), (g)(1)(iii), and (g)(1)(iv) of this section.

(2) FDA will not seek your comment before it implements a Level 1 guidance document if the agency determines that prior public participation is not feasible or appropriate.

(3) FDA will use the following procedures for developing and issuing Level 1 guidance documents under the circumstances described in paragraph (g)(2) of this section:

(i) After FDA prepares a guidance document, FDA will:

(A) Publish a notice in the Federal Register announcing that the guidance document is available;

(B) Post the guidance document on the Internet and make it available in hard copy;

(C) Immediately implement the guidance document; and

(D) Invite your comment when it issues or publishes the guidance document. Paragraph (h) of this section tells you how to submit your comments.

(ii) If FDA receives comments on the guidance document, FDA will review those comments and revise the guidance document when appropriate.

(4) FDA will use the following procedures for developing and issuing Level 2 guidance documents:

(i) After it prepares a guidance document, FDA will:

(A) Post the guidance document on the Internet and make it available in hard copy;

(B) Immediately implement the guidance document, unless FDA indicates otherwise when the document is made available; and

(C) Invite your comment on the Level 2 guidance document. Paragraph (h) of this section tells you how to submit your comments.

(ii) If FDA receives comments on the guidance document, FDA will review those comments and revise the document when appropriate. If a version is revised, the new version will be placed on the Internet.

(5) You can comment on any guidance document at any time. Paragraph (h) of this section tells you how to submit your comments. FDA will revise guidance documents in response to your comments when appropriate.

(h) *How should you submit comments on a guidance document?* (1) If you choose to submit comments on any guidance document under paragraph (g) of this section, you must send them to the Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(2) Comments should identify the docket number on the guidance document, if such a docket number exists. For documents without a docket number, the title of the guidance document should be included.

(3) Comments will be available to the public in accordance with FDA's regulations on submission of documents to the Division of Dockets Management specified in 10.20(j).

(i) *What standard elements must FDA include in a guidance document?* (1) A guidance document must:

(i) Include the term "guidance,"

(ii) Identify the center(s) or office(s) issuing the document,

(iii) Identify the activity to which and the people to whom the document applies,

(iv) Prominently display a statement of the document's nonbinding effect,

(v) Include the date of issuance,

(vi) Note if it is a revision to a previously issued guidance and identify the

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document that it replaces, and

(vii) Contain the word "draft" if the document is a draft guidance.

(2) Guidance documents must not include mandatory language such as "shall," "must," "required," or "requirement," unless FDA is using these words to describe a statutory or regulatory requirement.

(3) When issuing draft guidance documents that are the product of international negotiations (e.g., guidances resulting from the International Conference on Harmonisation), FDA need not apply paragraphs (i)(1) and (i)(2) of this section. However, any final guidance document issued according to this provision must contain the elements in paragraphs (i)(1) and (i)(2) of this section.

(j) *Who, within FDA, can approve issuance of guidance documents?* Each center and office must have written procedures for the approval of guidance documents. Those procedures must ensure that issuance of all documents is approved by appropriate senior FDA officials.

(k) *How will FDA review and revise existing guidance documents?* (1) The agency will periodically review existing guidance documents to determine whether they need to be changed or withdrawn.

(2) When significant changes are made to the statute or regulations, the agency will review and, if appropriate, revise guidance documents relating to that changed statute or regulation.

(3) As discussed in paragraph (f)(3) of this section, you may at any time suggest that FDA revise a guidance document.

(l) *How will FDA ensure that FDA staff are following GGP's?* (1) All current and new FDA employees involved in the development, issuance, or application of guidance documents will be trained regarding the agency's GGP's.

(2) FDA centers and offices will monitor the development and issuance of guidance documents to ensure that GGP's are being followed.

(m) *How can you get copies of FDA's guidance documents?* FDA will make copies available in hard copy and, as feasible, through the Internet.

(n) *How will FDA keep you informed of the guidance documents that are available?* (1) FDA will maintain on the Internet a current list of all guidance documents. New documents will be added to this list within 30 days of issuance.

(2) Once a year, FDA will publish in the Federal Register its comprehensive list of guidance documents. The comprehensive list will identify documents that have been added to the list or withdrawn from the list since the previous comprehensive list.

(3) FDA's guidance document lists will include the name of the guidance document, issuance and revision dates, and information on how to obtain copies of the document.

(o) *What can you do if you believe that someone at FDA is not following these GGP's?* If you believe that someone at FDA did not follow the procedures in this section or that someone at FDA treated a guidance document as a binding requirement, you should contact that person's supervisor in the center or office that issued the guidance document. If the issue cannot be resolved, you should contact the next highest supervisor. You can also contact the center or office ombudsman for assistance in resolving the issue. If you are unable to resolve the issue at the center or office level or if you feel that you are not making progress by going through the chain of command, you may ask the Office of the Chief Mediator and Ombudsman to become involved.

[65 FR 56477, Sept. 19, 2000, as amended at 83 FR 13416, Mar. 29, 2018]

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FDA **U.S. FOOD & DRUG ADMINISTRATION**

MEMORANDUM

Date: February 21, 2019

From: [redacted]
Deputy Director
Division of Nonclinical Science
Office of Science

[redacted] 2019.02.21 14:42:34 -05'00'

Through: [redacted]
Director
Division of Nonclinical Science
Office of Science

Digitally signed by [redacted]
Date: 2019.02.21 14:45:50 -05'00'

To: File

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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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 EPA[1] 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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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 <u>different</u> from that of an HPHC that is increased <u>cannot</u> 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

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 off-setting 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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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.

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[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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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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/

Appendix C. Timeline relevant to scientific input provided in writing from CTP staff regarding the qualitative approach

Date	Action	Notes
11/21/18	The draft toxicology review ([redacted]) was submitted for clearance to the DNCS Deputy Director	
11/21/18	The Deputy Director provided the 1st round of comments instructing reviewers to consider using the qualitative approach in the SE review	• Questions included "*Do you think that you could apply a qualitative approach to this HPHC data set?*" (full email below): 11_21_18 email from DD.pdf
11/27/18	The toxicology review was resubmitted for clearance to the Deputy Director The reviewers submitted scientific information and rationale why the qualitative approach was not appropriate	• Primary, Secondary, and Tertiary Reviewers agreed that a qualitative approach was not appropriate and provided the Deputy Director with the following scientific evidence and rationale to support their position: 11_27_18 Reviewer Response.pdf
11/29/18	The Deputy Director provided a 2nd round of edits and comments instructing reviewers on using the qualitative approach in the SE review	• Comments included insistence on use of a qualitative approach for the toxicological evaluation (full email below): 11_29_18 email from DD.pdf
12/7/18	The toxicology review was resubmitted for clearance to the Deputy Director The reviewers submitted additional scientific information and rationale why the qualitative approach was not appropriate	• The reviewers continued to agree that a qualitative approach was still not appropriate and provided the following further rationale to support their position: 12_7_18 Reviewer Follow-up Response.p • Response to comments were delayed because Secondary Reviewer was at Scientific Conference and Tertiary Reviewer was on leave
12/10/18	The Deputy Director provided a 3rd round of edits and comments instructing reviewers on using the qualitative approach in the SE review	• Deputy Director instructed the reviewers to include a "*rationale for why the* [redacted] *does not offset the* [redacted]" (i.e., why the qualitative approach could not be used; full email below): 12_10_18 email from DD.pdf
12/12/18	The amended toxicology review was resubmitted for clearance to the Deputy Director	• The review was edited to include the rationale required by the Deputy Director for why a qualitative approach could not be used; the added text is included following this table, however this information was deleted from the review based on subsequently instructions from the Deputy Director.
12/13/18	The Deputy Director provided a 4th round of edits and comments related to use of	• The Deputy Director indicated that he may need to write a non-concur memo for this review (full email below):

Appendix C. Timeline relevant to scientific input provided in writing from CTP staff regarding the qualitative approach

	the qualitative approach in the SE review The Deputy Director recognized that the scientific issues raised by the reviewers relate to the general use of the qualitative approach for HPHC comparisons and stated that these should be "*part of the longer discussion that we need to have"*; these concerns were not addressed prior to development and issuance of the HPHC Memorandum signed by the Deputy Director on Feb 21, 2019	 12_13_18 email from DD.pdf • In addition, the Deputy Director deleted the newly included rationale and provided the following comment: "*This language belongs in a memo and is part of the longer discussion that we need to have. There are differing view points on this issue and we need to hammer out the language to achieve consensus. It seems to me that this language is inconsistent with the use of any qualitative approach to evaluate HPHC comparisons between tobacco products. In the meantime, I think that it is wise to leave out.*"
12/13/18-12/14/18	The Primary Reviewer emailed the Division Director	• The Primary Reviewer informed the Division Director of her discomfort and sense of pressure to use the qualitative approach in the process of this review (full email below):  12_13_18 Primary Reviewer email to Dire • The reviewer was instructed to discuss these concerns with the Deputy Director (full email below):  12_14_18 email from Director.pdf
12/14/18	Meeting between the Primary Reviewer and Deputy Director via the phone regarding instructions received by the reviewers to use the qualitative approach in the SE review	• During the meeting the Deputy Director continued to reiterate the importance of using the qualitative approach; however, no scientific justification for why this is appropriate was provided. The Primary Reviewer informed the Deputy Director that she was feeling undue pressure and reiterated the previously raised scientific issues related to use of the qualitative approach. • Agreement was reached that the qualitative approach was not appropriate for this review; the reviewer agreed to accept the edits made by the Deputy Director to delete the rationale for why a qualitative approach could not be used from the review discussion.
12/14/18	The Deputy Director emailed the Secondary Reviewer regarding the meeting with the Primary Reviewer	• The Deputy Director provided his understanding of the main points of consensus reached with the Primary Reviewer during the call meeting (full email below):  12_14_18 email from DD.pdf • The summary information provided as a "consensus point" on why the qualitative approach was not considered appropriate in the review did not accurately capture the reviewers' position; this was clarified in follow-up emails sent 12/17/18:

Appendix C. Timeline relevant to scientific input provided in writing from CTP staff regarding the qualitative approach

		12_17_18 email from Secondary Reviewer.p
12/17/18	The amended toxicology review was resubmitted for clearance to the Deputy Director	• The reviewer accepted the edit deleting the justification for why the qualitative approach was not considered appropriate.
12/18/18	The toxicology review was cleared by the Deputy Director	• The toxicology review was signed by the reviewers on 12/19/2018; this document had only minor edits from the original draft review submitted for clearance on 11/21/2018.
12/18/18	The Deputy Director sent a follow-up email and reiterated that reviewers should use the qualitative approach in SE applications	• The Deputy Director responded to the reviewers' clarifications of scientific points contested by reiterating that the qualitative approach should be used in SE applications; no supporting scientific data or references were provided (full email below): 12_18_18 email from DD.pdf
2/22/19	Memorandum on qualitative approach is sent out to DNCS staff	• Memorandum "*Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports*" is sent to DNCS staff for implementation.

Text that was added to review to include the rationale required by the Deputy Director for why a qualitative approach could not be used: Although the equivalence analysis conducted on analytical data may not necessarily be representative of the relative risk between the new and predicate products it allows for a screening level assessment to identify the presence of constituents in the new product that are of potential toxicological concern. In such cases, although not required for an SE report, a baseline risk assessment can be conducted to better characterize the potential relative human health risks from exposures to the new and predicate products. Based on basic risk assessment principles and available guidance it is recommended practice for evaluations to retain all constituents with valid analytical measurements when evaluating human health risk from chemical mixtures (EPA 1986; EPA 1989; EPA 2002; IGHRC 2009). Although the equivalence evaluation between the new and predicate products identified some HPHCs to be within the equivalence margins, all measured constituents contribute to tobacco related disease risk. For this reason, eliminating any of the HPHCs from the risk assessment could result in the loss of important information (EPA 2002) that is relevant to the evaluation of relative cancer risk and noncancer hazard between the new and predicate products. Considering all the information available for the new and predicate product in these SE reports, a qualitative approach could not be used by the toxicology reviewer to reach a conclusion of the relative cancer risk and noncancer hazard between the new and predicate product. A properly conducted QRA would be needed to adequately estimate the relative cancer risk and noncancer hazard between the new and predicate products.

References:

IGHRC 2009. Chemical Mixtures: A Framework for Assessing Risk to Human Health (CR14). Institute of Environment and Health, Cranfield University, UK.

U.S. Environmental Protection Agency (USEPA). 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures.

U.S. Environmental Protection Agency (USEPA). 1989. Risk Assessment Guidance for Superfund Volume 1 Human Health Evaluation Manual (Part A).

U.S. Environmental Protection Agency (USEPA). 2002. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites.

Appendix C

OS Response to Toxicology Reviewers

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: [redacted]
Toxicology [redacted], CTP/OS/DNCS

[redacted]
Toxicology [redacted], CTP/OS/DNCS

[redacted]
Toxicology [redacted], CTP/OS/DNCS

From: [redacted]
Deputy Director of Regulatory Management, CTP/OS

cc: [redacted]
Director, CTP/OS

Subject: Concerns regarding DNCS's HPHC memo dated Feb. 21, 2019

Background

On February 21, 2019 the Deputy Director of Division of Nonclinical Science (DNCS), [redacted], issued a memorandum to staff titled "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports". This memo documents a change in process for DNCS staff review of Substantial Equivalence (SE) reports, including criteria for determining when a new approach for evaluating HPHC comparisons is to be used by division staff. [redacted]'s transmittal email stated in part that "This memo is both consistent with the overall OS approach to streamlining SE review in light of increasing regulatory demands from PMTA and MRTPA review and with many of the ideas that we have discussed at several of our reviewer rounds meetings. This memo describes approaches that work in concert with Division of Product Science' (DPS) new TOST analysis and standardizes thinking that we have already applied to SE reviews signed over the past few months.... I am sure that many of you will recognize the discussions that we had at reviewer rounds in this memo. This meeting will continue to be the place where we discuss new and emerging directions in SE review."

The SE application review process requires comparison of a new and predicate product to determine whether the products have same or different characteristics, and if different whether those differences raise different questions of public health. This comparison involves comparing level and health impact of substances that FDA has identified as HPHCs. The DNCS memo implements a new approach wherein "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."

On May 31, 2019, Drs. [redacted], [redacted], [redacted], and [redacted] (you) submitted a memo describing concerns with this DNCS memo, including both with the substance of the memo and the process by which the memo was

[1] Dr. [redacted] subsequently resigned from the Agency to take a position in private industry.

developed. On the first point you claim the DNCS memo is a guidance that was not developed in accordance with FDA's Good Guidance Practices (GGPs). Secondly, you assert that that the new review process is not supported by the best available science.

You requested an in-person meeting to discuss the issues. I met with you on July 3, 2019 to hear your concerns; Dr [redacted] was unable to attend. During that meeting, Drs. [redacted], [redacted] and [redacted] explained that their primary concern is with the substance of the division's new process for review of HPHC comparisons. As reviewers, you indicated that do not believe you have any justification to not consider all data a company includes in their Quantitative Risk Assessment (QRA). You also expressed concerns with not following the new memo but were unsure how to seek resolution of your concerns. Because of this, you explained that you ultimately decided to raise a concern with the process of developing the memo (i.e. that it was not done in accordance with GGPs) as a mechanism to dispute within the supervisory chain the substance of the DNCS memo.

Discussion

I will address your two concerns in order.

1. The DNCS memo is not in accordance with Good Guidance Practices (GGP)

Your memo states that GGP should have been followed in the development and implementation of the February 21, 2019, DNCS memo. You state this is necessary to ensure it is "developed with appropriate review and public participation, accessible and transparent to the public, of high quality."

The February 21, 2019, memo was prepared to provide direction to individual reviewers within DNCS regarding a change in division process for review of HPHC data in SE Reports. Guidance documents do not include documents relating to internal FDA procedures or "other communications directed to individual persons or firms." 21 CFR 10.115(b)(3). Thus, GGPs are not applicable to internal memos such as the this. Given this, I find that DNCS management's process for developing and communicating this information to affected staff was appropriate and consistent with Office policy.

2. The DNCS memorandum is not supported by the best available science

You object to changing from the "standard QRA approach" to the new approach in the February 21, 2019, DNCS memo. You state that the QRA approach is systematic and transparent, has a long history of being used to evaluate the health effects of environmental hazards including tobacco smoke, and more recently was used by CTP/OS in various regulatory decisions including review of SE applications. You do not provide any information to support the apparent presumption that this QRA approach is the best or only acceptable method for a the very specific regulatory SE Report requirement to compare and evaluate the health impact of HPHC differences between a predicate and new tobacco product. You claim that the intended uses for which the QRA approach was developed by other Agencies "has no bearing on whether this approach is applicable and appropriate" for SE review, but do not provide adequate justification for this claim.

You further imply that as a prerequisite to adopting a different approach for evaluating HPHC comparisons in SE Reports, DNCS must first demonstrate the "Standard QRA approach" is "not scientifically appropriate" for the SE review process. You contend that the DNCS memo does not provide adequate rationale for not using the QRA approach in that it does not mention any new information or scientific data to explain the change in approach. You broadly dismiss the DNCS memo's explanation that the SE review program involves unique considerations derived from regulatory requirements (e.g., comparison of HPHCs between two products, a comparison based on a list of HPHCs established by the Agency) that do not apply to common uses of the QRA approach.

I find that these claims are not supported. The fact that the QRA approach has been successfully used for other scientific purposes and even in some prior SE application reviews does not mean it is necessarily the only

acceptable or the most appropriate method for use in review of SE reports. Also, it is not necessary for DNCS management to demonstrate the standard QRA approach is not scientifically appropriate prior to implementing a new, alternative review process.

You also assert that the "qualitative or semi-qualitative approach" specified in the DNCS memo is "not supported by the best available science and does not consider all data and information provided by an applicant." You state that it is accepted practice to include all constituents when evaluating human health risks from chemical mixtures, and that doing so for review of SE applications can "provide a more comprehensive hazard evaluation." Your viewpoint reflects a preference to perform the most comprehensive evaluation in all circumstances. Your viewpoint does not appear to reflect a consideration of how the data needed for regulatory review and comparison of the health risks between two tobacco products in an SE report is uniquely different than what is needed for a standard cumulative human health risk assessment of complex mixtures. This viewpoint also does not consider the Agency's need to manage programs and resources to best benefit our public health mission. Indeed, Agency leadership has a responsibility to manage regulatory programs that are based on sound science, the intent of the law, alternative approaches, and the efficient use of resources to effectively address regulatory issues and protect public health. It is proper for DNCS management to explore and determine whether a regulatory review decision can be adequately supported with less than the "comprehensive" data that is generally used for cumulative human health risk assessments of complex mixtures.

The DNCS memo and transmittal email discussed at length the reason for implementing a new approach for assessing HPHC differences within the SE review program, including:

- the SE regulatory review does not require comprehensive, cumulative risk assessment of each tobacco product (e.g., over 7000 compounds in tobacco smoke), but rather comparison of selected HPHCs between two products (the predicate and new tobacco product) to address a specific regulatory standard;
- that the Agency has identified 93 chemicals (out of over 7000) of interest that are linked to the five serious health effects most commonly linked to tobacco use;
- that as part of a new comprehensive approach to SE Report review, the Division of Product Science (DPS), not DNCS, is responsible for determining whether a difference in HPHC quantity between the two products is analytically non-equivalent

The DNCS memo appropriately considers these important differences and describes key considerations which informed the new approach:

> "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."

Information in your May 31, 2019 memo dwells on concern with not using the QRA, but <u>does not demonstrate the new approach is inappropriate for the intended use</u>. I find that DNCS management appropriately communicated to staff the rationale for the change in review process to address this unique regulatory evaluation of SE Reports. For example, the DNCS memo explains that "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", and provides sound rationale for deferring to DPS to evaluate analytical equivalence and focusing the toxicological comparison on HPHC differences that are analytically non-equivalent. Also, staff performing a qualitative risk assessment can consider available reference toxicity values as part of their evaluation. This is consistent with the FDA principle of using best-available science in data-driven decision making. This new robust

approach relies on a sound scientific foundation, leverages scientific expertise (e.g. evaluation of analytical equivalence by chemists), and improves review program efficiency.

Although not a consideration in my decision, I note that your memo sometimes misconstrued information in the DNCS memo. For example, your May 31, 2019 memo states on page 6 that "The statement [in DNCS memo] that 'the cumulative human health risk of complex mixtures evaluated by organizations such as the EPA and the ATSDR are not specific to tobacco products' is not accurate; …"[2]. By taking only a portion of the sentence and presenting it out of context, your memo misrepresents the DNCS memo's clear message that the cumulative human health risk of complex mixtures QRA evaluation by organizations such as the EPA and the ATSDR is not tailored to efficiently address the specific regulatory requirements for comparing HPHCs (on an established list) between two tobacco products.

Conclusions

Leadership should periodically assess regulatory programs to identify opportunities for improvements. For example, the type and amount of information needed by FDA can change over time based on new knowledge or understanding of regulated products and evaluation methods, or new review approaches. As part of smart regulation, FDA senior leaders regularly look for opportunities to streamline processes and policies to improve efficiency, conserve resources, and develop alternative approaches that utilize the minimum amount of information necessary to adequately address the issue and render regulatory decisions within appropriate timeframes. For example, directors in CDER explore opportunities to reduce the burden of traditional clinical trials while still meeting the statutory and regulatory requirements.

