Supplemental Report – OSC File No. DI-20-0372

On January 8, 2021, in response to a referral from the Office of Special Counsel (OSC) (OSC File No. DI-20-0372), the Department of Health and Human Services (HHS) transmitted to OSC the report of an investigation and review conducted by the Food and Drug Administration (FDA) (FDA Report). (Attachment A). The FDA Report responded to allegations raised by an employee of FDA’s Center for Tobacco Products (CTP) relating to the process adopted by CTP for evaluating substantial equivalence (SE) applications for tobacco products, specifically the process for measuring and comparing harmful and potentially harmful constituents (HPHCs) of tobacco products, as described in a memorandum issued by management within CTP on February 21, 2019 (the HPHC Memo).

Based in part on advice received from an independent panel of experts (Expert Panel), the FDA Report concluded that CTP’s approach, as outlined in the HPHC Memo, was consistent with sound regulatory science. The FDA Report also outlined certain planned remedial actions, namely revisions to the HPHC Memo and clarifications to the agency’s process for scientific dispute resolution.

On August 10, 2021, OSC requested that FDA reconvene the Expert Panel to evaluate the FDA Report and provide further input on the scientific issues, including an evaluation of any revisions to the HPHC Memo, and that the agency submit a Supplemental Report describing the Expert Panel’s assessment. OSC also asked that the agency include in its Supplemental Report information on its progress in meeting the projected timeframes for the remedial actions described in the FDA Report. (Attachment B).

On February 28, 2022, FDA provided a copy of a revised version of the HPHC Memo (Revised HPHC Memo) to OSC, noting that the CTP employee who made the initial allegations participated in the HPHC Memo revision process. (Attachment C). FDA provided additional information informally to OSC on March 8 and March 18 to respond to the request for a status update on meeting the other goals described in the FDA Report. (Attachment D). Below we provide information on FDA’s progress in completing the remedial actions described in the FDA Report, including additional information to respond to OSC’s request for clarifying information.1

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1After consulting with OSC, FDA concluded that reconvening the Expert Panel was not necessary to ensure the concerns originally raised by the CTP employee and later by OSC are appropriately addressed and, accordingly, that doing so would be an inefficient use of the Agency’s limited resources. After reviewing the Revised HPHC Memo, FDA determined that it resolved the scientific disagreement leading to OSC’s initial request for a report. Moreover, the CTP employee who had raised the allegations with OSC participated in the revision of the HPHC Memo. FDA therefore determined that there would be little value gained from asking the Expert Panel to take time away from their regular duties to re-review the same scientific issues.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov
Progress in Addressing Goals Described in the FDA Report:  

**Goals 1 and 2:** Revision of the HPHC Memo to clarify (a) the three tiers of the new investigative method, (b) the methodology and criteria, (c) how CTP will resolve scientific uncertainty, and (c) that toxicologists have discretion to evaluate a quantitative assessment submitted with an application but that it is unlikely to produce a different outcome.

STATUS: Complete. (See Attachment C). As previously noted, the CTP employee who raised the allegations that led to the OSC referral participated in the HPHC Memo revision process. The discussion of the three tiers begins on page six of the memo, including methodology for evaluation of HPHCs. The revised memorandum also notes, “Where appropriate, reviewers may also recognize that well-developed quantitative approaches may be useful in some instances and employ such an approach if warranted.” As described in the FDA Report, the Expert Panel’s recommendations focused on the need for clarity in describing the methodology for comparing the risks of different HPHCs. FDA has concluded that the Revised HPHC Memo describes a clear and transparent process for evaluating and comparing HPHCs in SE applications.

**Goal 3:** Develop a decision tree to clearly lay out steps for SE determinations.

STATUS: Complete. (Attachment E).

**Goal 4:** Continue work to evaluate and revise the tiered qualitative/semi-quantitative process set out in the Revised HPHC Memo.

STATUS: Ongoing. As this is an emerging area of regulatory science, FDA/CTP intends to continue to evaluate and refine the process discussed in the Revised HPHC Memo as the agency gains additional insight and experience regarding HPHC evaluation.

**Goal 5a:** Eliminate the ambiguity in CTP’s internal scientific dispute resolution policy and procedures (SDR-ToPP) by clarifying the circumstances under which CTP staff may initiate the SDR process.

STATUS: Complete. (Attachment F).

**Goal 5b:** Create an institutionally knowledgeable point of contact for issues related to scientific dispute resolution (SDR) at the agency level.

STATUS: Complete. FDA created such a point of contact, added that resource information to its agency-level Staff Manual Guide on scientific dispute resolution (SDR-SMG) and has advertised the existence of the point of contact within CTP using the training effort described below. The following language was added to the SMG:

> The Office of Scientific Integrity within OC’s Office of the Chief Scientist will maintain an SDR POC to provide an agency-wide resource to assist with the application of the SDR policies and procedures described in this SMG. The SDR POC will be available to provide advice and recommendations related to the

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2 In preparing this Supplemental Report, we have used the framework provided to us by OSC in its August 10, 2021, email requesting the report.
application of SDR-related policies and procedures, coordinate with Center ombudsman and other personnel on SDR matters, and serve as a knowledgeable contact point on SDR issues for all FDA employees with questions or concerns. Current contact information for the SDR POC may be found on the Office of Scientific Integrity website or obtained via email to SDR@fda.hhs.gov.