In this case, I find that DNCS management provided adequate justification for developing an alternative, less burdensome, approach for comparison of HPHCs between new and predicate tobacco products. The new (current) DNCS approach is based on sound science and is properly tailored to address the unique regulatory requirements for decisions within the SE program while minimizing the amount of information and resources needed. For example, the new process conserves resources by directing staff to not review fatally flawed QRAs and provides staff with an important list of considerations when performing a qualitative risk evaluation.

In conclusion, I uphold DNCS' February 21, 2019, memo. It is a well-considered and appropriate management directive that DNCS staff are expected to follow. GGPs are not applicable to this internal memo. The qualitative process and underlying assumptions described in the DNCS memo are appropriate to protect the public health, conserve agency resources, and support sound and timely regulatory decisions. This approach will position DNCS to more efficiently review an expected increasing number of product applications in order to better protect public health and meet FDA performance goals.

[2] The quote in your memo is not verbatim from the DNCS memo. The statement in the DNCS memo is "While the cumulative human health risk of complex mixtures has been evaluated by organizations such as the EPA and the ATSDR, 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."

Appendix D

Special Counsel Letter

U.S. OFFICE OF SPECIAL COUNSEL
1730 M Street, N.W., Suite 300
Washington, D.C. 20036-4505

The Special Counsel

February 28, 2020

The Honorable Alex M. Azar II
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

VIA ELECTRONIC MAIL

Re: OSC File No. DI-20-0372

Dear Secretary Azar:

Pursuant to my responsibilities as Special Counsel, I am referring to you for investigation whistleblower disclosures regarding the Food and Drug Administration (FDA) Center for Tobacco Products (CTP) Office of Science (OS) Division of Nonclinical Science (DNCS). I have determined that there is a substantial likelihood that the allegations disclose a substantial and specific danger to public health and safety, as well as a potential abuse of authority and violation of law, rule, or regulation. A report of your investigation, including any remedial actions, if warranted, is due to the U.S. Office of Special Counsel (OSC) by April 28, 2020.

The whistleblower, [redacted], alleges that DNCS leadership has relaxed its standards in an effort to speed up reviews of new tobacco product applications. As a result it has allowed potentially more harmful products to enter the market. Specifically, according to the whistleblower, in early 2019, DNCS directed its toxicology reviewers—the scientists who are responsible for calculating the health risks posed by new tobacco products—to use a "qualitative or semi-qualitative" approach, rather than the more scientifically appropriate and rigorous quantitative one, when measuring and comparing harmful and potentially harmful chemical compounds in new versus old tobacco products (substantial equivalence (SE) product applications).[2] This approach, according to the whistleblower, is not based on the best available science and can result in arbitrary decisions on SE tobacco product applications, including allowing more harmful products to enter the market. Allegations to be investigated include:

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[1] [redacted] He consented to the release of his name.

[2] *See* Memorandum from [redacted], PhD, Deputy Director, OS DNCS, to file, through [redacted], PhD, Director, OS DNCS, dated February 21, 2019, "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalent [SE] report" ("HPHC Memorandum").

- The "qualitative or semi-qualitative" approach, as outlined in the HPHC Memorandum, is not based on the best available science.
- This "qualitative or semi-qualitative" approach can yield entirely different results than the quantitative approach, *i.e.*, one approach might result in a product being approved for market while the other approach would not.
- After several toxicology scientists, including the whistleblower, complained to CTP OS leadership about the issues outlined in this letter, DNCS leadership stopped sending those scientists SE product applications entirely.
- DNCS's actions have effectively prevented those concerned toxicology scientists, including the whistleblower, from being able to invoke FDA's scientific integrity dispute process to raise, and possibly resolve, these issues internally.

The Federal Food, Drug and Cosmetic Act (FD&C) requires new or modified tobacco products to obtain premarket authorization from the FDA before going to market.[3] To be approved, a new proposed tobacco product essentially must not be *more* harmful to public health than a product already on the market (*i.e.*, there must be SE).[4] Nearly all the premarket tobacco product applications that the FDA reviews are SE Reports by applicants seeking to demonstrate that their new product is SE to a predicate product.[5] If the applicant meets its burden, the FDA issues an SE order allowing that product to go to market.[6] If the applicant fails, or does not otherwise qualify for an exemption, FDA issues a 'not substantially equivalent' or NSE order making it illegal to sell, distribute, or import the product in the United States.[7]

In late 2018, the whistleblower alleges that DNCS management became concerned about an anticipated increase in e-cigarette premarket authorization applications. As a result, DNCS management allegedly began pushing scientists to adopt a faster, and less rigorous, 'qualitative or semi-qualitative' approach to reviewing SE applications. Under this approach, generally speaking, according to the whistleblower, scientists ask whether a certain HPHC increase in a new product can be offset by another HPHC decrease in that product and, if it can, then that product can be determined SE without assessing additional quantitative data. This approach to review, according to the whistleblower, is more akin to 'eyeballing it.'

The whistleblower reviewed these tobacco premarket authorization applications and, from 2013 to early 2020, oversaw a team of toxicology reviewer scientists who did

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[3] Section 910(a)(2), as modified by The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), Pub. L. No. 111-31 (2009).
[4] https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/substantial-equivalence.
[5] https://www.federalregister.gov/documents/2019/04/02/2019-05787/content-and-format-of-substantial-equivalence-reports-food-and-drug-administration-actions-on.
[6] *Id.*, https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/substantial-equivalence.
[7] *Id.*

the same. According to the whistleblower, prior to the late 2018 change in procedures, these scientists used a quantitative approach to measure the harmful and potentially harmful constituents (HPHCs), or chemical compounds, when comparing tobacco products on SE applications. Under this approach, according to the whistleblower, the reviewing scientist quantified the specific concentration and toxicity level of each HPHC, like formaldehyde or acetaldehyde, for example, using mathematical equations to evaluate cancer risks and noncancer hazards, like respiratory illness, for both the new and predicate tobacco product. This approach, the whistleblower explains, is based on the best available science and consistent with other federal regulatory agencies', including other components within the FDA's, approach to measuring the human health risks created by tobacco products and the chemical compounds found therein. Using this information, the agency decided whether the new and predicate products were SE or NSE.

Following the change of the late 2018 review procedures, several toxicology review scientists raised concerns to DNCS management about using this qualitative approach on SE applications, and some asked to write 'non-concur' opinions when they did not feel the approach was appropriate. DCNS management declined these requests and, on February 21, 2019, issued the HPHC Memorandum, essentially directing reviewers to use the qualitative or semi-qualitative approach whenever possible in lieu of the quantitative approach.

The whistleblower notes that the HPHC Memorandum cites no scientific sources or bases for using this approach, in contrast to the established and scientifically supported quantitative approach. The whistleblower also explained that he and several other scientists tested the quantitative and qualitative (as outlined in the HPHC Memorandum) approaches on several SE applications and found that the two approaches yielded different results for the same application. One new product, for example, was found to be SE using the qualitative approach—meaning it was safe enough to go to market—but was found to be *NSE* using the quantitative approach. Another product, when tested with both approaches, resulted in the inverse.

The whistleblower alleges that, after the whistleblower and several other toxicology reviewer scientists raised concerns directly to DNCS management and to CTP OS leadership about the new approach and the manner in which the agency effectuated the new approach,[8] management stopped routing any SE evaluations requiring risk assessments to the whistleblower and the other concerned scientists entirely. This, the whistleblower explained, functionally prevented the whistleblower and his colleagues from being able to dispute management's decision to use the qualitative approach on any

[8] The scientists alleged that the HPHC Memorandum equates to a guidance document that was not developed in accordance with the FD&C Act and FDA's Good Guidance Practices

specific reviews, thereby preventing them from invoking the FDA's internal scientific dispute processes.[9]

Pursuant to my authority under 5 U.S.C. § 1213(c), I have concluded that there is a substantial likelihood that the information provided to OSC discloses a substantial and specific danger to public health and safety and possibly abuse of authority and violation of law, rule, or regulation. Please note that specific allegations and references to specific violations of law, rule, or regulation, or other enumerated wrongdoing, are not intended to be exclusive. If, in the course of your investigation, you discover additional violations, please include your findings on these additional matters in the report to OSC. As previously noted, FDA must investigate these matters and produce a report, which must be reviewed and signed by you. Per statutory requirements, I will review the report for sufficiency and reasonableness before sending copies of the report, along with the whistleblower's comments and any comments or recommendations I may have, to the President and congressional oversight committees, and making these documents publicly available.

Additional important requirements and guidance on the agency report are included in the Appendix. If your investigators have questions regarding the statutory process or the report required under section 1213, please contact Elizabeth McMurray, Chief of the Retaliation and Disclosure Unit, at (202) 804-7089 for assistance. I am also available for any questions you may have.

As discussed above, your investigative report, including any remedial actions, if warranted, is due to OSC by April 28, 2020.

Sincerely,

Henry J. Kerner
Special Counsel

Enclosure

cc: Christi A. Grimm, Principal Deputy Inspector General, U.S. Department of Health and Human Services

[9] The whistleblower states he and his colleagues attempted to work with the agency's Ombudsman but were ultimately informed, for the reasons outlined above, they did not have standing to invoke the FDA's internal scientific dispute process.

APPENDIX
AGENCY REPORTS UNDER 5 U.S.C. § 1213

GUIDANCE ON 1213 REPORT

- OSC requires that your investigators interview the whistleblower at the beginning of the agency investigation when the whistleblower consents to the disclosure of his or her name.
- Should the agency head delegate the authority to review and sign the report, the delegation must be specifically stated and include the authority to take the actions necessary under 5 U.S.C. § 1213(d)(5).
- OSC will consider extension requests in 60-day increments when an agency evidences that it is conducting a good faith investigation that will require more time to complete.
- Identify agency employees by position title in the report and attach a key identifying the employees by both name and position. The key identifying employees will be used by OSC in its review and evaluation of the report. OSC will place the report without the employee identification key in its public file.
- Do not include in the report personally identifiable information, such as social security numbers, home addresses and telephone numbers, personal e-mails, dates and places of birth, and personal financial information.
- Include information about actual or projected financial savings as a result of the investigation as well as any policy changes related to the financial savings.
- Reports previously provided to OSC may be reviewed through OSC's public file, which is available here: https://osc.gov/PublicFiles. Please refer to our file number in any correspondence on this matter.

RETALIATION AGAINST WHISTLEBLOWERS

In some cases, whistleblowers who have made disclosures to OSC that are referred for investigation pursuant to 5 U.S.C. § 1213 also allege retaliation for whistleblowing once the agency is on notice of their allegations. The Special Counsel strongly recommends the agency take all appropriate measures to protect individuals from retaliation and other prohibited personnel practices.

EXCEPTIONS TO PUBLIC FILE REQUIREMENT

OSC will place a copy of the agency report in its public file unless it is classified or prohibited from release by law or by Executive Order requiring that information be kept secret in the interest of national defense or the conduct of foreign affairs. 5 U.S.C. § 1219(a).

EVIDENCE OF CRIMINAL CONDUCT

If the agency discovers evidence of a criminal violation during the course of its investigation and refers the evidence to the Attorney General, the agency must notify the Office of Personnel Management and the Office of Management and Budget. 5 U.S.C. § 1213(f). In such cases, the agency must still submit its report to OSC, but OSC must not share the report with the whistleblower or make it publicly available. See 5 U.S.C. §§ 1213(f), 1219(a)(1).

Appendix E

Expert Panel Report

July 31, 2020

To: Mitch Zeller, JD
Director of the Center for Tobacco Products
Food and Drug Administration

From: [redacted], PhD
Division of Laboratory Sciences, National Center for Environmental Health,
Center for Disease Control and Prevention

[redacted], PhD
Division of Biochemical Toxicology, National Center for Toxicological Research,
Food and Drug Administration

[redacted], PhD
Division of Cancer Epidemiology and Genetics, National Cancer Institute

[redacted], DO
Division of Laboratory Sciences, National Center for Environmental Health,
Center for Disease Control and Prevention

RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP.

The panel was provided documents including the May 31 2019 letter addressed to Drs [redacted], [redacted] and [redacted]r (CTP/OS) from Drs. [redacted] and with concurrence from Drs. [redacted] and [redacted] (CTP/OS/DNCS). This letter is in reference to a Division level memorandum (from their Division) entitled, "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" signed by Dr. [redacted] the Deputy Director of DNCS and stated as "through" the Division Director, Dr [redacted]. The HPHC memorandum dated February 21 2019 was attached as Appendix B to the May 31 2019 letter. We have also reviewed the response to the May 31 2019 memorandum from Dr [redacted] (CTP/OS) digitally signed on December 13, 2019 to Drs [redacted], [redacted] and [redacted] with a courtesy copy to the Director of CTP/OS, Dr [redacted]. We were additionally provided other documents including examples of actual SE tobacco product summaries.

Dr [redacted] memorandum of December 13 2019 indicated that DNCS management provided adequate justification for the current approach (initial qualitative or semi-quantitative approach followed by a fully quantitative approach when merited) and that it is based on sound science. [redacted] upheld the February 21 2019 memorandum.

RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP.

We were asked to provide opinions on the following two statements.

> The "qualitative or semi-quantitative" approach, as outlined in the relevant reviewer guide, is not based on the best available science.
>
> This "qualitative or semi-quantitative" approach can yield entirely different results than the quantitative approach, i.e., one approach might result in a product being approved for market while the other approach would not.

In our opinion, the best approach to assessing the risk of disease or disorder in humans from the exposure to a chemical or compound requires human data, such as the internal dose and human health.

We recognize that traditional quantitative risk assessment methodologies were not developed for tobacco products, which possess distinct regulatory challenges. For example, tobacco product emissions can include a mixture of more than 7000 compounds of which 93 appear in the FDA-CTP's HPHC list and others may be harmful. Within this context, we agree with Dr [redacted] in that there are potentially other scientific approaches to compare the risk of toxicity of two tobacco products in addition to the traditional quantitative risk assessment. Nevertheless, this does not mean that the "qualitative or semi-quantitative approach" is necessarily the ideal one for FDA-CTP because additional methods can be needed to assess the risk of toxicity of the chemicals or compounds on the list of HPHCs (Leong et al, 2013).

The management elected to modify the prior peer-reviewed quantitative risk assessment approach in favor of a unique and unfamiliar "qualitative or semi-quantitative approach." The quantitative risk assessment approach relies on 4 steps: 1) hazardous chemical identification, 2) dose-response assessment, 3) exposure assessment, and 4) risk characterization. The quantitative risk assessment can provide an estimate of the risk of toxicity with the level of uncertainty for an exposure to a chemical or compound. The methodology for the quantitative risk assessment can be found here (US EPA: https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance ; accessed 7/28/2020).

In general, the current "qualitative or semi-quantitative approach" involves a novel process, whereby reviewers focus specifically on 1) HPHC increases and decreases that are analytically non-equivalent between the new and predicate products, 2) whether the risk of toxicity from an identified increase in HPHC can be offset by a decrease in another HPHC, and 3) if there is evidence for an increase in potential toxicity from an HPHC, a fully quantitative assessment should be conducted. The performance of the above approach in the assessment of HPHCs is unknown to us.

Clearly, the quantitative approach produces a more comprehensive assessment of the risk of toxicity from the exposure to a chemical or compound than the qualitative approach. For example, quantitative risk assessment can provide an estimate of the risk of toxicity (Coleman

and Marks, 1999). Yet it also seems reasonable that there will be circumstances that do not need a quantitative assessment, such as the instance when an application is fatally flawed.

It is critical to consider that there can be differences between the conclusions drawn from quantitative and semi-quantitative approaches (structured framework [Leong et al. 2013]) because these approaches can lead to varying decisions, depending on the chemical or compound under assessment.

A reason for the variability in the decision is that the above approaches are used to answer different questions. For example, a qualitative assessment is used to provide a categorical answer (y/n) to a question, such as the existence of a difference between two products. A quantitative assessment is used to provide an answer to question with a measured response, such as the amount of difference between two products.

When a difference between two products is apparent, such as toxicity to the heart versus toxicity to the liver, the above approaches yield the same decision. However, when the difference between two products is not apparent because they are similar, such as carcinogens of different potency, the quantitative approach can provide information on the amount of "risk of cancer" for the two products. The difference in the "risk of cancer" between two products can be more (or less) than the expectation based on the qualitative assessment. It is important to specify the question about the chemical or compound under review.

The "qualitative or semi-quantitative approach," as described in the above [redacted] memo, appears to rely solely on the judgement of the subject matter expert and impressions of FDA-CTP reviewers as opposed to quantifiable standards or criteria; even when these comparisons are complex, such as considering multiple and potentially offsetting HPHCs. Given the environment in which FDA-CTP operates, the above situation can be a significant limitation of the semi-quantitative approach as presently described. For these reasons, we believe that the semi-quantitative approach would substantially benefit from increased transparency.

For example, the rationale supporting the below decision statement is not transparent (TOX REV SE0000004 MAR 20 2019):

"When the toxicological evidences highlighted above are taken together, there is no evidence to suggest that the additional cancer risk associated with the increased amount of *o*-cresol would outweigh the cancer risk that is expected to be decreased due to the decreased NNK for the new product compared with the predicate product, and hence the increase in *o*-cresol is not likely to cause the new product to raise different questions of public health from a toxicological perspective."

The above decision is stated without documenting the process or how the data were evaluated to make this decision. How and by what metric did the reviewer decide that the potential impact of higher amounts of o-cresol would be offset by lower amounts of NNK? This a professional opinion that is not transparent to the reader. In our opinion, more specific and transparent

guidance to FDA-CTP reviewers are needed to ensure consistent and effective decisions that reduce population harm caused by the use of tobacco products.

Recommendations:

1. The qualitative or semi-quantitative approach in the above [redacted] memo lacks sufficient detail and guidance to be enacted as a scientific methodology in its current form. For example,

a. Lack of methodology for assessing non-cancer chemical hazards
b. Lack of methodology for comparing cancer risks of different HPHCs using a quantitative analysis
c. Lack of methodology of how to examine HPHCs as a mixture
d. Lack of methodology for comparing risks of different organs
e. Failure to demonstrate a systematic review of risk analysis methodologies for application to HPHCs and the decision-making process

In the opinion of the panel, the process needs to have clear decision rules which guide the review and dictate the integration of the “qualitative or semi-quantitative" evaluation with quantitative risk assessment. These decision rules should be added to the review process to ensure adequate protection of public health.

2. Establish a well-defined workflow and review process for assessments that address the specific questions to be answered about the chemical or compound under review.

3. Develop and communicate standardized and objective criteria for deciding when a quantitative risk assessment should be conducted in a collaborative manner that includes CTP management and reviewers.

4. Establish a review process that monitors the quality of the decisions that result from the above workflow, and allows for continuous improvement and correction of the workflow.

5. Establish a defined process for reviewer agreement, including evaluating decision concordance. Also, have a process for resolving discrepancies.

6. Establish processes for regular training and information sharing among reviewers and management to facilitate standardized approaches and decision making.

References

Coleman M and Marks HM. (1999). Qualitative and quantitative risk assessment. Food Control 10(4):289-297. 10.1016/S0956-7135(99)00052-3.

RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP.

EPA Guidance documents: https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance

Leong J, McAuslane N, Walker S, Salek S. (2013) Is there a need for a universal benefit-risk assessment framework for medicines? Regulatory and industry perspectives. Pharmacoepidemiol Drug Saf. Sep;22(9):1004-12. doi: 10.1002/pds.3464. Epub 2013 Jun 5. PMID: 23740622

Appendix F

Email from Mitch Zeller, CTP Center Director, to [redacted], Director, Office of Science

From: Zeller, Mitchell <[redacted]@fda.hhs.gov>
Sent: Monday, August 17, 2020 4:53 PM
To: [redacted] R <[redacted]@fda.hhs.gov>
Subject: Scientific dispute case

[redacted],

As you are aware, several OS staff have expressed concerns regarding CTP's current approach to evaluating and comparing HPHCs during SE review. The FDA Office of the Chief Scientist convened an expert panel to provide an independent scientific analysis of the concerns raised by OS staff. Attached is the report from the expert panel.

Before I make my decision on next steps, I'd like to make sure I am fully informed, so I am asking OS management to review the expert panel's report for completeness and to get your perspective on the panel's recommendations.

Rather than an explanation for the current process, I'd like OS management to provide a general response to the report and its recommendation, as well as addressing:

- Are there relevant materials or information that the expert panel may not have been aware of, that should be considered?
- Has OS already implemented any policies or procedures that address recommendations made by the expert panel?
- What is the role of OS's experience with previous SE reviews in shaping how OS currently evaluates HPHCs?
- Do you have any high-level recommendations with respect to how CTP should address the panel's recommendations both in the short- and long-term?

I would appreciate OS's written response by September 4th. Please let me know if you have any questions.

Mitch

Appendix G

OS Response to Panel Report

Scientific Dispute Case

OS Response to the Scientific Panel Report

Responses to the Report Recommendations

Below is a list of the six recommendations from the panel followed by OS's responses:

1. The qualitative or semi-quantitative approach in the above [redacted] memo lacks sufficient detail and guidance to be enacted as a scientific methodology in its current form.