The FDA Agency Intramural Research Integrity Officer (AIRIO), currently Nate Sabel, is the point of contact, and responds to emails directed to that email address noted in the SMG. The SMG is at the following link: https://www.fda.gov/media/79659/download.

Goal 5c: Provide substantial education and training to CTP staff involved in scientific decision-making.

STATUS: Complete. FDA’s review of the whistleblower allegations cited a lack of familiarity with FDA’s existing SDR policies as one of the areas where remedial action was appropriate. To ensure that all staff at CTP who are engaged in scientific decision-making are aware of the SDR process, FDA’s Office of Scientific Integrity partnered with CTP’s Ombudsman’s Office, and CTP’s Office of Science to design, create, and deliver a training program to improve SDR policy and process awareness among CTP staff involved in scientific decision-making. Structurally, the training consisted of two parts. The online portion had a voice-directed discussion that walked participants through the purpose and importance of both informal and formal SDR at FDA and CTP, explained the procedural pathways available to all CTP employees in detail, and provided resources and contact information (including for FDA’s new agency-wide SDR point of contact) to assist employees navigating the SDR process. The first training component is available here: https://360.articulate.com/review/content/64c7a2c5-4032-4a6d-9b29-b6e35cfa8ec6/review.

Questions and feedback solicited during this first portion formed the starting point for a second, live session that included a discussion of hypothetical SDR examples, clarified and refined concepts from the first session in response to questions, and offered an opportunity for CTP staff to get to know the FDA personnel who are available to them to work through SDR issues (i.e. the AIRIO, the CTP Ombudsman, and the Associate CTP Ombudsman). The first section was mandatory and catalogued participation from 556 CTP Office of Science staff members at last count, including division directors, managers, and other supervisors as well as staff-level reviewers. The voluntary second session drew participation from over two hundred CTP scientists and review staff across two separate hour-long sessions. Feedback from participants of the training as a whole was positive and viewed as a successful effort to improve staff familiarity with the SDR process at FDA/CTP. FDA plans to use this training program as a model for expanding its SDR education to other agency components in the future.

As reflected in the SDR-SMG, which is available to both agency staff and the public, CTP’s process for resolving scientific disputes is consistent with the best practices and required procedural elements adopted by other agency components.

Additional Question: Whether the agency will be developing regular training for toxicology staff to facilitate standardization in evaluating SE applications.
STATUS: The ongoing evaluation of the scientific method is part of the daily work of staff within CTP’s Office of Science and is intended to be iterative, focused on working in teams to continue to improve FDA’s understanding of HPHCs within this novel regulatory framework. CTP continues to encourage its toxicology staff to remain engaged with these scientific issues as part of the daily duties in evaluating applications and intends for the Revised HPHC Memo to continue to evolve as CTP’s scientific understanding continues to improve. CTP does not have a formal training program centered on the Revised HPHC Memo but has instead integrated the memorandum into its standard training process for toxicologists and other relevant staff. New toxicologists at CTP who will be involved in implementing the Revised HPHC Memo receive that standard training, and the HPHC Memo will be part of the ongoing, regular training for existing staff with relevant responsibilities.

George M. Warren
Director
Office of Scientific Integrity
Attachment A
[HHS report titled “Review of Whistleblower Allegations,” which already accompanies this OSC File No. DI-20-0372 at https://osc.gov/PublicFiles, is omitted for brevity.]
Attachment B
Dear [Redacted]:

We are writing you in regard to the report of investigation produced by the Office of the Commissioner of the Food and Drug Administration (FDA), at the behest of the Secretary of Health and Human Services (HHS), in response to the Special Counsel’s February 28, 2020, referral to the Secretary (OSC File No. DI-20-0372). We reviewed the report submitted by Secretary Azar on January 8, 2021, as well as the whistleblower’s response to that report. In order to determine whether the report is reasonable, the U.S. Office of Special Counsel (OSC) is requesting a Supplemental Report, pursuant to 5 U.S.C. § 1213(e)(5), within 60 days.

Reconvene Expert Panel

We are requesting that you reconvene the independent panel of scientific experts (Expert Panel) that was initially used to evaluate and advise the Center for Tobacco Products (CTP) Director as to the first two allegations OSC referred for an investigation. The two allegations involved the scientific merit of a new qualitative or semi-quantitative risk assessment process and its comparability to a quantitative risk assessment process used for comparing harmful or potentially harmful constituent (HPHC) levels in tobacco products in the context of substantial equivalence (SE) applications to the FDA. The qualitative or semi-quantitative approach was set out in the HPHC Memo.

Significantly, we believe the Expert Panel’s input is important for evaluating the agency’s report because the CTP Director, in reaching his decision, relied in part on the fact that the Expert Panel did not have access to certain information when it made its recommendations. Specifically, the CTP Director noted that the panel “did not have access to ‘materials and information . . . that contribute to transparency in the review process,’” nor was it likely aware of many practices and processes to ensure SE review decisions are aligned with statutory standards, such as reviewer guides, training materials for specific roles, and a FDA-wide review agreement process. The Office of the Commissioner likewise obtained additional information from CTP managers that led it to conclude that Expert Panel did not accurately understand the new approach because the HPHC Memo did not clearly convey the reasoning behind its adoption or how the qualitative/semi-quantitative tiered process was intended to function.

Further, given the scientific complexities involved in the issues referred for investigation, we believe the evaluation of the External Panel will be invaluable. The panel members are external to the CTP, pre-screened for conflicts of interest, specially selected for their scientific
expertise in the areas at issue (toxicology and public health concerns related to tobacco products), and already familiar with the issues. Significantly, the Office of the Commissioner asserted that the planned revisions to the HPHC Memo were consistent with the Expert Panel’s recommendations and advice—an assertion best evaluated by the Expert Panel itself. In sum, the Expert Panel is well situated to provide guidance on whether the agency’s analysis of the issues, conclusions, and proposed corrective actions related to the first two allegations are reasonable.

Once the Expert Panel is reconvened, we request that you provide them with the following information:

• Any information the CTP Director noted undermined the Expert Panel’s conclusions;
• The most updated version of the HPHC Memo; and
• As much information as necessary regarding the newly implemented criteria and tiered system of analysis to ensure the Expert Panel has sound understanding of the system.

The Expert Panel should be tasked with the following:

1. determining whether its initial evaluation is still sound and what, if any, changes to their conclusions or recommendations are warranted;
2. evaluating the HPHC Memo to ensure that the instructions and standard of review are clear and scientifically sound;
3. analyzing the tier system to determine whether the tiers are overlapping, workable, and sufficiently clear; and
4. determining whether this new risk assessment method is more likely to result in an NSE result.

A copy of the Expert Panel’s assessment should be included as part of the Supplemental Report.

**Progress on corrective action**

The supplemental report should also include information on the agency’s progress toward or completion of the five goals set out in the agency’s initial report, the estimated timelines for some of which have elapsed. Below is a list of goals the agency initially laid out and their timelines:

A. Allegations 1-2

- Goals 1 and 2: Revision of the HPHC Memo to clarify (a) the three tiers of the new investigative method, (b) the methodology and criteria, (c) how CTP will resolve scientific uncertainty, and (c) that toxicologists have discretion to evaluate a quantitative assessment submitted with an application but that it is unlikely to produce a different outcome. Initial Timeframe: one to three months.
- Goal 3: Development of a decision tree to clearly lay out steps for SE/NSE determinations. Timeframe: four to nine months.
- Goal 4: Continue work to evaluate and revise the tiered qualitative/semi-quantitative process set out in the HPHC Memo. Timeframe: ongoing.
B. Allegation 4

- Goal 5: Eliminate the ambiguity in CTP’s internal scientific dispute resolution policy and procedures (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. Timeline: unspecified.

Additional Request

Additionally, we would like information on whether the agency will be developing regular training for toxicology staff to facilitate standardization in evaluating SE applications.

Sincerely,

[Signature]
Attorney
Retaliation and Disclosure Unit
U.S. Office of Special Counsel
1730 M Street, N.W.
Suite [Redacted]
Washington, D.C. 20036

NOTICE: This message and any attachments may contain information that is sensitive, confidential, or legally privileged. If you are not the intended recipient, please immediately notify the sender and delete this email from your system; you should not copy, use, or disclose its contents. Thank you for your cooperation.
Attachment C
MEMORANDUM

To: File

From: [Name], PhD, MPH
Supervisory Toxicologist
Division of Nonclinical Science, Office of Science

Digitally signed by [Name]  
Date: 2022.02.24 10:18:01 -05'00'  
For [Name]

Digitally signed by [Name]  
Date: 2022.02.25 07:26:54 -05'00'

Digitally signed by [Name]  
Date: 2022.02.24 10:55:20 -05'00'

Through: [Name], PhD
Associate Director
Division of Nonclinical Science, Office of Science

Digitally signed by [Name]  
Date: 2022.02.24 11:55:37 -05'00'

Digitally signed by [Name]  
Date: 2022.02.25 08:38:23 -05'00'

Digitally signed by [Name]  
Date: 2022.02.25 09:33:28 -05'00'

Subject: Harmful and potentially harmful constituent (HPHC) comparison and evaluation procedure for comparing two tobacco products in application review
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 primarily based on relative differences in ingredients and by-products that are associated with adverse health outcomes and may differentially impact users of those products. In SE Reports for example, decisions are distinctly based on comparisons between a new product and predicate product(s) 1. In PMTA, decisions can be based on comparisons between products where data indicate user-specific product replacement (complete and/or partial) 2.