   OS response: It is important to acknowledge that the approach captured in the memo is a *regulatory* scientific approach. From a purely scientific approach, I agree that a fully quantitative approach to evaluate HPHC differences between new and predicate products is ideal. However, as regulatory scientists, OS staff must consider practicality and public health impact of our decisions in context of a rigorous scientific standard. For the first eight years of the SE program, OS relied on a fully quantitative approach. However, over that time span, OS staff came to recognize the fully quantitative approach was unnecessarily burdensome to FDA and applicants and didn't impact public health in a meaningful way. Therefore, as the SE program evolved, OS staff gained a better understanding of HPHC data in SE Reports and recognized that the tiered approach in the memo allows a decision that aligns with our public health goal. FDA and other regulatory organizations (e.g., EPA) often use tiered approaches to scientifically evaluate products. Therefore, I believe the approach in the memo is scientifically sound.

2. Establish a well-defined workflow and review process for assessments that address the specific questions to be answered about the chemical or compound under review.

   OS response: Although not captured in the memo, OS already has a well-defined workflow and review process. The intention of the memo was to capture the change in our approach to evaluating HPHC data in SE Reports. However, there are other documents that guide OS staff in evaluating SE Reports. The overall review process has evolved since the SE program began as OS staff have gained more experience and knowledge. As OS staff continue to better understand tobacco products, the review process will continue to evolve, including improved understanding of whether HPHC differences raise different questions of public health.

3. Develop and communicate standardized and objective criteria for deciding when a quantitative risk assessment should be conducted in a collaborative manner that includes CTP management and reviewers.

   OS response: The memo does standardize the approach to assessing HPHC differences between new and predicate products. And, the criteria in the memo are as objectives as possible based on our current experiences. As we gain even more experience, we will likely be able to make the criteria even more objective than currently captured in the memo. Furthermore, the approach outlined in the memo was developed based on discussion by many OS toxicologists as well as OS leadership. The process to develop the memo and the degree of objectiveness of the criteria in the memo is consistent with FDA regulatory programs. It is typical that, for a given regulatory science issue, FDA begins with a less objective approach and evolves into a more objective approach based on gained knowledge and experience.

4. Establish a review process that monitors the quality of the decisions that result from the above workflow, and allows for continuous improvement and correction of the workflow.

   OS response: There is already a process in place to do this. In fact, it is that process which led to development of the approach in the memo. Every SE order undergoes quality control by OS staff and sometimes legal staff outside OS (i.e., OCC). In addition to evaluating each SE order, OS staff routinely look across our premarket application review programs to determine how we can improve our review process and decision-making. It was during those discussions that it became clear that OS staff were spending a lot of time doing fully quantitative assessments of HPHC data when it was obvious that the differences were not a public health concern. The SE program has evolved significantly since its start as result of this iterative evaluation of the program.

5. Establish a defined process for reviewer agreement, including evaluating decision concordance. Also, have a process for resolving discrepancies.

   OS response: OS has had a defined process for reviewer agreement for nearly as long as the SE program has existed. The process in OS aligns with the process used across FDA. Every OS staff member on a given SE review team is expected to document their conclusions from evaluating SE Reports. And, if anyone in leadership on the review team disagrees with a primary reviewer or someone at a lower level of leadership, then that lead documents their disagreement with the conclusion. For example, if the toxicology reviewer and branch conclude that HPHC differences raise public health concerns, they would finalize their

review as such. Then, if the TPL (Technical Project Lead) believes that the HPHC data doesn't raise public health concerns, they would draft a memo to document their conclusion and why they disagree with the toxicology reviewer and branch chief. There is also the FDA scientific dispute resolution process that can be employed by OS staff if an issue can't be resolved within OS.

6. Establish processes for regular training and information sharing among reviewers and management to facilitate standardized approaches and decision making.

   OS response: These processes already exist. OS has a lot of written materials regarding the SE program. This material is distributed to staff and is written based on the specific role that a given staff member fills. For example, there are specific training materials and policy memos for toxicology reviewers and different materials for chemistry reviewers. In addition, OS just launched its first office-wide SE training program over the summer.

<u>Additional Information for Consideration</u>

7. Are there relevant materials or information that the expert panel may not have been aware of, that should be considered?

   OS response: There are volumes of materials relevant to SE review that the expert panel was not aware of. In addition, every week, there are various meetings to discuss the SE program and improvements that can be made. The meetings involve all OS staff involved in SE review.

8. Has OS already implemented any policies or procedures that address recommendations made by the expert panel?

   OS response: As mentioned above, OS launched its first office-wide SE training program over the summer in an effort to improve consistency in decision making across OS.

9. What is the role of OS's experience with previous SE reviews in shaping how OS currently evaluates HPHCs?

   OS response: As discussed above, OS has nearly a decade of experience evaluating SE Reports and continually assesses how we evaluate the applications. Over that time, there has been extensive discussion about HPHC data within OS as well as outside OS (i.e., OCC and OCD). It is our experience spending many hours conducting a fully quantitative assessment of HPHC data even though we knew before the assessment that the HPHC data was not a public health concern.

10. Do you have any high-level recommendations with respect to how CTP should address the panel's recommendations both in the short- and long-term?

    OS response: I believe that the OS-wide training was an important step. The training is video-recorder so that staff can go back and re-watch it if necessary. In addition, it can be used by new staff that come onboard. I would also like FDA experts on the scientific dispute resolution process make a presentation to all OS staff in upcoming months.

Appendix 3

Expert Panel Report

July 31, 2020

To: Mitch Zeller, JD
Director of the Center for Tobacco Products
Food and Drug Administration

From: [redacted], PhD
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RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP.

The panel was provided documents including the May 31 2019 letter addressed to Drs [redacted] and [redacted] (CTP/OS) from Drs. [redacted] and with concurrence from Drs. [redacted] and [redacted] (CTP/OS/DNCS). This letter is in reference to a Division level memorandum (from their Division) entitled, "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" signed by Dr. [redacted] the Deputy Director of DNCS and stated as "through" the Division Director, Dr [redacted] The HPHC memorandum dated February 21 2019 was attached as Appendix B to the May 31 2019 letter. We have also reviewed the response to the May 31 2019 memorandum from Dr [redacted] (CTP/OS) digitally signed on December 13, 2019 to Drs [redacted] and [redacted] with a courtesy copy to the Director of CTP/OS, Dr [redacted] We were additionally provided other documents including examples of actual SE tobacco product summaries.

Dr [redacted] memorandum of December 13 2019 indicated that DNCS management provided adequate justification for the current approach (initial qualitative or semi-quantitative approach followed by a fully quantitative approach when merited) and that it is based on sound science. [redacted] upheld the February 21 2019 memorandum.

RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP.

We were asked to provide opinions on the following two statements.

> The "qualitative or semi-quantitative" approach, as outlined in the relevant reviewer guide, is not based on the best available science.
>
> This "qualitative or semi-quantitative" approach can yield entirely different results than the quantitative approach, i.e., one approach might result in a product being approved for market while the other approach would not.

In our opinion, the best approach to assessing the risk of disease or disorder in humans from the exposure to a chemical or compound requires human data, such as the internal dose and human health.

We recognize that traditional quantitative risk assessment methodologies were not developed for tobacco products, which possess distinct regulatory challenges. For example, tobacco product emissions can include a mixture of more than 7000 compounds of which 93 appear in the FDA-CTP's HPHC list and others may be harmful. Within this context, we agree with Dr [redacted] in that there are potentially other scientific approaches to compare the risk of toxicity of two tobacco products in addition to the traditional quantitative risk assessment. Nevertheless, this does not mean that the "qualitative or semi-quantitative approach" is necessarily the ideal one for FDA-CTP because additional methods can be needed to assess the risk of toxicity of the chemicals or compounds on the list of HPHCs (Leong et al, 2013).

The management elected to modify the prior peer-reviewed quantitative risk assessment approach in favor of a unique and unfamiliar "qualitative or semi-quantitative approach." The quantitative risk assessment approach relies on 4 steps: 1) hazardous chemical identification, 2) dose-response assessment, 3) exposure assessment, and 4) risk characterization. The quantitative risk assessment can provide an estimate of the risk of toxicity with the level of uncertainty for an exposure to a chemical or compound. The methodology for the quantitative risk assessment can be found here (US EPA: https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance ; accessed 7/28/2020).

In general, the current "qualitative or semi-quantitative approach" involves a novel process, whereby reviewers focus specifically on 1) HPHC increases and decreases that are analytically non-equivalent between the new and predicate products, 2) whether the risk of toxicity from an identified increase in HPHC can be offset by a decrease in another HPHC, and 3) if there is evidence for an increase in potential toxicity from an HPHC, a fully quantitative assessment should be conducted. The performance of the above approach in the assessment of HPHCs is unknown to us.

Clearly, the quantitative approach produces a more comprehensive assessment of the risk of toxicity from the exposure to a chemical or compound than the qualitative approach. For example, quantitative risk assessment can provide an estimate of the risk of toxicity (Coleman

and Marks, 1999). Yet it also seems reasonable that there will be circumstances that do not need a quantitative assessment, such as the instance when an application is fatally flawed.

It is critical to consider that there can be differences between the conclusions drawn from quantitative and semi-quantitative approaches (structured framework [Leong et al. 2013]) because these approaches can lead to varying decisions, depending on the chemical or compound under assessment.

A reason for the variability in the decision is that the above approaches are used to answer different questions. For example, a qualitative assessment is used to provide a categorical answer (y/n) to a question, such as the existence of a difference between two products. A quantitative assessment is used to provide an answer to question with a measured response, such as the amount of difference between two products.

When a difference between two products is apparent, such as toxicity to the heart versus toxicity to the liver, the above approaches yield the same decision. However, when the difference between two products is not apparent because they are similar, such as carcinogens of different potency, the quantitative approach can provide information on the amount of "risk of cancer" for the two products. The difference in the "risk of cancer" between two products can be more (or less) than the expectation based on the qualitative assessment. It is important to specify the question about the chemical or compound under review.

The "qualitative or semi-quantitative approach," as described in the above [redacted] memo, appears to rely solely on the judgement of the subject matter expert and impressions of FDA-CTP reviewers as opposed to quantifiable standards or criteria; even when these comparisons are complex, such as considering multiple and potentially offsetting HPHCs. Given the environment in which FDA-CTP operates, the above situation can be a significant limitation of the semi-quantitative approach as presently described. For these reasons, we believe that the semi-quantitative approach would substantially benefit from increased transparency.

For example, the rationale supporting the below decision statement is not transparent (TOX REV SE0000004 MAR 20 2019):

"When the toxicological evidences highlighted above are taken together, there is no evidence to suggest that the additional cancer risk associated with the increased amount of *o*-cresol would outweigh the cancer risk that is expected to be decreased due to the decreased NNK for the new product compared with the predicate product, and hence the increase in *o*-cresol is not likely to cause the new product to raise different questions of public health from a toxicological perspective."

The above decision is stated without documenting the process or how the data were evaluated to make this decision. How and by what metric did the reviewer decide that the potential impact of higher amounts of o-cresol would be offset by lower amounts of NNK? This a professional opinion that is not transparent to the reader. In our opinion, more specific and transparent

guidance to FDA-CTP reviewers are needed to ensure consistent and effective decisions that reduce population harm caused by the use of tobacco products.

Recommendations:

1. The qualitative or semi-quantitative approach in the above [redacted] memo lacks sufficient detail and guidance to be enacted as a scientific methodology in its current form. For example,

a. Lack of methodology for assessing non-cancer chemical hazards
b. Lack of methodology for comparing cancer risks of different HPHCs using a quantitative analysis
c. Lack of methodology of how to examine HPHCs as a mixture
d. Lack of methodology for comparing risks of different organs
e. Failure to demonstrate a systematic review of risk analysis methodologies for application to HPHCs and the decision-making process

In the opinion of the panel, the process needs to have clear decision rules which guide the review and dictate the integration of the “qualitative or semi-quantitative" evaluation with quantitative risk assessment. These decision rules should be added to the review process to ensure adequate protection of public health.

2. Establish a well-defined workflow and review process for assessments that address the specific questions to be answered about the chemical or compound under review.

3. Develop and communicate standardized and objective criteria for deciding when a quantitative risk assessment should be conducted in a collaborative manner that includes CTP management and reviewers.

4. Establish a review process that monitors the quality of the decisions that result from the above workflow, and allows for continuous improvement and correction of the workflow.

5. Establish a defined process for reviewer agreement, including evaluating decision concordance. Also, have a process for resolving discrepancies.

6. Establish processes for regular training and information sharing among reviewers and management to facilitate standardized approaches and decision making.

References

Coleman M and Marks HM. (1999). Qualitative and quantitative risk assessment. Food Control 10(4):289-297. 10.1016/S0956-7135(99)00052-3.

RE: Concerns regarding harmful and potentially harmful constituent (HPHC) comparison and evaluation procedures for comparing two tobacco products by FDA-CTP.

EPA Guidance documents: https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance

Leong J, McAuslane N, Walker S, Salek S. (2013) Is there a need for a universal benefit-risk assessment framework for medicines? Regulatory and industry perspectives. Pharmacoepidemiol Drug Saf. Sep;22(9):1004-12. doi: 10.1002/pds.3464. Epub 2013 Jun 5. PMID: 23740622

Appendix 4

May 2019 Appeal

May 31, 2019

To: [redacted]
Director, CTP/OS

[redacted]
Deputy Director of Regulatory Management, CTP/OS

[redacted]
Deputy Director of Regulatory Science, CTP/OS

From: [redacted]
Toxicology [redacted] CTP/OS/DNCS

[redacted] Toxicology [redacted], CTP/OS/DNCS

Concurring: [redacted]
Toxicology [redacted] CTP/OS/DNCS

[redacted]
Toxicology [redacted], CTP/OS/DNCS

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

We submit this letter to seek resolution[1] on matters related to the memorandum "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports" signed by Food and Drug Administration's (FDA's) Center for Tobacco Products (CTP) Office of Science (OS) Division of Nonclinical Science (DNCS) on February 21, 2019 (the HPHC Memorandum)[2].

First, we find that in issuing the HPHC Memorandum, DNCS issued a guidance document that set forth new Agency policy and provides DNCS staff guidance on a new approach for review of SE product applications but was not developed in accordance with the FD&C Act and FDA's regulations for good guidance practice (GGP)[3]. *Second*, we find that the HPHC Memorandum is a guidance document that is not supported by the best available science as required by FDA policies related to preservation and promotion of scientific integrity[4]. For these reasons, we do not find the qualitative (or semi-qualitative) approach outlined in the HPHC Memorandum appropriate for the toxicology review of tobacco product application, and thus are not able to apply this memorandum to our toxicological evaluations. The

[1] 21C.F.R.§10.115 states: "*If you believe that someone at FDA did not follow the procedures in this section* [GGP] *or that someone at FDA treated a guidance document as a binding requirement, you should contact that person's supervisor in the center or office that issued the guidance document*" (see Appendix A).
[2] See Appendix B
[3] FDA's Good Guidance Practices, 21 C.F.R. § 10.115(b); FDA 2011, Food and Drug Administration Report on Good Guidance Practice. Improving Efficiency and Transparency
[4] SMG 9001.1 FDA staff manual guides, volume iv – agency program directives

discussion below, includes, but is not limited to all issues with the February 21, 2019 memo. We respectfully request an in-person meeting so that we may have the opportunity to discuss these issues directly and receive concurrence that the reviewers do not need to apply the February 21, 2019 memo to tobacco product application review.

Introduction:

On Feb 22, 2019 DNCS staff were issued the memorandum entitled "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports", signed February 21, 2019. The HPHC 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*". The document sets forth the implementation of a "*new approach toward HPHC comparisons in SE reviews*"[5] for use by DNCS reviewers instead of the standard QRA framework and approach, used by DNCS in SE reviews since 2013, and indicates that the previously used approach is not "*designed to be compatible with the review of premarket product applications such as those reviewed by the FDA.*" The HPHC Memorandum does not provide scientific data and reasonable explanation for, nor does it mention how, the new approach to evaluating HPHCs is more appropriate than the established QRA approach previously used and considered appropriate by DNCS. We find the HPHC Memorandum to be a guidance document that is problematic in multiple respects:

First, the HPHC Memorandum, which was developed to inform DNCS staff of a new CTP policy and provide guidance on application of a new approach for evaluating SE product applications, was not developed in accordance with the FD&C Act and FDA's regulations for GGP[6]. The FD&C Act and FDA's GGP policies require any such substantial change in agency policies or those related to complex scientific issues to be made through notice and comment procedures; this is necessary to ensure adequate scientific deliberation, review and public input.

Second, we find that the HPHC Memorandum is a guidance document that is not supported by the best available science as required by FDA policies related to preservation and promotion of scientific integrity (SMG 9001.1); these FDA policies "*seek to strengthen the scientific quality, integrity and credibility of scientific reviews and decision-making at the agency.*" GGP procedures are also designed to allow adequate scientific deliberation, review and public input to ensure FDA guidance documents are of high quality. Also, the HPHC Memorandum does not provide a reasonable explanation or even mention how the new approach to evaluating HPHCs is more appropriate than the standard QRA approach which has been considered appropriate by DNCS in SE reviews since 2013[7], and has previously been used in regulatory decisions made by CTP. For example, DNCS has previously determined that the standard QRA approach was appropriate to make conclusions in findings of SE as NSE orders for tobacco product applications and was used to inform the development of the NNN product standard for

[5] 2/22/2019 Email from Dr. [redacted] to CTP-OS-DNCS on "New Memorandum on HPHC comparisons in toxicology SE reviews"

[6] FDA's Good Guidance Practices, 21 C.F.R. § 10.115(b); FDA 2011, Food and Drug Administration Report on Good Guidance Practice. Improving Efficiency and Transparency

[7] Toxicology Review of 905(j)(1)(A)(i) Report Second-Cycle Review of Additional Information for SE0003730; SE0003731; signed 06-03-2013

smokeless tobacco products[8]. In addition, there is a current DNCS Memorandum on "SE Review: Evaluating carcinogenic HPHC increases and assumptions of linearity for low-dose extrapolation", signed October 27, 2017[9], that continues to indicate that the standard QRA approach is appropriate for evaluating HPHCs in SE applications. Although scientific or policy conclusions can change based on new information or scientific data, such information should be provided and discussed to address prior findings and decisions, and to explain *why* the change in policy or conclusions is supported by the relevant data or references. Without such information, changes in policy or regulatory conclusions could be perceived as arbitrary and capricious[10].

Discussion:

1. <u>The HPHC Memorandum is not in accordance with GGP</u>

The HPHC Memorandum meets the definition of Guidance:

We find that the HPHC Memorandum issued to DNCS staff is a "*guidance document*" or its functional equivalent[11] within the meaning of the FD&C Act[12] and FDA's regulations and policies for GGP[13] because it is a document "*prepared for FDA staff*" to describe Agency policies that relate to "*the processing, content, and evaluation or approval of submissions.*" By informing staff of the new "*DNCS review practice for HPHC comparisons between two tobacco products*[14]", the HPHC Memorandum has broad applicability and future effect on CTP regulatory decisions related to tobacco product SE applications.

Prior to the 2019 HPHC Memorandum, DNCS used the standard QRA paradigm to support regulatory decisions related to tobacco product SE applications since 2013, to develop the draft NNN product standard for smokeless tobacco products[15], and in communications with stakeholders related to using the QRA approach for evaluating HPHCs in the context of SE product applications[16]; stakeholder input on the applicability of the standard QRA approach in the context of evaluating HPHCs in SE

[8] See FDA-2016-N-2527 Smokeless NNN PRIA

[9] DNCS Memoranda: SE Review: Evaluating carcinogenic HPHC increases and assumptions of linearity for low-dose extrapolation", signed October 27, 2017

[10] *W. Deptford Energy, LLC v. FERC,* 766 F.3d 10, 20 (D.C. Cir. 2014) ("an agency must 'provide a reasoned explanation for departing from precedent or treating similar situations differently")

[11] Policies and procedures for the development, issuance, and use of significant guidance documents by agencies are further refined in the Office of Management and Budget (OMB) Bulletin entitled, "Agency Good Guidance Practices" published January 18, 2007.

[12] FDA's Good Guidance Practices, 21 C.F.R. § 10.115(b): "*What is a guidance document? (1) Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue. (2) Guidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies*.

[13] FDA 2011, Food and Drug Administration Report on Good Guidance Practice. Improving Efficiency and Transparency

[14] HPHC Memorandum, p3: "*Currently, DNCS review practice for HPHC comparisons between two tobacco products is as follows*:"

[15] See FDA-2016-N-2527 Smokeless NNN PRIA

[16] Feedback on the use of QRA in SE applications has been provided to applicants as part of SE deficiencies. In addition, FDA has indicated that the QRA approach is appropriate for a comparison between two tobacco products in SE applications during meetings with applicants; as an example, see the August 17, 2016 Meeting Minutes for (b) (4) ; during the meeting, FDA noted that "*If* (b) (4) *does not provide a study with a complete datasets in its SE Reports, then other evidence might be useful, such as a quantitative risk assessment (QRA)*"

applications has been received by CTP not only in product applications, but also during the CTP Risk Assessment public workshop. As noted in the HPHC Memorandum, "… *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*." Given CTP's prior use and findings that the standard QRA approach in regulatory decision-making is appropriate, previous communications to stakeholders and public input regarding this approach, the HPHC Memorandum set forth policy changes that are more than minor in nature. In addition, the HPHC Memorandum relates to scientific principles and approaches used to evaluate risks to human health from HPHC exposures in tobacco products or tobacco smoke; these are complex scientific issues.