The determination of whether a tobacco product raises new toxicological issues, or more or less adverse health outcomes when compared to another tobacco product, is a multifactorial process considering 1), a comparison of the ingredients that make up each product; 2), the relative toxicant yields and likely exposures to users and nonusers of the products, including route of exposure and portal of entry effects; 3), differences in exposure magnitude and the relative direction of each difference; and 4), the potency of the toxicants in question. Section 904e of the Food, Drug, and Cosmetics Act requires FDA to establish and regularly define as appropriate a list of toxicants present in tobacco products termed Harmful and Potentially Harmful Constituents (HPHCs) to health 3. These HPHCs represent FDA’s current thinking on which constituents out of the large number of chemicals that are present in the consumable portion of a tobacco product that are, or potentially are, inhaled, ingested, or absorbed into the body (including as an aerosol, vapor, or any other emission), and causes or likely causes adverse health effects in users or non-users of tobacco products. The list of 93 HPHCs published in 2012 includes constituents linked to the five serious health effects commonly linked to tobacco use: cancer, cardiovascular disease, respiratory effects, developmental and reproductive problems, and addiction 4. Thus, the HPHC comparison between two tobacco products is critical in determining whether the two products have similar or differential toxicological outcomes, or differential risk of adverse health outcomes. The established list of 93 HPHCs 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, resulting in the potential for increased adverse health risk due to tobacco-related toxicant exposures. As the science advances, the overall HPHC list across product categories will be updated to include additional constituents based on available data 5-7.

This memorandum presents a framework for evaluating relative HPHC data sets (e.g. mass quantities per puff, mass quantities per user unit or session) between two tobacco products, sets out some key criteria by which HPHCs can be evaluated in the setting of tobacco product comparisons, and how to consider toxicological risks and potential health impacts resulting from key HPHC differences between the two products. In addition, it provides some important directions for further evaluation of human health risk insofar that certain HPHCs may drive specific adverse health outcomes for classes, groups, categories, or subcategories of tobacco products. DNCS plans to continue evaluating this topic, and, in time, develop more comprehensive thinking on this topic, including its applicability to the SE, PMTA, and MRTP application pathways.
Discussion:
It is well-established that cigarette smoke contains thousands of toxicants that pose both cancer and non-cancer health risks to users. Other types of tobacco products, such as oral (smokeless) tobacco, electronic nicotine delivery systems (ENDS, or commonly known as “vapes”), and hookah also expose users to many of these same toxicants. While human health risks of environmental chemicals have been evaluated by organizations such as the United States Environmental Protection Agency, or EPA, and the Agency for Toxic Substances and Disease Registry, or ATSDR, these assessments were not formulated or designed to assess relative risk between tobacco products presented in any of the present application pathways. Nonetheless, these assessments are a useful resource for tailoring a tobacco-specific toxicology approach that incorporates key tobacco mixture variables and constituents. Thus, the toxicological evaluation of chemical constituents found in tobacco products is based on identified HPHCs, and in the context of tobacco product review is a developing field that considers previous established approaches but must develop an analysis fit for purpose within CTP’s statutory framework. Moreover, unlike approaches such as those used by the EPA and ATSDR, the toxicological risk evaluation of tobacco products needs to consider the HPHC list, which are defined key toxicants that are believed to drive the majority of human health risk posed by tobacco products.

Federal agencies such as EPA have used the quantitative risk assessment (QRA) approach to evaluate cumulative human health risk from tobacco products. EPA, in particular, has developed a foundational set of documents for assessing chemical mixtures and quantifying overall potential hazard and risk. While the ideas developed and workflows utilized by EPA, such as those for quantitative risk assessment (QRA) of environmental toxicants, can be a good starting point for assessing chemical mixtures, it is important to note that EPA’s mission is distinctly different from CTP’s. For example, EPA methodologies are not specific to tobacco products and tobacco product comparisons. In addition, the QRA approach outlined by the National Academy of Science, or NAS, and built upon by EPA, FDA, and ATSDR, among others, was not developed for the regulatory evaluation of human health risks from HPHCs in tobacco products. Importantly, the NAS mainly outlines how to find and report uncertainty in risk assessment and risk management for single mixtures. This is important because in a comparative assessment, uncertainty may be constrained to the differences between products, indicating that a different but compatible (with EPA and NAS) process is needed for comparative tobacco product assessments. Areas discussed in the EPA and NAS frameworks that are of interest to Toxicology for making review decisions include exposure factors and measurements for and in relevant populations, relevance of peer-reviewed reference values for the specific route of exposure, the additivity or synergy or antagonism of risk from different toxicants in complex mixtures, and considerations per carcinogenicity of a substance. Importantly, for regulatory review purposes all this information would need to be discussed in the context of, or bridged to, the appropriate tobacco product use scenario.

In the context of tobacco product review, the relevant data are the scientific information available for HPHCs and ingredients – either by themselves or in mixtures. To understand the potential health impact of HPHCs on users, the analytical level of the HPHC and the magnitude and potency of the HPHC must be
considered, as both contribute to the risk level of a tobacco product and the potential for adverse health outcomes. However, as traditional tobacco products contain up to 10,000 constituents, comprehensive mixtures assessments would not be practical. While FDA has identified HPHCs for combusted products, oral products, and ENDS, as well as guidance that recommends reporting a specific number of HPHCs (based on product type) that have validated analytical methods, a full risk assessment per NAS or EPA guidelines for single substances and mixtures of each product would be time consuming. Therefore, as FDA is challenged with many applications with comparison to many products, FDA has a need to streamline the analysis of HPHCs to inform its toxicological evaluation of tobacco products. DNCS’s intention is to maintain consistency with other divisions in any new or updated framework and/or workflows for HPHC evaluations, and such a framework should help reduce uncertainty in toxicology decision-making.

The current workflow from the Division of Product Science (DPS) considers the analytical measurement when determining analytical equivalence, and any analytically inequivalent HPHCs are deferred to toxicology for further analysis of chemical potency and health impact of the HPHC(s) on users. The results of analytical equivalence evaluations depend on several factors, for example the decision criteria for equivalence (e.g., value considered a meaningful analytical difference) and data quality. In the context of risk assessment, such evaluations can aid the screening of constituents for further consideration and characterization of the current and potential human health risks from exposures to the hazardous substances when considered together with chemical potency. However, for tobacco product comparisons, FDA does not have health-based margins to determine whether differences in a toxicant’s level in product emissions is above or below a discernible level of toxicological concern, and in the absence of such criteria, no assumptions can be made regarding whether any toxicant level presents any hazard or risk. Importantly, many HPHCs are well-studied, and other federal and state agencies (e.g., EPA, ATSDR, Texas Commission on Environmental Quality, or TCEQ) have reference toxicity values that can be useful in assessing the potency of certain HPHCs relative to others that have similar adverse health outcomes (respiratory, cardiovascular, developmental, and reproductive, or cancer). The use of such reference toxicity values in DNCS decision making is outlined elsewhere. The approach outlined in this memo includes building upon the application of reference toxicity values vetted by various regulatory agencies and used to determine if constituents are reasonably likely to be present in product emissions at a level above or below which a deleterious health effect may be expected to occur, or describe a cancer risk in the context of continuous toxicant exposure at a defined concentration and time. However, these reference toxicity values were not derived from a specific tobacco product or tobacco product use scenario. In addition, when comparing two products, it is important to keep in mind from the toxicological perspective what could drive differential risk and hazard, which is a specific task in SE toxicology review. As such, analytical data, in combination with considerations of toxicant yield and potency, may serve as a baseline for the determination of whether differences in a chemical or

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1 Memorandum: Equivalence Testing for SE Evaluations; signed February 2017
2 Memorandum: Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products; signed March 2019
ingredient may impart different questions of public health from a toxicological perspective and thus drive differential risk between products.

An approach that could be applied in concert with the DPS-led equivalence analysis, and also further simplify HPHC analyses in product applications, is to focus qualitatively on the hazard and risk drivers. Risk drivers are the primary contributors of risk through their analytical magnitude and potency, and the basis of the driver concept is that baseline assessments are dominated by a few chemicals and a few routes of exposure. The established HPHC list and associated recommendations are a good starting point for applicants to consider and provide hazard and risk information for HPHCs that can drive risk for their products. In applying a risk driver concept, and as reviewers consider differences in toxicity between new and comparison products, a reviewer can also turn attention, if needed, to constituents of higher potency which may also be present at relatively higher yields compared to other HPHCs in the same tobacco product. The additional information may be useful for informing decisions about whether a new product presents toxicological concerns, or a potential increase in health risks relative to a comparison product. When considering these drivers, and other toxicants of higher yield that can also impact hazard and risk decisions, some baseline considerations must be taken into account including, but not limited to: a) conservative estimates applied to protect public health; b) analytical limitations in methodology and reporting increases uncertainty in the estimation of risks (e.g., detection level, quantitation level of constituents); c) most analyses have been performed on traditional tobacco products, typically cigarettes and smokeless tobacco; d) exposure regimens unique to tobacco products, different from any other exposure regimen used by other regulatory agencies; e) cancer and non-cancer endpoints are considered separately. Some notable chemical drivers of toxicological risk for tobacco products, as identified in the literature and regulatory agencies, include 1,3-butadiene, acetaldehyde, formaldehyde, acrylonitrile, isoprene, and NNK for cancer, and acrolein for non-cancer.

DNCS is continuously developing more comprehensive approaches and criteria to assist in the scientific evaluation and toxicological assessment of tobacco product applications, especially regarding comparative health risk analyses to address human health risk across all SE reviews, and across other application submission pathways seeking marketing approval. While this process will consider previous approaches (e.g., EPA, ATSDR, other FDA approaches) to risk assessment of complex mixtures, CTP needs to develop a tobacco-specific problem formulation and a risk assessment specifically designed to assess differential risks between a new product and a comparison product. As risk assessment methodology evolves, DNCS is committed to the ongoing evaluation and revision of its criteria for qualitative/semi-quantitative offsetting risks for product applications. This continuous process will ensure research and reconsideration of the current models to support consistency across applications and will consider any relevant scientific advancements to CTP review and CTP’s experiences in conducting such reviews.

The current approach includes:

1. A focus on relatively higher and lower HPHC yields that are deemed by Division of Product Science (DPS) review to be analytically non-equivalent between the new and predicate products,
or new and appropriate comparison products. It is critical that the determination of whether HPHC levels are analytically non-equivalent be made by a chemistry reviewer from the DPS.

2. An understanding that HPHC measurements considered equivalent are considered as part of a risk evaluation—they represent a component of risk or hazard that is not different between two products.

3. Use of qualitative or semi-quantitative analyses of HPHC data before applicant-submitted quantitative risk assessments (QRAs) are evaluated, or any reviewer-performed quantitative analysis may be warranted.