Guidance documents "*that set forth … changes in interpretation or policy that are of more than a minor nature; include complex scientific issues*" are within the definition of Level 1 Guidance under the FD&C act and FDA GGP policies procedures; these require public comment prior to implementation (21 C.F.R. § 10.115). However, not only was the HPHC Memorandum issued for implementation without public feedback, the guidance document was developed without addressing or considering relevant scientific data and rationale[17] provided by DNCS staff with expertise in human health risk assessment; although not yet established, a "*task force focusing on the toxicology risk assessment process and applicant-submitted QRAs*" was proposed by DNCS on March 5, 2019[18], after the HPHC Memorandum was signed and issued for implementation.

To ensure that the guidance document is "*developed with appropriate review and public participation, accessible and transparent to the public, of high quality*" (OMB 2007), we believe that FDA GGP should have been followed in the development, and prior to the issuance and implementation of this guidance document on how DNCS reviewers should evaluate HPHCs in the context of tobacco product SE application review.

2. The HPHC Memorandum is not supported by the best available science[19]

The standard QRA approach is a systematic and transparent process to evaluate human health risk from chemical exposures:

The framework for cumulative human health risk assessments of complex mixtures, as first outlined in the 1983 NAS Report, provides a predictable scientific approach and consistency across regulatory agencies for evaluation of cumulative human health risk from chemical exposures. The standard QRA approach provides a systematic and transparent process to (1) determine the type of adverse effects that may be caused by a chemical (hazard identification), (2) determine the relationship between the magnitude of exposure to a hazard and the probability and severity of adverse effects (dose-response assessment), (3) determines the extent to which exposure actually occurs (exposure assessment), and (4) to combine the information from the preceding steps to reach a conclusion about

[17] See Appendix C for a timeline and information related to the scientific concerns previously communicated by reviewers to the DNCS Deputy Director on the use the qualitative approach in the context of SE review.

[18] The Proposal for DNCS Internal Group Formation for a "Toxicology SE Reviewer Guide Task Force" was made by the DNCS IO and dated 5/13/2019

[19] This section highlights some of the main points of scientific disagreement the reviewers have with the HPHC Memorandum; it is not intended to list all the issues identified.

the nature and potential magnitude of risk (risk characterization)[20]. Although this approach for evaluating potential human health risks from complex mixtures is not specific to any given type of exposure or regulated products, it has broad applicability and has been widely adopted by federal agencies, including FDA, to support a wide array of regulatory decision making[21].

The standard QRA approach has been considered appropriate for over 30 years to evaluate human health risk from tobacco:

The standard QRA approach has been used for more than 30 years to evaluate human health risks from tobacco products. Some notable scientific publications that include a discussion of the applicability and use of the QRA approach in the context of tobacco products, include: the NAS 1986 report- Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects; the EPA 1993 Report- Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders; the NAS 2001 Report- Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction; the OEHHA 2005 Report- Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant; and several other publications[22,23,24,25, 26,27].

The standard QRA approach has been considered appropriate in CTP regulatory decisions (including in the context of SE applications) for over 6 years:

The applicability of the standard QRA approach in the context of tobacco product applications, was discussed at the public meeting held by CTP "Risk Assessment of Tobacco Products: A Public Workshop". The workshop focused specifically on the use of the standard QRA in the review of premarket tobacco product applications; during this meeting, CTP received information and feedback from a wide array of stakeholders in academia, industry, non-profit as well as other regulatory agencies. Although there are aspects relevant to tobacco product risk assessment that are developing, the general compatibility of the standard QRA approach with review of premarket tobacco product applications, including SE applications, was not an issue of dispute during the Public Workshop. Based on the available scientific information, including feedback CTP previously received from stakeholders during the

[20] GAO 2001. Report to Congressional Requests; Chemical Risk Assessment- Selected Federal Agencies' Procedures, Assumptions and Policies.

[21] GAO 2001 Report to Congressional Requests; Chemical Risk Assessment- Selected Federal Agencies' Procedures, Assumptions and Policies.

[22] Fowles and Dybing, 2003. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tob Control*, vol 12: 424-430.

[23] Fowles, Bates, and Dybing, 2000. The chemical constituents n cigarettes and cigarette smoke: Priorities for harm reduction. A report to the New England Ministry of Health.

[24] Cunningham, Fiekelkorn, Johnson, and Meredith, 2011. A novel application of the margin of exposure approach: Segregation of tobacco smoke toxicants. *Food and Chemical Toxicology*, vol. 49: 2921-2933.

[25] Haussmann, 2012, Use of hazard indices for a theoretical evaluation of cigarette smoke composition. Vol. 25(4):794-810.

[26] Xie et al. 2011. A probabilistic risk assessment approach used to prioritize chemical constituents in mainstream smoke of cigarettes sold in China. *Regulatory Toxicology and Pharmacology*, vol. 62: 355-362.

[27] Marano et al, 2012. Quantitative risk assessment of tobacco burning and tobacco-heating cigarettes. 66th Annual Tobacco Science Research Conference, Quantitative Risk Assessment: A Path Forward. Recent Advances in Tobacco Science, Vol. 38: 3-20.

Public Workshop[28], the standard QRA approach is applicable and appropriate to evaluate relative human health risks from tobacco products in SE applications.

The rationale in the HPHC Memorandum for why standard QRA approach is not to be used to evaluate HPHCs in SE applications is not supported by the best available science:

The HPHC Memorandum does not mention any new information or scientific data to explain why the change in DNCS policy related to the use of QRA in the evaluation of HPHCs is supported by the best available science. Rather, the HPHC Memorandum provides the following lines of justification (without any supportive references) as for why the new approach was developed and should be used for the evaluation of HPHCs in SE applications instead of the standard QRA approach and methods:

- The cumulative human health risk of complex "*mixtures evaluated by organizations such as the EPA and the ATSDR, are (1) not specific to tobacco products, (2) not designed to rapidly assess relative risk between complex mixtures, or (3) not designed to be compatible with the review of premarket product applications such as those reviewed by the FDA*." and
- "*…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*."

<u>This justification does not provide a reasoned rationale consistent with the best available science:</u>

1. The statement that "*the cumulative human health risk of complex mixtures evaluated by organizations such as the EPA and the ATSDR are not specific to tobacco products*" is not accurate; Federal agencies such as the EPA has used the QRA approach to evaluate cumulative human health risk from tobacco products. A notable example is the EPA 1993 report "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders", which used a risk assessment framework to classify secondhand smoke as a Group A carcinogen. However, whether agencies such as EPA and ATSDR evaluate health risk of complex mixtures specific to tobacco products, or if the QRA approach outlined by NAS (and built upon by EPA, FDA and ATSDR among others) was (or was not) developed to be specific for tobacco products has no bearing on whether this approach is applicable and appropriate for the evaluation of human health risks from HPHCs in tobacco products[29,30,31]. The appropriateness of using the standard QRA approach in the evaluation of HPHC exposures from tobacco products and tobacco smoke is evidenced in the multitude for regulatory decisions, including SE and NSE marketing orders

[28] Feedback received from industry regarding the use of QRA to compare relative risks between tobacco products was summarized in the publication by Marano et al, 2018 "Quantitative risk assessment of tobacco products: A potentially useful component of substantial equivalence evaluations" (*Regulatory Toxicology and Pharmacology*, vol. 95:371-384). While the paper has limitations, it synthesizes much of the workshop discussion, and shows how the established risk assessment paradigm can be used to inform tobacco product review.

[29] See footnotes 18 to 24 above, and see also NAS, EPA, and OEHHA references noted previously.

[30] NAS, 1983. Risk assessment in the federal government: Managing the process. National Research Council. "Risk assessment is the use of factual base to define health effects of exposure to individuals or populations to hazardous materials and situations."

[31] NAS, 2009. Science and Decisions: Advancing Risk Assessment. National Research Council. "[R]isk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk"; "[R]isk assessment remains the most appropriate available method for measuring the relative benefits of many possible interventions available to improve human health"

issued by CTP that have considered the standard QRA approach appropriate to evaluate human health risks from HPHCs in tobacco products. In addition, evaluation of HPHC data using the standard QRA approach has been provided by CTP as an option for applicants to address HPHC increases in new tobacco products as compared to corresponding predicate product(s)[32]; CTP also granted deficiency response extensions to allow reasonable time for applicants to conduct a QRA addressing deficiencies in product applications[33].

2. The HPHC Memorandum indicates that the standard QRA approach is not appropriate in the context of tobacco product review because it is "*not designed to rapidly assess relative risk between complex mixtures.*" The toxicology reviewer evaluates the appropriateness of a QRA (or assessment of relative risk between two complex mixtures) that has already been conducted and submitted by applicants to support tobacco product SE applications. Whether or not the QRA approach was specifically "*designed to rapidly*" evaluate the relative risks of complex mixtures, does not provide information relevant to why an HPHC evaluation (provided by applicants) that uses the standard QRA approach is not scientifically appropriate to evaluate relative human health risks in the context of SE product applications. Therefore, this statement does not provide a scientific rationale for why the new approach was developed and should be used for the evaluation of HPHCs in SE applications instead of the standard QRA approach.
3. The statement that the standard QRA paradigm is "*not designed to be compatible with the review of premarket product applications such as those reviewed by the FDA*" is not accurate. The risk assessment paradigm provides a framework for a systematic and consistent approach to evaluate human health risks (cancer and non-cancer) from chemical exposures. The standard QRA approach for evaluation of cumulative human health risk of complex mixtures has been widely adopted federal regulatory agencies including the FDA[34,35]; the standard QRA approach is compatible with, and has been used by the FDA to inform the evaluation of premarket applications for various regulated products, including foods[36], drugs and devices[37] as well as tobacco product applications[38].
4. The statement that "*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*

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[32] See August 17, 2016 Meeting Minutes for (b) (4) ; during the meeting, FDA noted that "*If* (b) (4) *does not provide a study with complete datasets in its SE Reports, then other evidence might be useful, such as a quantitative risk assessment (QRA*)"

[33] The FDA A/I Extension Granted letter dated November 30, 2018 (SE0014989) states "*we do believe that the extension granted is a reasonable amount of time which would enable you to provide a complete response through the combined approach of a quantitative risk assessment (QRA*)"

[34] GAO 2001. Report to Congressional Requests; Chemical Risk Assessment- Selected Federal Agencies' Procedures, Assumptions and Policies. Agencies (including FDA) generally following a transparent four-step risk assessment process recommended by the NAS in the context of the given diverse assessments for the agency, though the procedures used have many common basic assumptions; "Risk assessment is an important, but extraordinarily complex, element in federal agencies' regulation of potential risks associated with chemicals."

[35] Gaylor et al, 1997. Health risk assessment practices in the U.S. Food and Drug Administration. *Regulatory Toxicology and Pharmacology*, vol. 26: 307-321.

[36] March 2002. Report by the CFSAN Risk Analysis Working Group (accessed at https://www.fda.gov/food/cfsan-risk-safety-assessments/initiation-and-conduct-all-major-risk-assessments-within-risk-analysis-framework); Dickey, RW (2102) FDA Risk Assessment of Seafood Contamination after the BP Oil Spill; Environ Health Perspect.120(2)

[37] FDA 2005. Premarketing Risk Assessment Guidance for Industry

[38] See footnotes 18 to 24 above, and see also NAS, EPA, and OEHHA references noted previously.

tobacco products: the HPHC list", is not accurate and counter to FDA's final HPHC guidance for industry and FDA staff[39] and the April 2011 FR Notice[40]:

- The definition of HPHC does not limit the HPHC established list to the chemicals "*understood to drive the majority of human health risk posed by tobacco products.*" As defined in the HPHC Guidance document, the phrase "harmful and potentially harmful constituent" includes any chemical or chemical compound in a tobacco product or in tobacco smoke that: a) is, or potentially is, inhaled, ingested, or absorbed into the body, including as an aerosol (vapor) or any other emission; and b) causes or has the potential to cause direct or indirect harm to users or non-users of tobacco products.
- Consistent with the HPHC definition, as published in the April 2011 FR Notice, the HPHC established list was developed using a hazard-based approach that identified chemicals or chemical compounds in a tobacco product or in tobacco smoke that cause or have the potential to cause direct or indirect harm; this approach is different from the risk-based approach that would be necessary to determine (and limit) the HPHC established list to chemicals "*understood to drive the majority of human health risk posed by tobacco products.*"
- Furthermore, the Supplementary Information of the April 2012 FR Notice[41] specifies that the established HPHC list may not be comprehensive and is restricted by the scope and criteria used for its development.

However, even if this statement was accurate, it does not provide information relevant to why the standard QRA approach is not scientifically appropriate to evaluate relative human health risks in the context of SE product applications.

The "*qualitative or semi-quantitative approach*" outlined in the HPHC Memorandum is not supported by the best available science:

The HPHC Memorandum sets forth implementation of a "*qualitative or semi-quantitative approach"* for HPHC evaluations in SE reviews, without providing any scientific references or rationale explaining why this approach is supported by the best available science. Broadly, the HPHC Memorandum informs DNCS staff that when an applicant provides a QRA, "...*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*

[39] FDA 2016. Guidance for Industry and FDA Staff: "Harmful and Potentially Harmful Constituents' in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act" (Revised).
[40] FDA 2011. Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments. 76 FR 50226.
[41] FDA. 2012. Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List. 77 FR 20034

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."*

We find that application of a "*qualitative or semi-quantitative approach"* that meets the above criteria is not supported by the best available science and does not consider all data and information provided by an applicant in an SE application that contains a QRA:

1. A risk assessment approach that meets criteria a-c[42] and considers only HPHCs identified as "*analytically non-equivalent HPHC increases or decreases"* would not consider the totality of information provided in a QRA submitted by applicants in the context of SE applications. This could result in the loss of important risk information that is relevant to the toxicology evaluation of relative cancer risk and noncancer hazard (EPA 2002) between the new and predicate products. The results of the statistical or analytical equivalence evaluation depend on several factors such as the decision criteria for equivalence (e.g., value considered a meaningful analytical difference) and data quality among others. In the context of risk assessment, such evaluations are generally conducted as screening level assessments only[43]; this gives an indication that either 1) all constituents (e.g., HPHC) are below the pre-set health based criteria used to conduct the equivalence test and identify constituents of potential concerns and thus a risk assessment is not warranted or 2) there are constituents above the set criteria of concern (e.g., HPHC increases above the equivalence margin), and a risk assessment is informative. When a screening level assessment identifies constituents above a set level or criteria predetermined to be of concern (which in the case of the HPHC analysis is the equivalence margin), a baseline risk assessment is conducted to characterize the current and potential human health risks from exposures to the hazardous substances. Based on established risk assessment principles and available guidance it is accepted practice to include all constituents (with data of sufficient quality) in the risk or hazard calculations when evaluating human health risk from chemical mixtures[44,45,46,47].

[42] Criteria a-c are discussed together because they provided repeated instructions on which HPHCs submitted in SE applications that should be considered in the toxicology evaluation when the applicant submits a QRA.

[43] EPA 2002. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites

[44] IGHRC 2009. Chemical Mixtures: A Framework for Assessing Risk to Human Health (CR14). Institute of Environment and Health, Cranfield University, UK.

[45] EPA 1989. Risk Assessment Guidance for Superfund. Volume I. Human Health Evaluation Manual (Part A). EPA/540/1-89/002. Office of Emergency Response;

[46] EPA 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures Published on September 24, 1986, Federal Register 51(185):34014-34025. Risk Assessment Forum U.S. Environmental Protection Agency Washington

[47] EPA 2002. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. *"EPA cautioned that eliminating COPCs based on background (either because concentrations are below background levels or attributable to background sources) could result in the loss of important risk information for those potentially exposed, even though cleanup may or may not eliminate a source of risks caused by background levels*"

HPHC data provided in SE applications are intended to provide a comparison of the HPHC levels and potential user exposures from differences in product characteristics. A risk assessment approach that only considers compounds identified as "*analytically non-equivalent HPHC increases or decreases*" does not consider the totality of information provided and could result in the loss of important risk information that is relevant to the evaluation of relative cancer risk and noncancer hazard between the new and predicate products. A risk assessment approach that includes all measured HPHCs can provide a more comprehensive hazard identification; this is more representative of the relative cumulative cancer risk and noncancer hazards and thus is more appropriate for a comparison between tobacco products in SE applications.

2. The statement *"Considers HPHC measurements that are analytically equivalent per the Chemistry discipline as equivalent for purposes of toxicological comparison between the two compared products"* is not accurate. The equivalence margins used in the HPHC evaluation are set based on analytical methods and analytical variability, not health-based equivalence margins. Because the evaluation does not use health-based equivalence margins, it cannot be concluded that HPHC increases or decreases found by Chemistry as analytically equivalent are also "*equivalent for purposes of toxicological comparison*" in terms of human health risks especially given the differences in potency for the different HPHCs.
3. The statement 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"* is not accurate and inconsistent with previous CTP regulatory decisions**.** As mentioned above, the results of the analytical equivalence evaluation depend on several factors, such as the decision criteria for equivalence (e.g., value considered a meaningful analytical difference). For this reason, several scenarios exist where while there are only non-equivalent HPHC increases (i.e., without non-equivalent decreases), the totality of data and information submitted by an applicant could be adequate to demonstrate that the differences between two products are unlikely to raise different questions of public health. Although CTP does not have an established criterion or threshold for a *de minimis* risk in the context of SE applications, there could be specific scenarios for which the HPHC increase (and associated increase in risk) is unlikely to raise different questions of public health. For example, the Memoranda written by Dr. [redacted] for SE0006198, SE0006199, SE0006211 (signed May 3rd, 2018)[48] and for SE0000603 (signed July 27th, 2018)[49] provide two specific HPHC comparison scenarios where (without mention of offsetting HPHC decreases), Dr. [redacted] concluded that based on the totality of information, "*the increases in formaldehyde do not cause the new products to raise different questions of public health."* In addition, an HPHC comparison scenario where the equivalence test identified a non-equivalent HPHC increase (without concomitant non-equivalent decreases) but the standard QRA approach (i.e., using on all measured HPHCs) shows that there is no increase in the overall

[48] From Dr. [redacted] (OS Director) to File; R.J. Reynolds Tobacco Company SE Reports: SE0006198, SE0006199, SE0006211; signed 05-03-2018.
[49] From Dr. [redacted] (OS Director) to File Philip Morris USA SE Report: SE0000603; signed 07-27-2018.

risk or hazard from the new product would be adequate to demonstrate that the non-equivalent HPHC increase does not raise different questions of public health from a toxicology perspective.

Taken together, the use of this "*qualitative or semi-quantitative approach"* in the toxicology evaluation of HPHCs and associated QRAs could result in product review conclusions (and issuance of marketing orders) that are made without consideration of all relevant toxicology information submitted in the tobacco product SE applications. To be consistent with the Administrative Procedure Act (APA)[50] and FDA policies that govern the scientific integrity of the product review process, we believe that all relevant information should be considered, and the Toxicology review conclusions should "rely on the best available science"[51].

Summary:

As discussed in detail above, we find application of the HPHC Memorandum to our Toxicology reviews of SE applications problematic for several reasons, including:

- Although the HPHC Memorandum signed February 21, 2019 meets the definition of Guidance, the process outlined by FDA GGP does not appear to have been followed in the development, prior to its issuance and implementation, of this guidance document by DNCS. Following the process for FDA GGP is needed to ensure guidance is "*developed with appropriate review and public participation, accessible and transparent to the public, of high quality*" (OMB 2007).
- Also, we find that the HPHC Memorandum is a guidance document that is not supported by the best available science. The standard QRA approach is a systematic and transparent process to evaluate human health risk from chemical exposures, has been considered appropriate to evaluate human health risk from tobacco products in general, and has also been identified as appropriate and informative specifically for the toxicology review of tobacco product SE applications for over six years. As discussed previously in this document, the rationale provided in the HPHC Memorandum for why the standard QRA approach is not appropriate to evaluate HPHCs in SE applications is not supported by the available science. In addition, the HPHC Memorandum set forth implementation of a "*qualitative or semi-quantitative approach*" for HPHC evaluations in SE reviews, without providing a reasonable explanation, scientific references, or even mentioning how the new approach to evaluating HPHCs is more appropriate than the standard QRA approach used by DNCS since 2013[52], especially considering previous recommendations to industry in the context of SE applications, previous regulatory decisions DNCS has made, as well as other CTP memoranda currently implemented by DNCS for SE application reviews. Moreover, the available information indicates that the "*qualitative or semi-*

[50] *See,* 5 U.S.C. § 55

[51] Under 21 CFR Part 10, Administrative Practices and Procedures, 21 CFR 10.70 states "*FDA employees responsible for handling a matter are responsible for insuring the completeness of the administrative file relating to it. The file must contain appropriate documentation of the basis for the decision…" also,*
FDA SMG9001.1 FDA Staff Manual Guides, Volume IV- Agency Program Directives/ General or Multidiscipline/Scientific Integrity states "*FDA must rely on the best available science to make difficult decisions with respect to those products. In making those decisions, an unbiased presentation and full evaluation and analysis of the data, including its uncertainties, is absolutely critic*al".

[52] Toxicology Review of 905(j)(1)(A)(i) Report Second-Cycle Review of Additional Information for SE0003730; SE0003731; signed 06-03-2013

quantitative approach" outlined in the HPHC Memorandum is not grounded in the best available science and use of this approach in the toxicology evaluation of HPHCs and associated QRAs could result in product review conclusions (and issuance of marketing orders) that are made without consideration of all relevant toxicology information submitted in the tobacco product SE applications.

Possible Impacts on CTP Regulatory Decisions:

Applying the February 21, 2019 HPHC Memorandum to our current evaluations of SE Reports would result in toxicology review conclusions, and consequently tobacco product marketing orders, that do not consider all relevant information are not adequately supported by the available science. For example, in (b) (4) (new product vs. predicate product 1) the equivalence test identified analytically important (non-equivalent) increases in two carcinogens, with no concomitant analytically important (non-equivalent) decreases in carcinogens; based on the HPHC Memorandum the toxicology review, without full consideration of all relevant information provided, would have to conclude that the new product is NSE to predicate product 1. However, results from the applicant's submitted QRA, which included smoke yields for 17 measured HPHCs, indicate that there is no increase in the cumulative estimated cancer risk for the new product relative to predicate product 1; if the reviewer conducts the evaluation based on the totality of relevant information provided by the applicant, the tentative conclusion is that the new product as compared to predicate product 1 is unlikely to raise different questions of public health, and thus is SE to predicate product 1. CTP's own website states that "*decisions made by the FDA in the regulation of tobacco products are grounded in science*[53]"; regulatory decisions that would be made by CTP made without consideration of all relevant information and that are not supported by the available science could be incorrect and may be overturned if challenged.

The HPHC Memorandum could also have negative consequences that reach far beyond those related to specific product review applications. Because the February 21, 2019 HPHC Memorandum 1) was not developed and issued following the process for FDA GGP to ensure appropriate review, public participation, and transparency; 2) provides information inconsistent with other current CTP Guidance and FR Notices[54] related to HPHCs as well as other current documents related to HPHC evaluations in SE applications[55]; and 3) it is not grounded in, and conflicts with the best available science, the HPHC memorandum could have a negative impact on the extent to which CTP and the Agency are perceived as trustworthy, competent, and credible. Consequently, this can have a negative impact on the effectiveness with which CTP and FDA carry out the mission to protect public health.

[53] https://www.fda.gov/tobacco-products/products-guidance-regulations (last accessed 05/30/2019)

[54] FDA 2016. Guidance for Industry and FDA Staff "Harmful and Potentially Harmful Constituents" in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry and FDA Staff"; "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List," 77 FR 20034 (April 3, 2012); "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments," 76 FR 50226 (August 12, 2011.

[55] DNCS Memoranda: SE Review: Evaluating carcinogenic HPHC increases and assumptions of linearity for low-dose extrapolation", signed October 27, 2017

Appendix A

CFR - Code of Federal Regulations Title 21

The information on this page is current as of April 1 2018.

For the most up-to-date version of CFR Title 21, go to the Electronic Code of Federal Regulations (eCFR).[6]

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TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A--GENERAL

PART 10 -- ADMINISTRATIVE PRACTICES AND PROCEDURES

Subpart B--General Administrative Procedures

Sec. 10.115 Good guidance practices.

(a) *What are good guidance practices?* Good guidance practices (GGP's) are FDA's policies and procedures for developing, issuing, and using guidance documents.

(b) *What is a guidance document?* (1) Guidance documents are documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue.

(2) Guidance documents include, but are not limited to, documents that relate to: The design, production, labeling, promotion, manufacturing, and testing of regulated products; the processing, content, and evaluation or approval of submissions; and inspection and enforcement policies.

(3) Guidance documents do not include: Documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or other communications directed to individual persons or firms.

(c) *What other terms have a special meaning?* (1) "Level 1 guidance documents" include guidance documents that:

(i) Set forth initial interpretations of statutory or regulatory requirements;

(ii) Set forth changes in interpretation or policy that are of more than a minor nature;

(iii) Include complex scientific issues; or

(iv) Cover highly controversial issues.

(2) "Level 2 guidance documents" are guidance documents that set forth existing practices or minor changes in interpretation or policy. Level 2 guidance documents include all guidance documents that are not classified as Level 1.

(3) "You" refers to all affected parties outside of FDA.

(d) *Are you or FDA required to follow a guidance document?* (1) No. Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.

(2) You may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations. FDA is willing to discuss an alternative approach with you to ensure that it complies with the relevant statutes and regulations.

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(3) Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.

(e) *Can FDA use means other than a guidance document to communicate new agency policy or a new regulatory approach to a broad public audience?* The agency may not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time. These GGP's must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.

(f) *How can you participate in the development and issuance of guidance documents?* (1) You can provide input on guidance documents that FDA is developing under the procedures described in paragraph (g) of this section.

(2) You can suggest areas for guidance document development. Your suggestions should address why a guidance document is necessary.

(3) You can submit drafts of proposed guidance documents for FDA to consider. When you do so, you should mark the document "Guidance Document Submission" and submit it to Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. If you wish to submit the draft of a proposed guidance document electronically, submit it through *https://www.regulations.gov* at Docket No. FDA-2013-S-0610. It is only necessary to submit one copy.

(4) You can, at any time, suggest that FDA revise or withdraw an already existing guidance document. Your suggestion should address why the guidance document should be revised or withdrawn and, if applicable, how it should be revised.

(5) Once a year, FDA will publish, both in the Federal Register and on the Internet, a list of possible topics for future guidance document development or revision during the next year. You can comment on this list (e.g., by suggesting alternatives or making recommendations on the topics that FDA is considering).

(6) To participate in the development and issuance of guidance documents through one of the mechanisms described in paragraphs (f)(1), (f)(2), or (f)(4) of this section, you should contact the center or office that is responsible for the regulatory activity covered by the guidance document.

(7) If FDA agrees to draft or revise a guidance document, under a suggestion made under paragraphs (f)(1), (f)(2), (f)(3) or (f)(4) of this section, you can participate in the development of that guidance document under the procedures described in paragraph (g) of this section.

(g) *What are FDA's procedures for developing and issuing guidance documents?* (1) FDA's procedures for the development and issuance of Level 1 guidance documents are as follows:

(i) Before FDA prepares a draft of a Level 1 guidance document, FDA can seek or accept early input from individuals or groups outside the agency. For example, FDA can do this by participating in or holding public meetings and workshops.

(ii) After FDA prepares a draft of a Level 1 guidance document, FDA will:

(A) Publish a notice in the Federal Register announcing that the draft guidance document is available;

(B) Post the draft guidance document on the Internet and make it available in hard copy; and

(C) Invite your comment on the draft guidance document. Paragraph (h) of this section tells you how to submit your comments.

(iii) After FDA prepares a draft of a Level 1 guidance document, FDA also can:

(A) Hold public meetings or workshops; or

(B) Present the draft guidance document to an advisory committee for review.

(iv) After providing an opportunity for public comment on a Level 1 guidance document, FDA will:

(A) Review any comments received and prepare the final version of the guidance document that incorporates suggested changes, when appropriate;

(B) Publish a notice in the Federal Register announcing that the guidance

Appendix A

document is available;

(C) Post the guidance document on the Internet and make it available in hard copy; and

(D) Implement the guidance document.

(v) After providing an opportunity for comment, FDA may decide that it should issue another draft of the guidance document. In this case, FDA will follow the steps in paragraphs (g)(1)(ii), (g)(1)(iii), and (g)(1)(iv) of this section.

(2) FDA will not seek your comment before it implements a Level 1 guidance document if the agency determines that prior public participation is not feasible or appropriate.

(3) FDA will use the following procedures for developing and issuing Level 1 guidance documents under the circumstances described in paragraph (g)(2) of this section:

(i) After FDA prepares a guidance document, FDA will:

(A) Publish a notice in the Federal Register announcing that the guidance document is available;

(B) Post the guidance document on the Internet and make it available in hard copy;

(C) Immediately implement the guidance document; and

(D) Invite your comment when it issues or publishes the guidance document. Paragraph (h) of this section tells you how to submit your comments.

(ii) If FDA receives comments on the guidance document, FDA will review those comments and revise the guidance document when appropriate.

(4) FDA will use the following procedures for developing and issuing Level 2 guidance documents:

(i) After it prepares a guidance document, FDA will:

(A) Post the guidance document on the Internet and make it available in hard copy;

(B) Immediately implement the guidance document, unless FDA indicates otherwise when the document is made available; and

(C) Invite your comment on the Level 2 guidance document. Paragraph (h) of this section tells you how to submit your comments.

(ii) If FDA receives comments on the guidance document, FDA will review those comments and revise the document when appropriate. If a version is revised, the new version will be placed on the Internet.

(5) You can comment on any guidance document at any time. Paragraph (h) of this section tells you how to submit your comments. FDA will revise guidance documents in response to your comments when appropriate.

(h) *How should you submit comments on a guidance document?* (1) If you choose to submit comments on any guidance document under paragraph (g) of this section, you must send them to the Division of Dockets Management (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(2) Comments should identify the docket number on the guidance document, if such a docket number exists. For documents without a docket number, the title of the guidance document should be included.

(3) Comments will be available to the public in accordance with FDA's regulations on submission of documents to the Division of Dockets Management specified in 10.20(j).

(i) *What standard elements must FDA include in a guidance document?* (1) A guidance document must:

(i) Include the term "guidance,"

(ii) Identify the center(s) or office(s) issuing the document,

(iii) Identify the activity to which and the people to whom the document applies,

(iv) Prominently display a statement of the document's nonbinding effect,

(v) Include the date of issuance,

(vi) Note if it is a revision to a previously issued guidance and identify the

Appendix A

document that it replaces, and

(vii) Contain the word "draft" if the document is a draft guidance.

(2) Guidance documents must not include mandatory language such as "shall," "must," "required," or "requirement," unless FDA is using these words to describe a statutory or regulatory requirement.

(3) When issuing draft guidance documents that are the product of international negotiations (e.g., guidances resulting from the International Conference on Harmonisation), FDA need not apply paragraphs (i)(1) and (i)(2) of this section. However, any final guidance document issued according to this provision must contain the elements in paragraphs (i)(1) and (i)(2) of this section.

(j) *Who, within FDA, can approve issuance of guidance documents?* Each center and office must have written procedures for the approval of guidance documents. Those procedures must ensure that issuance of all documents is approved by appropriate senior FDA officials.

(k) *How will FDA review and revise existing guidance documents?* (1) The agency will periodically review existing guidance documents to determine whether they need to be changed or withdrawn.

(2) When significant changes are made to the statute or regulations, the agency will review and, if appropriate, revise guidance documents relating to that changed statute or regulation.

(3) As discussed in paragraph (f)(3) of this section, you may at any time suggest that FDA revise a guidance document.

(l) *How will FDA ensure that FDA staff are following GGP's?* (1) All current and new FDA employees involved in the development, issuance, or application of guidance documents will be trained regarding the agency's GGP's.

(2) FDA centers and offices will monitor the development and issuance of guidance documents to ensure that GGP's are being followed.

(m) *How can you get copies of FDA's guidance documents?* FDA will make copies available in hard copy and, as feasible, through the Internet.

(n) *How will FDA keep you informed of the guidance documents that are available?* (1) FDA will maintain on the Internet a current list of all guidance documents. New documents will be added to this list within 30 days of issuance.

(2) Once a year, FDA will publish in the Federal Register its comprehensive list of guidance documents. The comprehensive list will identify documents that have been added to the list or withdrawn from the list since the previous comprehensive list.

(3) FDA's guidance document lists will include the name of the guidance document, issuance and revision dates, and information on how to obtain copies of the document.

(o) *What can you do if you believe that someone at FDA is not following these GGP's?* If you believe that someone at FDA did not follow the procedures in this section or that someone at FDA treated a guidance document as a binding requirement, you should contact that person's supervisor in the center or office that issued the guidance document. If the issue cannot be resolved, you should contact the next highest supervisor. You can also contact the center or office ombudsman for assistance in resolving the issue. If you are unable to resolve the issue at the center or office level or if you feel that you are not making progress by going through the chain of command, you may ask the Office of the Chief Mediator and Ombudsman to become involved.

[65 FR 56477, Sept. 19, 2000, as amended at 83 FR 13416, Mar. 29, 2018]

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FDA **U.S. FOOD & DRUG ADMINISTRATION**

MEMORANDUM

Date: February 21, 2019

From: [redacted]
Deputy Director
Division of Nonclinical Science
Office of Science

[redacted] 2019.02.21 14:42:34 -05'00'

Through: [redacted]
Director
Division of Nonclinical Science
Office of Science

Digitally signed by [redacted]
Date: 2019.02.21 14:45:50 -05'00'

To: File

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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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 EPA[1] 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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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 <u>different</u> from that of an HPHC that is increased <u>cannot</u> 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

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 off-setting 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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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.

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[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.

Appendix B

Memo: HPHC comparison and evaluation procedure for comparing two tobacco products in the SE Reports

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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/

Appendix C. Timeline relevant to scientific input provided in writing from CTP staff regarding the qualitative approach

Date	Action	Notes
11/21/18	The draft toxicology review ([redacted]) was submitted for clearance to the DNCS Deputy Director	
11/21/18	The Deputy Director provided the 1st round of comments instructing reviewers to consider using the qualitative approach in the SE review	• Questions included "*Do you think that you could apply a qualitative approach to this HPHC data set?*" (full email below): 11_21_18 email from DD.pdf
11/27/18	The toxicology review was resubmitted for clearance to the Deputy Director The reviewers submitted scientific information and rationale why the qualitative approach was not appropriate	• Primary, Secondary, and Tertiary Reviewers agreed that a qualitative approach was not appropriate and provided the Deputy Director with the following scientific evidence and rationale to support their position: 11_27_18 Reviewer Response.pdf
11/29/18	The Deputy Director provided a 2nd round of edits and comments instructing reviewers on using the qualitative approach in the SE review	• Comments included insistence on use of a qualitative approach for the toxicological evaluation (full email below): 11_29_18 email from DD.pdf
12/7/18	The toxicology review was resubmitted for clearance to the Deputy Director The reviewers submitted additional scientific information and rationale why the qualitative approach was not appropriate	• The reviewers continued to agree that a qualitative approach was still not appropriate and provided the following further rationale to support their position: 12_7_18 Reviewer Follow-up Response.p • Response to comments were delayed because Secondary Reviewer was at Scientific Conference and Tertiary Reviewer was on leave
12/10/18	The Deputy Director provided a 3rd round of edits and comments instructing reviewers on using the qualitative approach in the SE review	• Deputy Director instructed the reviewers to include a "*rationale for why the* [redacted] *does not offset the* [redacted]" (i.e., why the qualitative approach could not be used; full email below): 12_10_18 email from DD.pdf
12/12/18	The amended toxicology review was resubmitted for clearance to the Deputy Director	• The review was edited to include the rationale required by the Deputy Director for why a qualitative approach could not be used; the added text is included following this table, however this information was deleted from the review based on subsequently instructions from the Deputy Director.
12/13/18	The Deputy Director provided a 4th round of edits and comments related to use of	• The Deputy Director indicated that he may need to write a non-concur memo for this review (full email below):

Appendix C. Timeline relevant to scientific input provided in writing from CTP staff regarding the qualitative approach

	the qualitative approach in the SE review The Deputy Director recognized that the scientific issues raised by the reviewers relate to the general use of the qualitative approach for HPHC comparisons and stated that these should be "*part of the longer discussion that we need to have"*; these concerns were not addressed prior to development and issuance of the HPHC Memorandum signed by the Deputy Director on Feb 21, 2019	 12_13_18 email from DD.pdf • In addition, the Deputy Director deleted the newly included rationale and provided the following comment: "*This language belongs in a memo and is part of the longer discussion that we need to have. There are differing view points on this issue and we need to hammer out the language to achieve consensus. It seems to me that this language is inconsistent with the use of any qualitative approach to evaluate HPHC comparisons between tobacco products. In the meantime, I think that it is wise to leave out.*"
12/13/18-12/14/18	The Primary Reviewer emailed the Division Director	• The Primary Reviewer informed the Division Director of her discomfort and sense of pressure to use the qualitative approach in the process of this review (full email below):  12_13_18 Primary Reviewer email to Dire • The reviewer was instructed to discuss these concerns with the Deputy Director (full email below):  12_14_18 email from Director.pdf
12/14/18	Meeting between the Primary Reviewer and Deputy Director via the phone regarding instructions received by the reviewers to use the qualitative approach in the SE review	• During the meeting the Deputy Director continued to reiterate the importance of using the qualitative approach; however, no scientific justification for why this is appropriate was provided. The Primary Reviewer informed the Deputy Director that she was feeling undue pressure and reiterated the previously raised scientific issues related to use of the qualitative approach. • Agreement was reached that the qualitative approach was not appropriate for this review; the reviewer agreed to accept the edits made by the Deputy Director to delete the rationale for why a qualitative approach could not be used from the review discussion.
12/14/18	The Deputy Director emailed the Secondary Reviewer regarding the meeting with the Primary Reviewer	• The Deputy Director provided his understanding of the main points of consensus reached with the Primary Reviewer during the call meeting (full email below):  12_14_18 email from DD.pdf • The summary information provided as a "consensus point" on why the qualitative approach was not considered appropriate in the review did not accurately capture the reviewers' position; this was clarified in follow-up emails sent 12/17/18:

Appendix C. Timeline relevant to scientific input provided in writing from CTP staff regarding the qualitative approach

		12_17_18 email from Secondary Reviewer.p
12/17/18	The amended toxicology review was resubmitted for clearance to the Deputy Director	• The reviewer accepted the edit deleting the justification for why the qualitative approach was not considered appropriate.
12/18/18	The toxicology review was cleared by the Deputy Director	• The toxicology review was signed by the reviewers on 12/19/2018; this document had only minor edits from the original draft review submitted for clearance on 11/21/2018.
12/18/18	The Deputy Director sent a follow-up email and reiterated that reviewers should use the qualitative approach in SE applications	• The Deputy Director responded to the reviewers' clarifications of scientific points contested by reiterating that the qualitative approach should be used in SE applications; no supporting scientific data or references were provided (full email below): 12_18_18 email from DD.pdf
2/22/19	Memorandum on qualitative approach is sent out to DNCS staff	• Memorandum "*Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports*" is sent to DNCS staff for implementation.

Text that was added to review to include the rationale required by the Deputy Director for why a qualitative approach could not be used: Although the equivalence analysis conducted on analytical data may not necessarily be representative of the relative risk between the new and predicate products it allows for a screening level assessment to identify the presence of constituents in the new product that are of potential toxicological concern. In such cases, although not required for an SE report, a baseline risk assessment can be conducted to better characterize the potential relative human health risks from exposures to the new and predicate products. Based on basic risk assessment principles and available guidance it is recommended practice for evaluations to retain all constituents with valid analytical measurements when evaluating human health risk from chemical mixtures (EPA 1986; EPA 1989; EPA 2002; IGHRC 2009). Although the equivalence evaluation between the new and predicate products identified some HPHCs to be within the equivalence margins, all measured constituents contribute to tobacco related disease risk. For this reason, eliminating any of the HPHCs from the risk assessment could result in the loss of important information (EPA 2002) that is relevant to the evaluation of relative cancer risk and noncancer hazard between the new and predicate products. Considering all the information available for the new and predicate product in these SE reports, a qualitative approach could not be used by the toxicology reviewer to reach a conclusion of the relative cancer risk and noncancer hazard between the new and predicate product. A properly conducted QRA would be needed to adequately estimate the relative cancer risk and noncancer hazard between the new and predicate products.

References:

IGHRC 2009. Chemical Mixtures: A Framework for Assessing Risk to Human Health (CR14). Institute of Environment and Health, Cranfield University, UK.

U.S. Environmental Protection Agency (USEPA). 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures.

U.S. Environmental Protection Agency (USEPA). 1989. Risk Assessment Guidance for Superfund Volume 1 Human Health Evaluation Manual (Part A).

U.S. Environmental Protection Agency (USEPA). 2002. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites.

Appendix 5

OS Appeal Decision

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: [redacted]
Toxicology [redacted], CTP/OS/DNCS

[redacted]
Toxicology [redacted], CTP/OS/DNCS

[redacted]
Toxicology [redacted] CTP/OS/DNCS

From: [redacted]
Deputy Director of Regulatory Management, CTP/OS

cc: [redacted]
Director, CTP/OS

Subject: Concerns regarding DNCS's HPHC memo dated Feb. 21, 2019

Background

On February 21, 2019 the Deputy Director of Division of Nonclinical Science (DNCS), [redacted], issued a memorandum to staff titled "Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in the substantial equivalence reports". This memo documents a change in process for DNCS staff review of Substantial Equivalence (SE) reports, including criteria for determining when a new approach for evaluating HPHC comparisons is to be used by division staff. Dr. [redacted]'s transmittal email stated in part that "This memo is both consistent with the overall OS approach to streamlining SE review in light of increasing regulatory demands from PMTA and MRTPA review and with many of the ideas that we have discussed at several of our reviewer rounds meetings. This memo describes approaches that work in concert with Division of Product Science' (DPS) new TOST analysis and standardizes thinking that we have already applied to SE reviews signed over the past few months.... I am sure that many of you will recognize the discussions that we had at reviewer rounds in this memo. This meeting will continue to be the place where we discuss new and emerging directions in SE review."

The SE application review process requires comparison of a new and predicate product to determine whether the products have same or different characteristics, and if different whether those differences raise different questions of public health. This comparison involves comparing level and health impact of substances that FDA has identified as HPHCs. The DNCS memo implements a new approach wherein "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."

On May 31, 2019, Drs. [redacted] and [redacted] (you) submitted a memo describing concerns with this DNCS memo, including both with the substance of the memo and the process by which the memo was

[1] Dr. [redacted] subsequently resigned from the Agency to take a position in private industry.

developed. On the first point you claim the DNCS memo is a guidance that was not developed in accordance with FDA's Good Guidance Practices (GGPs). Secondly, you assert that that the new review process is not supported by the best available science.