In addition to these points, a tiered, stepwise approach to analysis of HPHCs, and how to consider potential drivers of toxicological risk, is presented below. This proposed tiering structure for comparative HPHC evaluation considers both the analytical levels of HPHCs and the potency of HPHCs, and is at this time limited to 20 HPHCs with validated analytical methods. The approach begins by analyzing situations where all HPHCs are all analytically higher, analytically lower, or analytically equivalent, and follows through to describing key considerations for when submitted HPHC data is of such complexity that a qualitative approach may not be immediately feasible. As such, application of a qualitative or semi-quantitative approach that focuses on relatively higher and lower HPHC yields (as confirmed via equivalence testing) can allow DNCS reviewers to make focused conclusions about the toxicological impacts posed by the differences in measured HPHCs. Where appropriate, reviewers may also recognize that well-developed quantitative approaches may be useful in some instances and employ such an approach if warranted:

- Tier 1: All HPHC changes are analytically inequivalent but directionally the same (all are higher or all are lower), or all analytically equivalent;
- Tier 2: Some HPHCs are analytically confirmed to be higher or lower and may be appropriate for qualitative/semi-quantitative offsetting, and drivers of differential toxicological risk may be identified;
- Tier 3: Many HPHCs are either higher or lower but conceptually difficult to discuss in a qualitative or offsetting manner.

The following is a description of the tiers of HPHC evaluation based upon the HPHC data submitted, and the need for evaluation of any submitted QRAs. However, the reviewer has discretion to use their scientific judgement to deviate from this tiering system in situations where they can provide a rationale for this deviation.

**TIER 1: All HPHC changes are analytically inequivalent but directionally the same (all are higher, or all are lower), or all analytically equivalent.**
1. **In the event** all HPHC changes in the new product(s) are analytically inequivalent but directionally the same (all are higher, or all are lower), or when HPHCs show no meaningful analytical differences after equivalency analysis by DPS, the reviewer may ask the question: *Is it possible for a qualitative or quantitative approach to establish or describe differential cancer risk or non-cancer hazard between two tobacco products?*

   a. No, this is an inherently decisive HPHC comparison. Simply put, if all the HPHCs are higher, all associated cancer risks and noncancer hazards are likely higher; if all the HPHC changes are lower, all associated cancer risks and noncancer hazards are likely lower. This observation encompasses all potential drivers and non-drivers of health risk, and no further risk assessment is needed to complete the review.

   b. If all HPHCs are equivalent between the two products, this tends to indicate that there are no changes in differential adverse health outcomes due to HPHCs between the products; Reviewers should still evaluate ingredient issues separately in comprehensively evaluating all sources of increased adverse health outcomes HPHC measurements that are analytically equivalent (and thus considered unchanged between two compared products) per the Chemistry discipline are equivalent for purposes of toxicological comparison between the two compared products, and as such are not the main drivers of differences in cancer risk or non-cancer hazard between compared tobacco products.

   However, in some cases when DPS deems HPHCs analytically equivalent between a new product and a comparison product, if a particularly potent HPHC, (perhaps a risk driver for this class or category of products) exhibits a modest yet visually higher analytical yield, a reviewer may need to consider further whether any new toxicological concerns may emerge. This is an emerging and developing area in DNCS, as noted in the introduction. The reviewer, in consult with his or her supervisor or secondary reviewer, reserves the right to propose a concern from the toxicological perspective in such a case.

In HPHC comparison scenarios with only analytically inequivalent higher HPHC yields and no concomitant lower HPHC yields, a qualitative or quantitative approach based on the same analytical data cannot 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 need to be direct about this point. A common scenario encountered in applications is that a new product has higher HPHC yields in several high-potency HPHCs that may drive risk, without any offsetting lower HPHC yields that may otherwise have similar potency and associated adverse health outcomes. In this situation, a full risk assessment is not needed to complete the review as the data indicate increases in risk, even if only one risk driver is analytically higher. Logically, any comparative QRA following basic risk assessment principles would simply reflect an elevated non-cancer hazard or cancer risk associated with the higher HPHC yields.
c. QRAs that are not necessary: Consider a case in which all HPHCs are lower, or another in which analytically lower HPHCs of high potency outweigh the analytically higher HPHCs of lower potency (discussed further in Tier 2). In such an evaluation, scientific support in considering whether the risk due to one HPHC can be offset by another logically needs to include qualifying the HPHC associated adverse health outcomes. The HPHC list provides a good starting point (e.g., cancer, respiratory disease, cardiovascular disease) in considering the relative impact of concurrent HPHC changes. In these cases, a qualitative or semi-quantitative approach, indicating that the magnitude the of lower HPHCs and associated potency of effect, is larger and therefore adequately offsets higher HPHCs of lesser potency or magnitude but otherwise have similar adverse health outcomes. Such a determination could thus support a conclusion of no different questions of public health. If all HPHCs are analytically equivalent, any further qualitative or semi-quantitative approaches are not needed and no toxicological concerns emerge from the HPHC data. Therefore, a QRA is not necessary to address the changes between the two tobacco products and if submitted to support the HPHC data, does not need review for the cases described here.