You requested an in-person meeting to discuss the issues. I met with you on July 3, 2019 to hear your concerns; Dr. [redacted] was unable to attend. During that meeting, Drs. [redacted] and [redacted] explained that their primary concern is with the substance of the division's new process for review of HPHC comparisons. As reviewers, you indicated that do not believe you have any justification to not consider all data a company includes in their Quantitative Risk Assessment (QRA). You also expressed concerns with not following the new memo but were unsure how to seek resolution of your concerns. Because of this, you explained that you ultimately decided to raise a concern with the process of developing the memo (i.e. that it was not done in accordance with GGPs) as a mechanism to dispute within the supervisory chain the substance of the DNCS memo.

Discussion

I will address your two concerns in order.

1. The DNCS memo is not in accordance with Good Guidance Practices (GGP)

Your memo states that GGP should have been followed in the development and implementation of the February 21, 2019, DNCS memo. You state this is necessary to ensure it is "developed with appropriate review and public participation, accessible and transparent to the public, of high quality."

The February 21, 2019, memo was prepared to provide direction to individual reviewers within DNCS regarding a change in division process for review of HPHC data in SE Reports. Guidance documents do not include documents relating to internal FDA procedures or "other communications directed to individual persons or firms." 21 CFR 10.115(b)(3). Thus, GGPs are not applicable to internal memos such as the this. Given this, I find that DNCS management's process for developing and communicating this information to affected staff was appropriate and consistent with Office policy.

2. The DNCS memorandum is not supported by the best available science

You object to changing from the "standard QRA approach" to the new approach in the February 21, 2019, DNCS memo. You state that the QRA approach is systematic and transparent, has a long history of being used to evaluate the health effects of environmental hazards including tobacco smoke, and more recently was used by CTP/OS in various regulatory decisions including review of SE applications. You do not provide any information to support the apparent presumption that this QRA approach is the best or only acceptable method for a the very specific regulatory SE Report requirement to compare and evaluate the health impact of HPHC differences between a predicate and new tobacco product. You claim that the intended uses for which the QRA approach was developed by other Agencies "has no bearing on whether this approach is applicable and appropriate" for SE review, but do not provide adequate justification for this claim.

You further imply that as a prerequisite to adopting a different approach for evaluating HPHC comparisons in SE Reports, DNCS must first demonstrate the "Standard QRA approach" is "not scientifically appropriate" for the SE review process. You contend that the DNCS memo does not provide adequate rationale for not using the QRA approach in that it does not mention any new information or scientific data to explain the change in approach. You broadly dismiss the DNCS memo's explanation that the SE review program involves unique considerations derived from regulatory requirements (e.g., comparison of HPHCs between two products, a comparison based on a list of HPHCs established by the Agency) that do not apply to common uses of the QRA approach.

I find that these claims are not supported. The fact that the QRA approach has been successfully used for other scientific purposes and even in some prior SE application reviews does not mean it is necessarily the only

acceptable or the most appropriate method for use in review of SE reports. Also, it is not necessary for DNCS management to demonstrate the standard QRA approach is not scientifically appropriate prior to implementing a new, alternative review process.

You also assert that the "qualitative or semi-qualitative approach" specified in the DNCS memo is "not supported by the best available science and does not consider all data and information provided by an applicant." You state that it is accepted practice to include all constituents when evaluating human health risks from chemical mixtures, and that doing so for review of SE applications can "provide a more comprehensive hazard evaluation." Your viewpoint reflects a preference to perform the most comprehensive evaluation in all circumstances. Your viewpoint does not appear to reflect a consideration of how the data needed for regulatory review and comparison of the health risks between two tobacco products in an SE report is uniquely different than what is needed for a standard cumulative human health risk assessment of complex mixtures. This viewpoint also does not consider the Agency's need to manage programs and resources to best benefit our public health mission. Indeed, Agency leadership has a responsibility to manage regulatory programs that are based on sound science, the intent of the law, alternative approaches, and the efficient use of resources to effectively address regulatory issues and protect public health. It is proper for DNCS management to explore and determine whether a regulatory review decision can be adequately supported with less than the "comprehensive" data that is generally used for cumulative human health risk assessments of complex mixtures.

The DNCS memo and transmittal email discussed at length the reason for implementing a new approach for assessing HPHC differences within the SE review program, including:

- the SE regulatory review does not require comprehensive, cumulative risk assessment of each tobacco product (e.g., over 7000 compounds in tobacco smoke), but rather comparison of selected HPHCs between two products (the predicate and new tobacco product) to address a specific regulatory standard;
- that the Agency has identified 93 chemicals (out of over 7000) of interest that are linked to the five serious health effects most commonly linked to tobacco use;
- that as part of a new comprehensive approach to SE Report review, the Division of Product Science (DPS), not DNCS, is responsible for determining whether a difference in HPHC quantity between the two products is analytically non-equivalent

The DNCS memo appropriately considers these important differences and describes key considerations which informed the new approach:

> "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."

Information in your May 31, 2019 memo dwells on concern with not using the QRA, but <u>does not demonstrate the new approach is inappropriate for the intended use</u>. I find that DNCS management appropriately communicated to staff the rationale for the change in review process to address this unique regulatory evaluation of SE Reports. For example, the DNCS memo explains that "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", and provides sound rationale for deferring to DPS to evaluate analytical equivalence and focusing the toxicological comparison on HPHC differences that are analytically non-equivalent. Also, staff performing a qualitative risk assessment can consider available reference toxicity values as part of their evaluation. This is consistent with the FDA principle of using best-available science in data-driven decision making. This new robust

approach relies on a sound scientific foundation, leverages scientific expertise (e.g. evaluation of analytical equivalence by chemists), and improves review program efficiency.

Although not a consideration in my decision, I note that your memo sometimes misconstrued information in the DNCS memo. For example, your May 31, 2019 memo states on page 6 that "The statement [in DNCS memo] that 'the cumulative human health risk of complex mixtures evaluated by organizations such as the EPA and the ATSDR are not specific to tobacco products' is not accurate; …"[2]. By taking only a portion of the sentence and presenting it out of context, your memo misrepresents the DNCS memo's clear message that the cumulative human health risk of complex mixtures QRA evaluation by organizations such as the EPA and the ATSDR is not tailored to efficiently address the specific regulatory requirements for comparing HPHCs (on an established list) between two tobacco products.

Conclusions

Leadership should periodically assess regulatory programs to identify opportunities for improvements. For example, the type and amount of information needed by FDA can change over time based on new knowledge or understanding of regulated products and evaluation methods, or new review approaches. As part of smart regulation, FDA senior leaders regularly look for opportunities to streamline processes and policies to improve efficiency, conserve resources, and develop alternative approaches that utilize the minimum amount of information necessary to adequately address the issue and render regulatory decisions within appropriate timeframes. For example, directors in CDER explore opportunities to reduce the burden of traditional clinical trials while still meeting the statutory and regulatory requirements.

In this case, I find that DNCS management provided adequate justification for developing an alternative, less burdensome, approach for comparison of HPHCs between new and predicate tobacco products. The new (current) DNCS approach is based on sound science and is properly tailored to address the unique regulatory requirements for decisions within the SE program while minimizing the amount of information and resources needed. For example, the new process conserves resources by directing staff to not review fatally flawed QRAs and provides staff with an important list of considerations when performing a qualitative risk evaluation.

In conclusion, I uphold DNCS' February 21, 2019, memo. It is a well-considered and appropriate management directive that DNCS staff are expected to follow. GGPs are not applicable to this internal memo. The qualitative process and underlying assumptions described in the DNCS memo are appropriate to protect the public health, conserve agency resources, and support sound and timely regulatory decisions. This approach will position DNCS to more efficiently review an expected increasing number of product applications in order to better protect public health and meet FDA performance goals.

[2] The quote in your memo is not verbatim from the DNCS memo. The statement in the DNCS memo is "While the cumulative human health risk of complex mixtures has been evaluated by organizations such as the EPA and the ATSDR, 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."

Appendix 6

OS Management Response

Scientific Dispute Case

OS Response to the Scientific Panel Report

Responses to the Report Recommendations

Below is a list of the six recommendations from the panel followed by OS's responses:

1. The qualitative or semi-quantitative approach in the above [redacted] memo lacks sufficient detail and guidance to be enacted as a scientific methodology in its current form.

   OS response: It is important to acknowledge that the approach captured in the memo is a *regulatory* scientific approach. From a purely scientific approach, I agree that a fully quantitative approach to evaluate HPHC differences between new and predicate products is ideal. However, as regulatory scientists, OS staff must consider practicality and public health impact of our decisions in context of a rigorous scientific standard. For the first eight years of the SE program, OS relied on a fully quantitative approach. However, over that time span, OS staff came to recognize the fully quantitative approach was unnecessarily burdensome to FDA and applicants and didn't impact public health in a meaningful way. Therefore, as the SE program evolved, OS staff gained a better understanding of HPHC data in SE Reports and recognized that the tiered approach in the memo allows a decision that aligns with our public health goal. FDA and other regulatory organizations (e.g., EPA) often use tiered approaches to scientifically evaluate products. Therefore, I believe the approach in the memo is scientifically sound.

2. Establish a well-defined workflow and review process for assessments that address the specific questions to be answered about the chemical or compound under review.

   OS response: Although not captured in the memo, OS already has a well-defined workflow and review process. The intention of the memo was to capture the change in our approach to evaluating HPHC data in SE Reports. However, there are other documents that guide OS staff in evaluating SE Reports. The overall review process has evolved since the SE program began as OS staff have gained more experience and knowledge. As OS staff continue to better understand tobacco products, the review process will continue to evolve, including improved understanding of whether HPHC differences raise different questions of public health.

3. Develop and communicate standardized and objective criteria for deciding when a quantitative risk assessment should be conducted in a collaborative manner that includes CTP management and reviewers.

   OS response: The memo does standardize the approach to assessing HPHC differences between new and predicate products. And, the criteria in the memo are as objectives as possible based on our current experiences. As we gain even more experience, we will likely be able to make the criteria even more objective than currently captured in the memo. Furthermore, the approach outlined in the memo was developed based on discussion by many OS toxicologists as well as OS leadership. The process to develop the memo and the degree of objectiveness of the criteria in the memo is consistent with FDA regulatory programs. It is typical that, for a given regulatory science issue, FDA begins with a less objective approach and evolves into a more objective approach based on gained knowledge and experience.

4. Establish a review process that monitors the quality of the decisions that result from the above workflow, and allows for continuous improvement and correction of the workflow.

   OS response: There is already a process in place to do this. In fact, it is that process which led to development of the approach in the memo. Every SE order undergoes quality control by OS staff and sometimes legal staff outside OS (i.e., OCC). In addition to evaluating each SE order, OS staff routinely look across our premarket application review programs to determine how we can improve our review process and decision-making. It was during those discussions that it became clear that OS staff were spending a lot of time doing fully quantitative assessments of HPHC data when it was obvious that the differences were not a public health concern. The SE program has evolved significantly since its start as result of this iterative evaluation of the program.

5. Establish a defined process for reviewer agreement, including evaluating decision concordance. Also, have a process for resolving discrepancies.

   OS response: OS has had a defined process for reviewer agreement for nearly as long as the SE program has existed. The process in OS aligns with the process used across FDA. Every OS staff member on a given SE review team is expected to document their conclusions from evaluating SE Reports. And, if anyone in leadership on the review team disagrees with a primary reviewer or someone at a lower level of leadership, then that lead documents their disagreement with the conclusion. For example, if the toxicology reviewer and branch conclude that HPHC differences raise public health concerns, they would finalize their

review as such. Then, if the TPL (Technical Project Lead) believes that the HPHC data doesn't raise public health concerns, they would draft a memo to document their conclusion and why they disagree with the toxicology reviewer and branch chief. There is also the FDA scientific dispute resolution process that can be employed by OS staff if an issue can't be resolved within OS.

6. Establish processes for regular training and information sharing among reviewers and management to facilitate standardized approaches and decision making.

   OS response: These processes already exist. OS has a lot of written materials regarding the SE program. This material is distributed to staff and is written based on the specific role that a given staff member fills. For example, there are specific training materials and policy memos for toxicology reviewers and different materials for chemistry reviewers. In addition, OS just launched its first office-wide SE training program over the summer.

<u>Additional Information for Consideration</u>

7. Are there relevant materials or information that the expert panel may not have been aware of, that should be considered?

   OS response: There are volumes of materials relevant to SE review that the expert panel was not aware of. In addition, every week, there are various meetings to discuss the SE program and improvements that can be made. The meetings involve all OS staff involved in SE review.

8. Has OS already implemented any policies or procedures that address recommendations made by the expert panel?

   OS response: As mentioned above, OS launched its first office-wide SE training program over the summer in an effort to improve consistency in decision making across OS.

9. What is the role of OS's experience with previous SE reviews in shaping how OS currently evaluates HPHCs?

   OS response: As discussed above, OS has nearly a decade of experience evaluating SE Reports and continually assesses how we evaluate the applications. Over that time, there has been extensive discussion about HPHC data within OS as well as outside OS (i.e., OCC and OCD). It is our experience spending many hours conducting a fully quantitative assessment of HPHC data even though we knew before the assessment that the HPHC data was not a public health concern.

10. Do you have any high-level recommendations with respect to how CTP should address the panel's recommendations both in the short- and long-term?

    OS response: I believe that the OS-wide training was an important step. The training is video-recorder so that staff can go back and re-watch it if necessary. In addition, it can be used by new staff that come onboard. I would also like FDA experts on the scientific dispute resolution process make a presentation to all OS staff in upcoming months.

Appendix 7

CTP Addendum

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

Date: October 13, 2020

To: [redacted], Supervisory Regulatory Counsel, FDA, Office of the Chief Scientist, Office of Scientific Integrity

From: Mitchell Zeller, Director, FDA, Center for Tobacco Products

Re: Addendum to CTP Response to Allegations in Whistleblower Complaint (OSC File No. DI-20-0372)

Background

This addendum to the review by the Office of the Center Director (OCD), Center for Tobacco Products (CTP), FDA, responding to certain whistleblower allegations described in a letter from the Office of the Special Counsel dated February 28, 2020 (OSC File No. DI-20-0372) supplements my September 29, 2020 memo to you on this matter.

The purpose of this addendum is to provide additional information to explain how the evolution of the toxicology risk assessment to a qualitative or semi-quantitative approach remains protective of public health.

In general, the substantial equivalence (SE) review of a new tobacco product compares it to a "predicate" product (i.e., per statute one that was on the market as of or on February 15, 2007). This comparison ordinarily includes a scientific review by several disciplines, including engineering, toxicology, chemistry, and behavioral pharmacology to determine if the differences between the two products raise different questions of public health.

The toxicology review portion of SE review is an important component because it helps determine if the new tobacco product presents more or less health risk than a predicate product. To do this, CTP toxicologists compare the ingredients of each product and consider the relevant toxicant exposures to users and non-users of the products. CTP has established a list of 93 harmful and potentially harmful constituents (HPHCs) to health that are contained in tobacco products and are linked to serious health effects such as cancer and cardiovascular disease. CTP's review and comparison of HPHCs of the two products during SE review is critical in determining the difference in health risk.

The issue under discussion is how CTP toxicologists evaluate differences in HPHCs between two tobacco products during SE review. Initially, CTP toxicologists completed their review of HPHCs by using a quantitative approach, that is, by reviewing quantitative risk assessments

(QRA) submitted by applications that attempted to calculate the risk based on comparing toxicant levels between the two products, the dosage and route of exposure, and estimated toxicological impact. It is OS practice to review the entire content of each application, even when the content provided does not bear on the questions of import to an SE determination. Over time, with experience completing thousands of SE reviews and with input from staff, CTP's Office of Science (OS) updated the process on how to evaluate HPHC comparisons between two tobacco products.

In February 2019, OS management provided a memo to staff explaining that "[a]pplication 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." Under the new approach, reviewers may not need to evaluate the QRA, if provided by the applicant, in certain circumstances. To illustrate how the qualitative or semi-quantitative risk assessment protects public health, we provide examples below.

> Example 1: An SE evaluation of two cigarettes. The new product has an analytically non-equivalent decrease in formaldehyde and lead when compared to the predicate product. All other HPHCs were analytically equivalent in the new and predicate product. In this case, the memo instructs the reviewer to not evaluate the QRA because all the changes effectively reduce the risk of the new tobacco product.
>
> Example 2: An SE evaluation of two cigarettes. The new product data indicates an analytically non-equivalent increase in formaldehyde and lead with all other HPHCs being analytically equivalent between the new and predicate products. The memo states that there is no way that a QRA could succeed in establishing that the cancer risk or non-cancer hazard due to the HPHC changes is equivalent between the two compared products. Therefore, evaluation of the QRA is not necessary.
>
> Example 3: An SE evaluation of two cigarettes. The new product is reported to have an analytically non-equivalent increase in formaldehyde and a decrease in acrolein, total TSNA, and lead and cadmium. The memo indicates that the toxicologist should evaluate the potential for off-setting risks. In this case, the formaldehyde is a respiratory irritant and a carcinogen. The increase in formaldehyde is compared to the decrease in TSNAs and to the decrease in acrolein. If the decreases off-set the increase, then there is no need to evaluate the QRA.
>
> Example 4: An SE evaluation of two cigarettes. The new product is reported to have an analytically non-equivalent increase in formaldehyde and acrolein and a decrease in total TSNA. In this case, there appears to be a greater likelihood of an increase in risk

associated with a change. The memo indicates that in this case the toxicologist should evaluate the QRA if one has been submitted.

Follow-up Questions from the Office of the Commissioner

Here are our responses to the follow-up questions provided by the Office of the Commissioner.

Q: The HPHC memo acknowledges that, after application of the qualitative or semi-quantitative risk assessment, there are circumstances in which the a full QRA will be appropriate. Is a full QRA always appropriate if applying the qualitative or semi-quantitative risk assessment is inconclusive? If so, how are reviewers expected to determine inconclusiveness? Does inconclusiveness turn exclusively on whether the qualitative or semi-quantitative risk assessment demonstrates that substantial equivalence is a close call in the reviewer's judgment?

A: CTP strives to have as much clarity and transparency in the product review process as possible, however, in all cases, toxicology reviews are based on the reviewers' judgment. This judgment is informed by training, experience, and collaboration with other subject matter experts. Even with the full QRA, toxicology reviewers still need to use their judgment in assessing the quality of the QRA and the outcomes. To date, CTP has not received any QRAs that would be considered complete and accurate. The QRA provides additional information to the reviewer if the reviewer feels the qualitative or semi-quantitative approach has not been conclusive, but the QRA does not provide a definitive answer.

OS has instituted a system to help ensure the SE reviews are consistent, accurate, and comprehensive. This involves the review of each analysis by, at a minimum, the reviewer's Team Lead, the Branch Chief, and a member of OS's senior management. This process ensures that the toxicology reviews, as well as the other scientific discipline reviews, are not subject to one reviewer's judgment. There are also regular meetings of the toxicology reviewers to discuss issues that have arisen during reviews to ensure consistency across reviews.

Q: Is there a way of weighing or tiering the HPHCs in a manner consistent with the more qualitative approach that would enable a toxicologist to determine whether a full QRA is necessary when there are some increases and some decreases in analytically non-equivalent HPHCs? (In other words, are there certain HPHCs that CTP views as far more problematic than others, e.g. Formaldehyde?) If not, is it possible to provide additional criteria that would assist a toxicological reviewer in determining whether a full QRA is necessary beyond what is already in the HPHC memo? For example, is there a way to further explain how non-analytically equivalent HPHCs are offset in terms of carcinogenicity, toxicity, and organ affected or how they might be grouped for such a purpose?

A: For SE reviews, toxicants identified as harmful or potentially harmful constituents (HPHCs) are categorized based on the outcome as either carcinogenic or non-carcinogenic. Within these categories, CTP does not see a scientific basis to rank toxicants as more or less "problematic." CTP does not group the toxicants based on the end organ effected because toxicants can impact more than one organ.

Q: Do you have any concern regarding the cumulative effect of the differences in analytically equivalent HPHCs when the value amounts are based on averages involving multiple smoke tests?

A: No. Because tobacco products are agricultural products, there can be natural variability within a specific product (for example, twenty cigarettes in a single pack can vary in toxicant levels). Increasing the number of measurements, and using the average value, is the best way to account for this variability in individual products.

Q: Are there any additional materials provided to reviewers through training or otherwise that: (a) provide additional instruction with respect to how to apply the qualitative or semi-quantitative risk assessment or (b) shed light on how that assessment in combination with other disciplines and analysis adequately identifies products that raise different questions of public health?

A: OS has established training on the qualitative or semi-quantitative approach for reviewers that is intended to provide clarity on the use of the qualitative or semi-quantitative approach, including when the approach is not sufficient and reviewers need to consider the QRA in their determination. OS provides this training on an ongoing basis, including when new staff are brought on board and when questions regarding the topic arise. Team Leads have also been trained so that they in turn can provide additional training to their team members, as needed.

As described above, toxicology is one review discipline that is a part of the SE premarket review process. The toxicology reviewers decide on whether or not there are different questions of public health from a toxicological point of view. Every SE application has a Technical Project Lead (TPL), who is the OS staff member who looks at the outcomes of all of the scientific discipline reviews and determines whether the new product raises different questions of public health.

Appendix 8

SDR-SMG

SMG 9010.1

FDA STAFF MANUAL GUIDES, VOLUME IV - AGENCY PROGRAM DIRECTIVES

GENERAL OR MULTIDISCIPLINE

DISPUTE RESOLUTION

SCIENTIFIC DISPUTE RESOLUTION AT FDA

Effective Date: 01/13/2009
Changed: 06/19/2019

1. PURPOSE

As part of the ongoing effort to improve the process of internal scientific dispute resolution, and to encourage open communication throughout the agency, this document describes how issues of scientific dispute are managed throughout FDA.

This document sets forth mandatory elements to be included in all scientific dispute resolution processes at the Centers, Office of Regulatory Affairs (ORA) and Office of the Commissioner (OC). In addition, the document provides recommendations for "best practice" activities related to scientific dispute resolution that are either ongoing in Centers, ORA, OC, other agencies or other outside organizations, or that have been suggested by focus groups with FDA employees.

This document also establishes an agency-wide appeals process for internal scientific disputes. Scientific disputes should be resolved whenever possible at the working level within the organization, and after full and frank discussion involving interested parties. When that is not possible, the process contained in this document provides all FDA staff an avenue to further pursue significant scientific disputes that they feel has not been adequately addressed within their Center, ORA or OC.

2. BACKGROUND

The September 2007 Values and Vision all hands broadcast communicated the organizational values that are important to the agency and set the course for the future with a three-part plan to develop leadership, improve processes and enhance resources for a science-led agency, and empower employees through effective communication. In addition, six Agency core values were unveiled: integrity, excellence, accountability, equity, diversity and transparency. The Commissioner, Dr. Andrew von Eschenbach, highlighted the importance to a scientific agency of encouraging and valuing presentation and discussion of differences of opinion. In that spirit, the process of addressing internal differing scientific opinions at FDA is being strengthened.

3. SCOPE AND POLICY

This Staff Manual Guide (SMG) is issued under the following guiding principles:

- FDA encourages the resolution of scientific disputes at the working level in the organization, starting with frontline employees and their immediate supervisors or team leaders.

- The agency's appeals process for scientific disputes is not a replacement for robust and fair Center-level processes.

It is the Agency's policy that all staff should be aware of the paths available to them in case of issues of scientific dispute, that all staff, including initiators of disputes, are treated with openness and respect, and that the agency procedures should not be unnecessarily burdensome.

The FDA Scientific Dispute Resolution (SDR) program is intended to address serious scientific disputes concerning issues that could have a significant impact on public health. They are NOT intended to address issues related to personnel and work environment situations; these types of disputes already have processes in place for their resolution, as do other types of non-scientific disputes.

Every effort will be made to provide FDA staff with an opportunity to resolve scientific disputes internally. The agency-wide program for SDR has two components: agency requirements for the adoption of robust SDR processes at the Centers, ORA and OC (hereafter "Centers"), and an agency-wide process review. Through these processes, the agency will assure that all valid scientific disputes can and, if needed, will receive a full and fair hearing. (see Section Heading 5, sub heading E, for a description of the scope of the review that occurs at the Agency level).

Section 6.1 of this document details FDA's requirements for the minimum standards for scientific dispute resolution processes in the Centers. The Center SDR

requirements serve two purposes. First, robust Center processes foster the principle of resolution at the working levels within the organization. Second, the agency requires that a Center Director will provide a written decision on a case before the Commissioner will address it. These requirements ensure that disputes will be eligible for the agency's appeals process.

Section 6.2 of the document provides a collection of "best practice" SDR activities. The recommendations are not mandatory, but do reflect some of the best ideas for what thoughtful and effective Center SDR processes could include, and may be adopted by Centers as applicable to their own needs.

Section 6.3 of the document describes an appeals process for scientific disputes that are not resolved to the satisfaction of all involved at the Center level. The appeals process provides an avenue to internally resolve disputes by submitting a case for review to the Office of Accountability and Integrity and receiving a final decision from the Commissioner regarding the Centers' compliance with its procedures.

It is the responsibility of all those involved to ensure that all initiators of disputes are protected from any retaliation by their supervisors, peers, leadership and others, related to initiating or engaging in this process. This Staff Manual Guide does not supersede the fundamental protections pursuant to the Whistleblower Protection Act of 1989, the Federal Employee Anti-discrimination and Retaliation (No FEAR) Act of 2002 and all applicable federal laws, regulations and Executive Orders that afford protection under the law.

4. DEFINITIONS

A. Agency Scientific Dispute Process Review Board: The Agency Scientific Dispute Process Review Board (hereafter Board) is a standing committee comprised of representatives of the Office of Accountability and Integrity, Ombudsmen from all Centers and the agency (or officials so designated) and representative(s) from the Office of the Chief Scientist. The Board is chaired by the Chief Scientist. At the discretion of the Chair, additional members may be assigned to the Board on a case by case basis. The Board will assess whether Center processes were followed.

B. Initiator: In the Agency dispute process, the initiator is the party that believes that a significant scientific issue has not been adequately addressed by Center dispute resolution processes. The initiator may be an individual, group, or organizational unit (division, office, etc.). Because scientific disputes at the agency might span more than one Center, initiators need not come from the same Center where the decision was made.

C. Scientific Dispute: Disputes addressed through this process must be scientific in nature. Eligible disputes may, for example, involve the interpretation of science and decisions taken upon that interpretation. The following disputes are NOT

considered to be scientific disputes and would not be eligible for this process: personnel disputes such as EEO disputes, administrative disputes, labor and employment disputes, enforcement policy disputes and disputes related to the rule-making process.

5. RESPONSIBILITIES

A. Initiator of SDR process: The initiator is responsible for submitting the initial documents needed for entry into the SDR appeals process to the Office of Accountability and Integrity (see Section 6.3.C.1 for requirements for complete submission). As soon as it is apparent that Center-level dispute resolution procedures have not resolved the dispute, the initiator should consider the potential public health impact and promptly file a formal SDR request, if appropriate. In addition, the initiator is responsible for fully cooperating with the formal SDR process; this participation may include presenting his or her case to the agency SDR committee(s), providing other documentation as necessary to the case review, and being interviewed by the committees.

B. Center and agency Ombudsman, or designated official from the Office of the Director: Ombudsmen at the Centers and agency, or officials so designated, are responsible for being sufficiently familiar with the formal SDR process to effectively counsel potential initiators who approach their offices. At any point in the dispute process, these officials may be approached by the initiator, or any other persons involved in the dispute for consultation. Ombudsmen from the Centers and Agency will serve on the Agency Scientific Dispute Process Review Board. However, the Ombudsman of the involved Center will only participate in presenting the case and the Center's procedures to the Board, but will recuse him/her self from the Board's deliberations.

C. Center leadership: Leaders at each Center are responsible for designing a new, or modifying an existing, SDR process for their organization, such that it incorporates all aspects as required by this SMG. Center leaders are also responsible for instituting SDR processes that reflect the guiding principles of openness and resolution of scientific disputes at the lowest organizational level possible. Finally, Center leaders are responsible for communicating the SDR process and training all Center staff on the informal and formal procedures available to resolve scientific dispute internally.

D. Center Directors: For each scientific issue under dispute, Center Directors are responsible for ensuring that the SDR process in their organization is documented, communicated, implemented, and conforms to the standards required by the agency (see 21 CFR 10.70 and Section 6.1). This responsibility includes maintaining and providing a complete administrative record of the SDR process that was followed for each dispute. They are also responsible for rendering written decisions on disputes that have advanced to them through the scientific dispute resolution processes in their individual organizations. Center Directors are

also responsible for cooperating with the agency's appeals process through interviews, information requests, and presentations to the agency SDR committees, as necessary. Finally, the Center Director is responsible for working closely with the agency SDR committee, the Chief Scientist and the Commissioner throughout an appeal, and carrying out any corrective actions that the Commissioner requires.

E. Agency Scientific Dispute Process Review Board: Responsible for conducting full and fair evaluations of the disputes to assess whether the Center's processes were followed, whether the Center considered all relevant evidence bearing on the scientific question at issue, and whether the initiator was provided an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director.

Specific responsibilities of the Board include the following:

- Collecting all information needed to fairly and objectively review a case
- Consulting all expert opinions that are relevant to the review of each case
- Documenting the findings and rationale behind any recommendations it makes
- Communicating the findings and recommendations to the Commissioner

The Board is also responsible for notifying the Center Director when a decision at their Center is being appealed. In every dispute, members of the Board from Center(s) where disputes arise will recuse themselves from the dispute review process.

F. Chief Scientist (CS): The Chief Scientist will chair the Agency Scientific Dispute Process Review Board. The CS will make recommendations to the Commissioner about whether a Center failed to follow its processes and/or did not provide an adequate opportunity to the initiator to express his or her concerns; that all relevant evidence bearing on the scientific question at issue has been considered; and, whether the dispute should be remanded to the Center Director.

G. FDA Commissioner: When Center decisions are appealed, the FDA Commissioner will be responsible for rendering a final decision on whether a Center followed its processes, whether the Center provided an adequate opportunity to the initiator to express his or her concerns; whether all relevant evidence bearing on the scientific question at issue has been considered; and whether the dispute should be remanded to the Center Director for corrective action. The Commissioner will work with the Center Director to determine what corrective actions must be taken, if any.

6. PROCEDURES

6.1 REQUIREMENTS FOR SDR PROCESSES AT THE CENTERS

Center management shall create an atmosphere in which consultation and open discussion on controversial issues are encouraged. When disagreements occur, it is necessary to follow appropriate procedures for resolving them. Informal methods, using good management practices for resolving conflict, should be employed prior to instituting the more formal procedures described here. Notwithstanding informal good management practices used to try to resolve the conflict, timely written reviews of the scientific matter in dispute should be completed by all members of a review group, including initiator and supervisors, to enable as open and complete a discussion of the issues as possible at the working level of the organization. If informal attempts fail, requirements for the formal procedures for resolving disagreements at each Center are described below.

A. Requirements for Inclusion in the Formal Scientific Dispute Resolution Process at Each Center

The following requirements should be considered mandatory process inclusions, and must be incorporated into Center activities within Fiscal Year 2008:

1. Required elements of each Center's Standard Operating Procedure (SOP)

    a. Each Center is required to have an SDR SOP

    b. If a dispute is not resolved before reaching a Center Director, the Director must render a written opinion on the matter, as this step is a central criterion for advancement to the agency-level appeals process.

    c. While the scientific dispute resolution process is pending, work on the application and a final regulatory decision will continue unless the Center Director decides that:

        (1) The appeal raises substantial questions involving a significant risk to the public health, and

        (2) Postponing the decision would not result in a negative impact on the public health.

        Further, center personnel are not expected to postpone regulatory decisions on INDs, IDEs, Food Contact Substance Notices, etc.

d. Timeframe for rendering a written opinion must be included, and should be developed by each Center consistent with regulatory/statutory timeframes.

e. Each SOP must make reference to the agency-level process as the appeals process for a dispute, should the Center-level dispute resolution process be exhausted.

f. Timeframes for elevating a dispute to the agency scientific dispute appeals process must be included in the Center SOP.

g. Each SOP should include a process by which disputes of sufficient immediacy and scale of impact to public health are able to 'opt-up' to the Center Director in order that he or she can make a decision on the matter within a condensed timeframe.

h. SOPs must include certain key messages for SDR

(1) SOPs will encourage dispute resolution at the lowest organizational level possible.

(2) SOPs will encourage open communication throughout the organization.

(3) SOPs will clearly state that initiators will be protected from any repercussion or retaliation by supervisors, Center leadership, and peers.

i. Each SOP will make clear the roles and responsibilities of Center staff in the SDR process, including that of the Ombudsman, where one exists.

2. Required communication in each Center's SDR process

a. Center leadership is responsible for developing and disseminating clear written procedures for internal scientific dispute processes, including the timeline for rendering a written opinion. Center leadership is also responsible for communicating SDR responsibilities to all levels of staff on an annual basis.

b. FDA's Administrative Practices and Procedures Regulations provides that all FDA employees responsible for handling a matter are also responsible for insuring the completeness of the administrative file (see 21 CFR 10.70).

c. In addition to documentation required by 21 CFR 10.70, decisions related to the formal SDR process and their supporting rationale will be documented.

d. At all Centers, decisions related to the formal SDR process and their supporting rationale will be communicated to appropriate parties.

6.2 RECOMMENDATIONS FOR SDR PROCESSES AT THE CENTERS

The following recommendations are offered as FDA's perspective on "best practice" SDR activities. While these recommendations are not considered mandatory, they do reflect some of the best ideas for what a thoughtful and effective Center SDR process could include, and can be adopted by Centers as applicable to their own needs.

A. Best Practices for Formal Scientific Dispute Resolution Processes at the Centers

1. Recommended communication in each Center's SDR process

   a. Centers could employ various mechanisms to disseminate their SOPs

      (1) Mechanisms for dissemination could include, but are not limited to, one or more of the following: e-mail, orientation for new staff, workshops, hard copy distribution, online training programs, and an interactive SDR website, interactive SDR slide presentation.

      (2) Centers may decide to regularly reinforce the importance of SDR via Center retreats or other annualized training programs

   b. Center SOPs should require that only written documentation of a dispute will trigger a formal dispute resolution process. This step would ensure that the necessary historical record of the dispute is available should it advance to the agency-level appeals process.

   c. Centers may require each side of the scientific issue under dispute to present their case in writing to enable transparent review at successive steps of the process. It is also considered best practice to document all decisions made at successive levels in the dispute process.

      Additionally, in-person meetings with the initiator of the dispute to communicate final decision(s) and rationale may be adopted by Centers as they see fit.

2. Recommended role of the Center Ombudsman, or designated official in the Office of the Director, in the Center's SDR process.

The Center Ombudsman could informally communicate with initiators throughout the SDR process to increase the initiators' comfort with it.

3. Training and mentorship as tools to encourage open communication and the resolution of scientific disputes

    a. Because supervisors and scientists are often the first level where scientific disputes arise, they may be trained on good management practices, including how to resolve disputes.

        (1) Centers may institute training programs for all staff on the SDR process and good dispute resolution practices in general.

        (2) Centers may implement procedures to evaluate supervisors on their management skills and ability to resolve scientific disputes.

        (3) Centers may enable a "feedback loop" through Center Ombudsmen to counsel individuals (e.g., supervisors or working-level staff) who are frequently involved in formal scientific disputes.

    b. Mentorship and training programs to encourage open communication

        (1) Scientists may be paired with non-supervisory mentors.

        (2) Institute training to produce team norms, process of managing conflict in teams, team charters, etc. for review teams and other groups.

4. Monitoring use of the SDR process

    Centers may include questions on annual staff surveys to gauge awareness of and satisfaction with SDR process.

5. Possible formal avenues for scientific dispute resolution apart from chain-of-command mechanisms

    a. Utilize external experts to seek objective perspective, additional scientific expertise, and practical knowledge. Examples of these are experts from other Centers, ORA and OC, other agencies, and SGEs, who can be used for written consultation.

    b. Make several avenues available to address scientific issues: regulatory briefings, advisory committees, internal discussions with Center Directors, standing subject matter committees, and multi-disciplinary teams.

B. Best Practices for Informal Scientific Dispute and Communication

Every effort should be made to informally resolve differences in opinion on scientific matters. There are a variety of methods that Centers and other organizations already employ to foster informal dispute resolution, and still more that were suggested by internal focus groups.

A non-exhaustive list of informal resolution mechanisms includes the following:

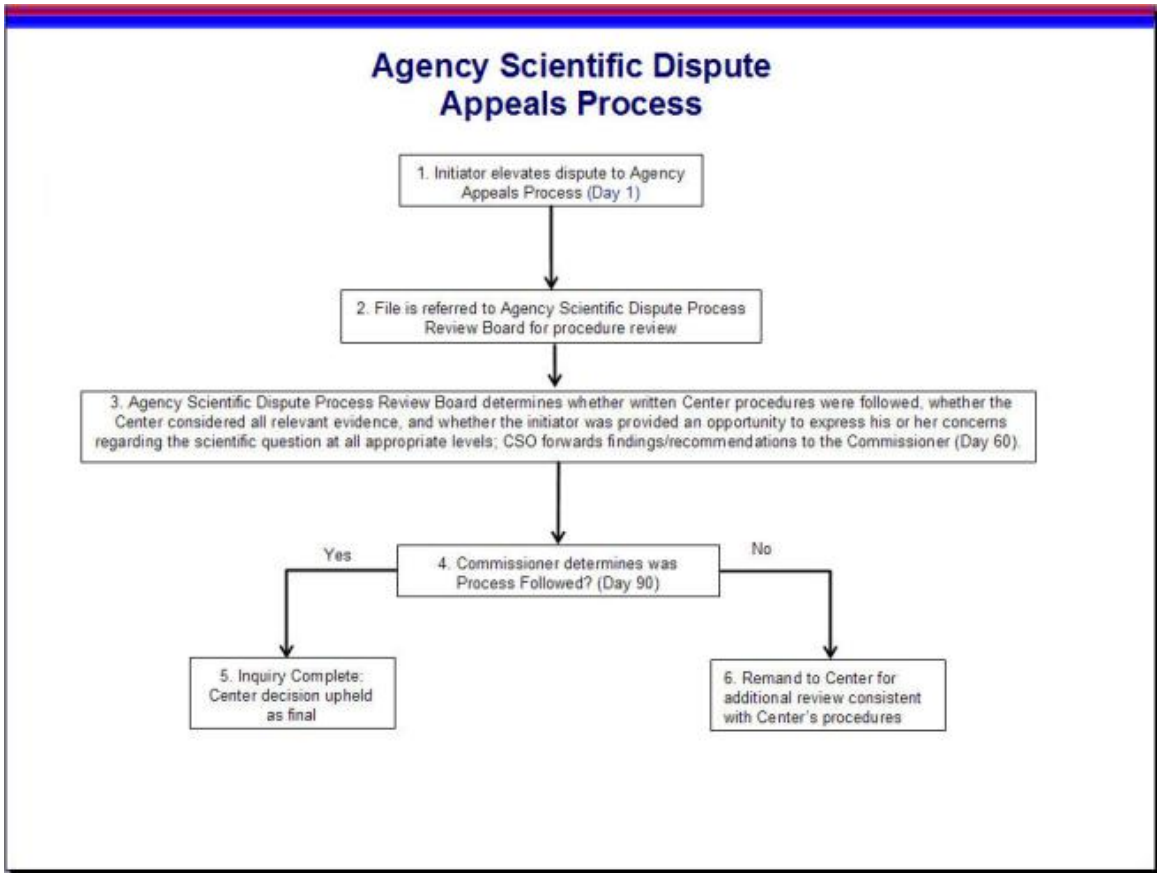
1. Institute informal peer review and / or round table discussions. One method could be to institute formalized weekly meetings to informally discuss "hot topics," or issues of potential dispute.

2. Use Center Ombudsman (if applicable) for informal perspective and to help filter personnel-related issues.

3. Increase two-way communication within the review process. For example, Centers could choose to have employees meet regularly with their supervisors as a review team to discuss on-going reviews, substantive problems and their recommendations.

6.3 DESCRIPTION OF THE AGENCY'S APPEALS PROCESS FOR SCIENTIFIC DISPUTES

If an initiator is not satisfied after engaging in the scientific dispute resolution process at the Center, this appeals process provides an additional avenue to resolve disputes internally. All scientific disputes under appeal will be reviewed by the Agency Scientific Dispute Process Preview Board, and the Commissioner will make a final decision about the issue under dispute.



A. Description of appeals process for scientific disputes

1. Elevation of disputes to the appeals process marks entry of internal scientific disputes into the formalized agency SDR appeals process. Disputes can advance from the individual Center-level SDR processes into the appeals process if the initiator feels that the dispute has not adequately been addressed / resolved at that level. The initiator must elevate the scientific dispute issue to the agency appeals process within 10 days of receiving the written opinion rendered by the Center.

   At this step, the initiator must submit the case, in writing, to the Office of Scientific Integrity (OSI). Receipt of case by OSI will be mark the first day of the agency scientific dispute appeals process. The submission will include:

   - Description of how the initiator's position differs from Center's perspective

   - Assessment of possible impact to public health should initiator's position not be adopted

- Detailed description of the history of the dispute, including initiator's description of the Center SDR procedures followed and/or not followed, dates of meetings, and decisions rendered throughout the process

- Action, decision or remedy sought

2. The Agency Scientific Dispute Process Review Board will review the initiator's file, and obtain any other information necessary, to evaluate whether it meets the criteria for review. Other necessary information may include written documentation from the Center. They will assess the information and conclude whether the case meets the following criteria:

   - At a minimum, the dispute must be scientific in nature. The Board will not evaluate disputes that are not based on science.

   - The Center Director must have rendered a decision on the scientific issue under dispute.

   The Board will notify the Center Director that a scientific dispute has been submitted for appeal.

3. The Board will gather all necessary additional information that will enable a fully-informed recommendation on the case. The Board will obtain the full administrative record of the Center's processes for the dispute and review the Center's published SOP(s). As needed, the Board will conduct interviews with all relevant parties in the dispute, which may include the initiator, team leader, Center Director, and others. They will review the information to determine whether written Center processes were followed

   The goal of this review is to determine if the processes followed in the Center fully considered all relevant evidence and provided the initiator with an opportunity to express his or her concerns at all appropriate levels, prior to and including the Center Director. The Board will document findings and recommendations and the Chief Scientist will present his or her recommendations to the Commissioner. Representatives of the involved Center will not participate in this review.

   The Board should complete its review by the sixtieth (60) calendar day in the agency SDR appeals process.