TIER 2: QUALITATIVE/SEMI-QUANTITATIVE OFFSETTING

1. In the event some HPHCs are analytically confirmed to be higher yield while others are concurrently lower, the reviewer may ask the question: Can increases in hazard and risk associated with higher yield HPHCs be offset by decreases in hazard and risk associated with any lower yield HPHCs? In such a situation, the following considerations may be applied to determine whether an offsetting approach is appropriate and places the application in Tier 2:

   a. Equivalence analysis of the HPHC data, from DPS, confirms analytically important HPHC differences that are both relatively higher and relatively lower, and all measured HPHCs are included in the applicant’s screening for further assessment. The consideration emerges that analytically different HPHCs contribute to differences in cancer risk or non-cancer hazard between two compared products. As with Tier 1, HPHCs yields that are equivalent do not have an impact on the conclusion as they are not the main drivers of differential cancer risk or non-cancer hazard between compared products. If all analytically different HPHCs are not included in a meaningful way, the applicant’s assessment may be rejected, and a deficiency issued for the missing HPHC information.

   b. An increase in some health effect due to a higher yield HPHC can be offset by a different but lower yield HPHC if they have similar adverse health outcomes. In this case, adverse health outcomes have the exact resolution as the established HPHC list. For example, the impact of a higher-yield HPHC that is identified as a respiratory toxicant, may be offset, fully or to some degree, by another identified respiratory toxicant that has a confirmed lower yield. A higher yield HPHC, that has a health endpoint different from that of an HPHC that is lower yield, cannot offset the concern for the higher yield HPHC’s associated impact. For example, toxicity associated with a higher yield (and therefore potentially higher exposure) of a carcinogenic
HPHC implicated in lung cancer (such as benzo[a]pyrene, or B[a]P) cannot be offset, fully or to some degree, by a lower yield (and therefore higher exposure) of a non-carcinogenic HPHC implicated in COPD (such as acrolein). However, if both higher and lower yield HPHCs are observed or logically considered within a group of HPHCs implicated for the same toxicity endpoint, the offsetting approach is appropriate and can proceed.

c. **Considerations in offsetting adverse health outcomes due carcinogenic HPHCs:**
   
a. *At this time, carcinogenic endpoints are considered equivalent.* This is consistent with the idea that the cancer risk due to a specific toxicant can be added together with the risk due to another toxicant to equal a total cancer risk, which is supported by and explored elsewhere.\(^{12,13,21}\) Thus, given that a change in a specific type of cancer risk can also change the overall total cancer risk, the relativity of each outcome can be conceptually weighed against the total cancer risk change, in essence offsetting each other via impacts to the total cancer risk (assuming additivity as starting point). For example, an HPHC confirmed to be higher and that evidence indicates cause liver cancer, can be offset by a HPHC confirmed to be lower and that evidence indicates causes lung cancer. Further considerations regarding cancer slope and inhalation unit risk as detailed in (b) below should be considered. 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 applicant-conducted QRAs.

b. *Cancer slope factor (CSF) or inhalation unit risk (IUR) need to be considered when comparing carcinogenic HPHCs that are relatively higher and lower, in concert with the magnitude of change.* EPA defines the CSF as the cancer risk (proportion affected) per unit of dose and can be used to compare the relative potency of different chemical substances based on chemical weight, such as mg/kg body weight/day.\(^{22-24}\) An increase in a carcinogenic HPHC that has a steep CSF or IUR 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. For example, a chemical with a steeper CSF or IUR, such as benzo[a]pyrene (IUR of 6 x 10\(^{-4}\) \(\mu\)g/m\(^3\),\(^{25}\) versus acetaldehyde with an inhalation unit risk of 2.2 x 10\(^{-6}\) \(\mu\)g/m\(^3\)\(^{26}\) results in a greater number of cancer cases at a smaller concentration of the chemical.

c. *At this time, any analytically non-equivalent carcinogenic HPHC with an IARC classification of Group 2B through Group 1 is considered when evaluating the carcinogenic potential of a new versus a comparison product.* FDA continues to evaluate the evidence of harm and potential harm, including carcinogenic potential for tobacco products, for each of the HPHCs on its list.

d. **Considerations in offsetting adverse health outcomes due to non-carcinogenic HPHCs**
   
a. *The health impact of a lower-yield non-carcinogenic HPHC cannot offset the health impact of a higher-yield non-carcinogenic HPHC, if they have different health endpoints*
and/or different MOAs. Toxicity endpoints due to confirmed non-carcinogenic HPHC changes are central to the toxicological comparison between two tobacco products. For example, consider non-cancer effects of formaldehyde and benzene, which exert toxicity at different sites. An increase in respiratory irritation due to a higher level of formaldehyde cannot be offset by a lower level of benzene, as benzene is not a respiratory toxicant. However, a comparison between a higher level of formaldehyde and lower level of acrolein may be appropriate as both are respiratory toxicants. In this case, there would potentially be added certainty for related conclusions as there are important similarities regarding the adverse health endpoints due to formaldehyde and acrolein, as both are implicated in chronic respiratory disease.

b. In the case of one to few analytically significant higher yield non-carcinogenic HPHCs, comparison to peer-reviewed reference values may be an appropriate first step for determining if the yield changes are acceptable from a toxicology perspective. However, critical uncertainty characterization pertaining to the upper and lower limits of related exposure variables (e.g. concentration to mean mass/volume, volume, frequency, duration) is likely needed from the applicant to support an appropriate comparison with a toxicity reference value. In addition, given noncancer reference toxicity values typically only provide a level below which adverse health outcomes are not expected, further discussion about the nature/shape of the toxicants dose-response curve above the reference toxicity value may be warranted. More information on selection and application of reference values is detailed elsewhere in DNCS memoranda.