4. If the Agency Scientific Dispute Process Review Board determines that the Center's processes and procedures were followed appropriately, that the Center fully considered all relevant evidence and the initiator was provided an opportunity to express his or her concerns regarding the scientific question bearing on the dispute, the Center's decision will be

upheld as final and a written recommendation will be distributed to all internal parties involved in the dispute. The Board findings will be forwarded to the Commissioner and the agency SDR process will be concluded.

5. If the Agency Scientific Dispute Process Review Board finds that the Center's processes and procedures were not followed appropriately, that the Center did not fully consider all relevant evidence and/or the initiator was not provided an opportunity to express his or her concerns regarding the scientific question bearing on the dispute, the Chief Scientist will provide a written recommendation to the Commissioner that the case be returned to the Center for additional review consistent with the Center's procedures. This memo will consist of the Board's rationale for the recommendation, all minority opinions from panelists, and a proposed statement to be used to communicate the Commissioner's decision.

6. The Commissioner will review the Board's recommendation and render a final decision on whether a Center followed its processes, whether the Center provided an adequate opportunity to the initiator to express his or her concerns, and whether the dispute should be remanded to the Center Director for corrective action. The Commissioner will work with the Center Director to determine what corrective actions must be taken, if any.

   The Commissioner will communicate this decision, and a short rationale for the decision, in writing to each side of the dispute.

   The final decision will be rendered by the Commissioner, by the ninetieth (90) calendar day of the agency SDR appeals process.

B. Anticipated timing of the scientific dispute resolution appeals process

1. From the time that the initiator submits a dispute to the Office of Accountability and Integrity for review, the SDR appeals process will be completed within 90 calendar days.

2. At the discretion of the Commissioner, the process may be accelerated because of statutory or regulatory timelines or urgency of agency decision.

C. Documentation requirements throughout the SDR appeals process

1. Documentation required for entry to the process

   The initiator's written case must include the following elements:

   (1) Description of how the initiator's position differs from Center's perspective

(2) Assessment of possible impact to public health should initiator's position not be adopted

(3) Detailed description of history of the dispute, including initiator's description of the Center SDR procedures followed and/or not followed, dates of meetings, and decisions rendered throughout the process

(4) Action, decision or remedy sought

7. EFFECTIVE DATE

The effective date of this guide is January 13, 2009.

8. Document History -- SMG 9010.1, Scientific Dispute Resolution at FDA

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	01/12/2009	N/a	OC/OP/OAI , HF-22	Susan C. Winckler, FDA Chief of Staff
Change	06/19/2019	Sect. 6.3.A.1 change OAI to OSI	OC/OCS/ OSI	Matthew Warren, Director, OC/OCS/OSI

Back to Agency Program Directives, Volume IV (4000-9100)

Appendix 9

SDR-ToPP

ToPP: Internal Scientific Dispute Resolution (SDR) in Regulatory Decision Making

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A. Purpose

The process of internal scientific dispute resolution (SDR) at the Food and Drug Administration (FDA) is a two-tiered approach: Tier 1) each Center is to have a Standard Operating Procedure on resolving internal scientific disputes to include particular mandatory requirements for robust processes; and Tier 2) the Office of the Commissioner has an Agency-level appeals process for use by employees who are not satisfied after engaging in the SDR process at a Center level.

This document sets forth the Tier 1 Tobacco Policy and Procedure (ToPP) for internal SDR processes at the Center for Tobacco Products (CTP).

FDA Staff Manual Guide (SMG) 9010.1 on Scientific Dispute Resolution, sets forth the Tier 2 Agency-level appeals process. SMG 9010.1 mandates that each Center implement certain requirements or minimum standards for SDR processes. These include: Center processes must foster the principle of dispute resolution at the working levels within the organization starting with employees and their immediate supervisors/team leaders; and a Center Director must provide a written opinion on a dispute that has reached his/her level before the Agency level will address it on appeal. These requirements ensure that disputes will be eligible for the Agency-level appeals process, if needed.

This ToPP and the Agency's SMG 9010.1 support and facilitate diversity of opinion which is very important in a science-led agency like FDA. Through these processes, valid scientific disputes can receive a full and fair hearing at all levels of the Agency, including the highest levels.

B. Coverage

This ToPP covers all CTP employees involved in scientific regulatory decision making, including, but not limited to, those responsible for writing or reviewing scientific and technical documents and making recommendations to their supervisor or team leader. The recommendations may subsequently be reviewed by a supervisor, Division Director, Office Director, and sometimes the Center Director, for final approval and action.

Disputes addressed through this ToPP must be scientific in nature and arise during the regulatory process and be applicable to or support a regulatory decision or policy issue regarding the regulation of tobacco products. Such a dispute may, for example, involve the interpretation of science that is applicable to or supports a regulatory decision or action taken upon that consideration

In order for a dispute to be eligible for resolution under this ToPP, it must be consequential to a decision. A dispute is consequential to a decision if taking one position on an issue would lead to a different decision than taking another position, for example, whether a tobacco product is, or is not, substantially equivalent. Also, the difference in the decision may have a significant negative impact on public health.

This ToPP is primarily for disputes between a CTP employee and his/her supervisor or manager within one particular Office. However, it could also be used, with appropriate modification by the CTP Ombudsman on a case by case basis, in disputes between CTP Offices, or between employees in one or more Offices; in these cases the appropriate supervisory chains in each Office must be engaged in the dispute resolution process.

Routine, minor, or trivial disputes that arise during the course of coming to a decision are not eligible for resolution under this ToPP; these kinds of disputes can be addressed through informal procedures for documenting and responding to different scientific and regulatory viewpoints. In the process of developing consensus, many scientific views may be expressed. Most of these may be resolved very quickly as the issue is discussed. It is not necessary to document every such discussion as a team works together. Rather, this ToPP should be reserved for the most serious disputes that could not be resolved informally, and when an action or inaction by CTP could have a significant negative impact on public health.

The following kinds of disputes are also not eligible for resolution under this ToPP: non-scientific disputes; issues related to personnel disputes such as EEO, labor and employment disputes and work environment situations; disputes related to the rulemaking process; disputes related to enforcement policy; administrative disputes; scientific disputes that relate to non-regulatory activities; or disputes that challenge an established CTP, Agency or Department policy. Other pathways may be available to resolve these kinds of disputes.

C. Policy

CTP managers shall create an atmosphere in which consultation and open discussion on evolving scientific findings (e.g. draft reviews) and controversial issues are encouraged. When disagreements occur, it is necessary to follow existing procedures for resolving them. Informal methods, such as using good management practices for resolving conflict, should be employed prior to the dispute resolution procedures in this ToPP. Employees and supervisors should have as open and complete a discussion of the issues as possible. If these and other informal attempts fail, requirements for the formal procedures for resolving disagreements at CTP, as described in this ToPP, may then be used.

It is inevitable, indeed intended and encouraged, that employees, supervisors, and managers bring different perspectives and concerns to their respective analyses of data and information. FDA has a long history of valuing scientific exchange, openness and transparency to facilitate reaching optimal and fully considered public health decisions. Thus, it is necessary for everyone to work together informally to discuss evolving scientific findings and to resolve differences when they occur so that an institutional decision may be reached. The basic approach to accomplishing this is to attempt consensus development and agreement through discussion among participants as the work proceeds. In cases where an employee disagrees and cannot accept a planned regulatory decision/action, resolution of differences may need to be achieved by using the formal dispute resolution process described in this ToPP.

It is essential that all persons who dispute a scientific matter be respected, and that the administrative file reflect any significant dispute as well as the ultimate resolution.

D. Procedures

Intent: The intent of this section is to describe the procedures for resolving internal scientific disputes within CTP. These procedures apply to all CTP employees involved in regulatory science-based decision making. Dispute resolution at the lowest organizational level possible is strongly encouraged.

Documentation of Administrative Files:

1. 21 CFR Part 10, Administrative Practices and Procedures, section 10.70 states: “FDA employees responsible for handling a matter are responsible for insuring the completeness of the administrative file relating to it. The file must contain appropriate documentation of the basis for the decision, including relevant evaluations, reviews, memorandums, letters, opinions of consultants, minutes of meetings, and other pertinent written documents.” The file must also contain “recommendations and decisions of individual employees, including supervisory personnel, responsible for handling the matter” and “reveal significant controversies or differences of opinion and their resolution.” An employee who “has

worked on a matter may record individual views on that matter in a written memorandum, which is to be placed in the file." For a full description of the administrative file, see 21 CFR 10.70.

2. The CTP Ombudsman will maintain the administrative files on internal scientific disputes that are not associated with specific Office- or Center-level administrative files.

3. In the event of a difference of opinion or informal dispute, the supervisor/manager may not order an employee to change the original draft, or final, document. A supervisor who does not concur with, and thus overturns, a staff-level review memorandum/recommendation must document his/her decision in a memorandum. Both the staff and supervisory memorandums should be included in the administrative file for that regulatory decision/action. This would not trigger a formal dispute as per this ToPP unless the staff-level employee (not the supervisor/manager) decides to become the initiator of such a dispute. In any event, both memorandums must remain part of the administrative file.

4. Differences of opinion or disputes resolved informally, and not via this ToPP, do not usually have to be documented in the file unless they are significant. Documentation of every difference of opinion expressed, particularly those that are trivial, is not necessary.

5. Written documents in an administrative file should avoid intemperate language, undocumented charges or irrelevant remarks (e.g., personal comments about individuals). Once completed, the documents in the file may not be removed. Subsequent brief amendments (corrections, revisions, additions, notes, comments, recommendations) may be made directly on the document, but must be initialed, or signed, and dated; longer amendments should be made in a new document, with date and signature.

6. The official administrative file may be a paper or electronic file. As electronic policies and procedures change, CTP will ensure that they conform with, and support, the requirements of this ToPP.

The Resolution Process:

1. In the process of coming to a science-based regulatory decision, differences of opinion or disputes may arise between staff members and their supervisors/managers. When this occurs, the parties should make every effort to resolve these differences through informal means, such as open and respectful discussions.

2. If efforts to resolve differences of opinion or disputes through informal means fail, and an employee cannot accept a science-based regulatory decision because he/she believes it would result in significant harm to the public health, that employee may choose to become the initiator of the formal SDR process. Once an employee decides to be an initiator, he/she

should follow the procedures in this ToPP promptly so that the issues may be fully examined and resolved in a timely manner.

3. In order to begin the formal SDR process, an employee must write an initiation memorandum to the next highest supervisor/manager above the initiator's immediate supervisor or team leader, with copies to that supervisor/team leader, others involved in the dispute, and the CTP Ombudsman. For example, if the employee's supervisor is a team leader, and the employee becomes the initiator of a dispute, he/she would write the initiation memorandum to the Division Director, (who is the next highest level supervisor up the chain.)

4. The initiation memorandum, to be complete, should clearly document: (1) the nature of any dispute; (2) the basis of the initiator's position on each issue raised; (3) what additional information or evaluations, if any, would be needed to resolve each issue raised; (4) the initiator's recommendation on each issue raised and the basis for each recommendation; and (5) possible negative consequences to public health. Scientific assertions in the memorandum should be supported by scientific evidence. The initiation memorandum must also be added to the administrative file.

5. The CTP Ombudsman will determine the completeness of the initiation memorandum and the eligibility of the dispute for resolution under this ToPP, and provide written notification of this determination to the appropriate parties no later than ten (10) business days after receiving a complete memorandum.

6. Dispute resolution will be addressed at successively higher supervisor/manager levels up the chain until resolution is achieved; i.e. all parties agree with, or at least accept, a decision by a particular level in the chain of command. This means that issues that cannot be resolved at one level may be taken to the next highest level, e.g. Division Director, Office Director, Center Director. Also, discussions held and decisions reached in this process will be appropriately documented in the file. If the initiator is not satisfied with the decision at one level and chooses to continue the dispute resolution process at the next highest level, he/she has ten (10) business days after receipt of the decision to submit the initiation memorandum to the next highest level, updated if necessary, to continue the process at the next highest level.

7. Supervisors and managers at each successively higher level may turn to relevant scientific, technical or other resources on the matter at issue to gain a better understanding of the issues in dispute and to aid in addressing them. A relevant resource may be other Center, Agency, or appropriate federal government staff with related expertise, Special Government Employee (SGE) "homework assignments," journal articles, etc. Relevant resources should rely on scientific evidence to support any conclusions and or recommendations.

After review, discussion, and consideration of all documents and points of view from all parties to the dispute and any relevant resources he/she may have consulted, the supervisor/manager at the level where the dispute is currently being reviewed should make a decision. He/she should then issue a decision memorandum, clearly documenting: (1) the efforts made to resolve the dispute at this level of the supervisory chain; and (2) his/her decision(s) on the issue(s) raised and the basis for each decision. Scientific assertions in the memorandum should be supported by scientific evidence. The supervisor/manager should send a copy of the decision memorandum to the involved parties, with a copy to the CTP Ombudsman, no later than thirty (30) business days after receipt of the complete and eligible initiation memorandum, unless the manager had consulted with other individuals not involved in the disagreement (such as SGEs or other Agency staff members). If the manager consulted with other individuals not involved in the disagreement, he/she should issue the decision memorandum no later than forty-five (45) business days after receipt of the complete and eligible initiation memorandum. The decision memorandum must be added to the administrative file.

8. If the dispute has progressed up the chain to the Office Director level, and the Office Director is unable to resolve the dispute, the initiator may elect to bring the matter to the next highest manager, the Center Director. The Center Director will render an opinion/decision as quickly as possible (normally within sixty (60) business days) after the initiator has submitted the dispute to him/her, taking into consideration any statutory or regulatory timelines, any urgency of a decision, and the complexity of the issues in dispute. The Center Director must issue a written opinion/decision on the matter to the initiator, with copies to the lower-level supervisors and managers, and the CTP Ombudsman, and will record it in the administrative file. If the initiator decides not to appeal to the Agency level, then the Center Director's opinion/decision is final.

9. If the parties to the dispute resolve their differences at any stage of the process or the initiator chooses to withdraw the dispute, a memorandum to this effect written by the initiator will be added to the file, with a copy to the CTP Ombudsman. The initiator will also notify the official at the level where the dispute is currently pending and any other parties to the dispute. The Ombudsman will periodically check with the initiator to determine if the differences have been resolved or the dispute is to be withdrawn.

10. Because resolution cannot be predicted at any given supervisory level, it is important to move as quickly as possible throughout the process, especially with regard to a scientific dispute that involves a decision on a submission, such as a marketing application. To the extent possible, the formal SDR process should take into account any pertinent regulatory review time frames to help ensure that they are not exceeded unnecessarily. When a pending dispute has the potential to impact, one way or the other, the outcome of a decision on a submission, the Office Director will notify the Center Director.

- As required by the Agency SMG 9010.1, while the SDR process is pending, work on a final regulatory decision/action will continue up to and including the actual issuance of the regulatory decision/action unless the Center Director decides

  that; the dispute raises substantial questions involving a significant risk to the public health, and postponing the decision would not result in a negative impact on the public health.

11. Whatever the Center Director decides regarding continuing or postponing work on a decision/action including issuance of the final regulatory decision/action that is subject to a dispute, he/she should place in the administrative file a memorandum clearly documenting his/her rationale.

    - If an accelerated timeline is needed for dispute resolution because of a significant action due date or imminent public health concern, the CTP Ombudsman should be contacted to determine if the dispute resolution process could be accelerated.
    - At the discretion of the Center Director, the CTP Ombudsman may notify an affected company if a final regulatory action related to that company's submission will be delayed because of a pending dispute.
    - The mere act of initiating or being involved in the process described in this ToPP, will not adversely affect any employee's performance rating.

Expedited Review:

As required by the Agency SMG 9010.1, this ToPP provides that, regarding disputes of sufficient immediacy and scale of impact on public health or other compelling factor, an initiator may 'opt-up' to the Center Director to request expedited review of the dispute (go directly to the Center Director by skipping over supervisors and managers lower in the chain of command so that the Center Director may make a decision within a condensed timeframe). If the Center Director does not agree that his/her immediate review is warranted, the Center Director will send the dispute to the appropriate lower level in the management chain.

Appeal to the Agency Level:

If the initiator is not satisfied with the Center Director's opinion/decision, and the Center-level DRP is thus exhausted, the initiator may decide to appeal to the Agency-level DRP. The Agency SMG 9010.1 requires that this be done within ten (10) calendar days of receiving the Center Director's written opinion/decision. (Note that all other timelines in this ToPP are in business days.)

Communication:

1. The intent of this ToPP is to promote thoughtful and independent scientific work products; effective communication among staff, supervisors and managers; and good relationships in reaching institutional decisions. It is also important to have a record of individual accountability in institutional decision-making.
2. When differences of opinion and disputes arise, discussion is to be handled in the spirit of open communication and without personal animosity. All employees and supervisors have an obligation to identify and bring to management's attention those developing controversies that may require resolution, through various means including internal meetings, policy guidance, presentation to an advisory committee, presentation at scientific rounds, and consultation with line management.
3. Effective informal communication throughout the regulatory process (e.g. while a review is being drafted) is the best approach to avoiding and resolving differences. Open communication throughout the organization is encouraged. Managers have an obligation to meet with individual staff members, or teams, and supervisors as necessary to discuss evolving issues and differences of opinion and to create an atmosphere of openness, trust, and respect for each other's views in resolving differences.
4. The following kinds of communication are required by this ToPP:
    - The Center is responsible for developing and disseminating clearly written procedures for internal SDR processes, including any timelines for rendering a written opinion by the Center Director. It is also responsible for periodically communicating SDR responsibilities to all levels of staff.
    - Decisions made as a result of the SDR process and their supporting rationale will be communicated to appropriate parties including the initiator.

E. Guidelines

This ToPP describes procedures for the documentation and resolution of internal scientific disputes among CTP employees, supervisors, and managers, who review, analyze, consult on, or otherwise provide input associated with science-based regulatory decisions that are related to CTP's mission. Institutional positions are typically reached informally on such decisions. This ToPP indicates how and when an informal dispute or difference of opinion rises to the level of a formal dispute (when an employee writes a dispute initiation memorandum.) Each CTP employee/supervisor/manager involved in a dispute and its resolution is to document his/her views. This ToPP is intended to address serious internal scientific disputes that could have a significant negative impact on public health.

This process is only for internal CTP use to address disputes in the regulatory process; it is not applicable, for example, to scientific disputes between CTP and external stakeholders, such as the tobacco industry.

This ToPP is being issued under the following guiding principles:

FDA staff should have an avenue at the Agency level to appeal a dispute they feel has not been adequately addressed or resolved within their Center. However, the Agency-level appeals process for scientific disputes is not a replacement for robust and fair Center-level processes. All staff, including initiators of disputes, is to be treated with openness and respect. Resolution procedures should not be unnecessarily burdensome for disputing employees to use.

It is the responsibility of everyone to ensure that initiators of disputes are protected from retaliation by their peers, supervisors, Center leadership and others. Concerns and complaints about retaliation should be reported to the CTP Ombudsman.
This ToPP supplements and does not supersede applicable provisions of the Whistleblower Protection Act of 1989, the Federal Employee Anti-discrimination and Retaliation (No FEAR) Act of 2002 and all applicable federal laws, regulations and Executive Orders that afford protection under the law.

F. Roles and Responsibilities

Initiator: In the dispute resolution process, the initiator is the party who disagrees with a decision made or about to be made in CTP and decides to invoke the process in this ToPP to challenge that decision with an initiation memorandum. The initiation memorandum is the trigger that changes the resolution process from informal to formal. The initiator may be an individual, group, or organizational unit. Note: though an initiator may be more than one person, this ToPP uses this term in the singular.

CTP Ombudsman: The CTP Ombudsman should evaluate the initiation memorandum to determine: (1) whether or not it is complete and (2) whether or not the dispute is eligible to be addressed through this ToPP. He/she should notify the initiator and supervisor whether or not the memorandum is complete and eligible no later than ten (10) business days after receipt of the memorandum. The CTP Ombudsman is also responsible for being knowledgeable about the two-tiered (CTP and Agency) SDR processes in order to confidentially counsel potential initiators who approach his/her office, and to help filter out personnel-related issues. At any point in the dispute process, the Ombudsman may be approached by the initiator, or any other persons involved in the dispute, for consultation. The Ombudsman may communicate with the initiator throughout the SDR process to increase the initiator's comfort with it. Once the formal CTP process is initiated, the Ombudsman will maintain a record of the dispute, as well as monitor and track it.

Managers: CTP managers are responsible for instituting and implementing SDR processes, such as this ToPP, that reflect the guiding principles of openness and resolution of scientific disputes at the lowest organizational level possible. CTP supervisors and managers are responsible for communicating the SDR process and for training appropriate staff on the procedures available to resolve internal scientific disputes at the Center and at the Agency-level.

Center Director: For each scientific issue under dispute, the Center Director (or the CTP Ombudsman as delegatee) is responsible for:

- Ensuring that the SDR process in the Center is documented, communicated, implemented, and conforms to the standards required by the Agency (see 21 CFR 10.70);
- Issuing written opinions/decisions on disputes that have advanced to him/her through the scientific dispute resolution processes in CTP;
- Cooperating with the Agency's appeals process through interviews, information requests, and presentations, as necessary; and
- Working closely with the Agency SDR entities and officials throughout an appeal, and carrying out any resulting follow-up actions.

G. Definitions

N/A

H. References

SMG 9010.1 on Scientific Dispute Resolution

21 CFR 10.70

I. Appendix

N/A

J. Summary of Changes

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3	Reflects new template

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