e. For HPHCs with both carcinogenic and non-carcinogenic endpoints, when considering appropriateness of an offsetting approach, carcinogenicity is given more weight over non-cancer effects. The potential for increased cancer risk from a relatively higher HPHC yields, for which scientific data indicate both cancer and non-cancer associated toxicities, should be considered first, and as stated above, non-cancer endpoints cannot offset carcinogenicity. Cancer is a leading cause of death in the United States. In general, cancer studies are typically conducted for long chronic periods, at low doses, and for sensitive endpoints. The current DNCS thinking is that the process for assessing cancer risk supports toxicology review decisions regarding the impact of any relative difference in tobacco product constituent yields.

f. If an offsetting approach is deemed appropriate, a consideration of the smoking regimen (e.g., CI vs ISO) under which the HPHC data was obtained may be warranted. Machine smoking regimens do not directly mimic user topography and this area of evaluation remains an opportunity for further refinement of the scientific review process. For cigarettes, the CI smoking regimen yields have been reported to be equal to or greater than the mouth level exposure of 86 – 97% of smokers. In addition, puff volume (e.g. the amount of smoke or aerosol drawn into the mouth), inspiratory volume (e.g. the amount of air used to pull the puff

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into the lungs), and puff frequency are variable across tobacco product users, including cigarette smokers and ENDS users, as well as across tobacco products, or even within a class of tobacco products, such as cigarette types. In other models of particle deposition or toxicant deposition in the lung, the inter-individual variations in lung morphometry, volumes, and topography are considerable and unavoidable sources of variability and uncertainty. For instance, in cigarettes, the puff volumes at the beginning of a smoking session can be significantly larger than the last puffs, likely due to nicotine satiation over the course of cigarette. Conversely, the associated inhalation volumes of individual smokers tend to be relatively constant during the consumption of a cigarette despite the tapering of puff volume. Such variability in data may allow for reviewers to consider whether, lower yields of HPHCs measured under CI may offset higher HPHC with otherwise similar adverse health outcomes as measured under the ISO smoking regimen per a reviewer’s scientific evaluation. However, such may need to be discuss in the context of whether smokers will use the new product at the same intensity as the predicate product which may fall outside of toxicology review criteria and is subject to further development. Any differences in new product use constitute an uncertainty in this area regarding its impact and feasibility in reaching toxicology review decisions. If considering an offset between CI and ISO, reviewers may also consider whether the HPHC data sets are complementary (whether they report the same or overlapping HPHC deliveries, or if the same HPHC(s) shows a yield directionally identical under each method). Another approach may consider yields under the ISO regimen as a lower boundary of possible exposure, and CI yields as an upper boundary, but such would necessitate that the changes observed under each regimen are substantiated by the other. In an instance where ISO data indicate potential issues that are not confirmed or maintained in some way by the CI data, the ability to perform offsetting will therefore be handled on a case-by-case basis.

For ingredients that are higher or added and also have inherent toxicities, consider if any HPHC changes offset the toxicity imparted by such a change. For example, the addition of a small amount of carcinogenic defoamer might be offset by a lower yield of a carcinogenic HPHC. In this case, the toxic ingredient may be neither an HPHC nor an ingredient that is known to lead to an increase in one or more HPHCs and therefore cannot be evaluated via the associated HPHCs. However, given both constituents are implicated in the same toxicity endpoint (cancer), offsetting may be appropriate. Reviewers need to clearly outline the approach taken for such an evaluation.

TIER 3: MANY CONFIRMED HIGHER AND LOWER HPHCS

In the event of many analytically inequivalent higher and lower HPHC yields, if the qualitative evaluation of HPHC data indicates a potential toxicity increase between the new and predicate or regarding a comparison product, then a QRA, if provided by the applicant, may be useful. In such a case, the overall estimation of hazard and risk difference due to all the higher and lower yield HPHCs is so complicated that a qualitative description of potential adverse health outcomes, or a quality comparison using reference values as a basis, is not achievable. In a subsequent review cycle, if an
The applicant submits HPHC data intended to wholly replace previously submitted data and Chemistry accepts the analytics any QRA based on the original data is therefore no longer relevant.

Applications demonstrating the scenario described above will likely include evaluation of any QRA submitted by the applicant. Historically, applicants have submitted QRAs to show that when considering all the reported HPHCs, not just those that are relatively higher or lower, the composite or total non-cancer hazard and cancer risk do not differ between products. In this way though, the results of a QRA may not truly reflect how the differences between products impact toxicological outcomes and this process also tends to leave out the structure and reliability of the analytical evaluation. Nonetheless, well-developed QRAs detail a transparent, systematic approach to estimate adverse health effects likely to occur in a specified user population as a result of exposure to one or more toxicants due to tobacco product use. As such, the information, assumptions, and uncertainty submitted and discussed in a QRA may be useful for supporting toxicology decisions in which there are many changes to evaluate.

The utility of QRAs in the evaluation of HPHCs in the context of product applications is a matter of ongoing improvement and refinement as Office of Science gains more review experience. QRAs are not always necessary to form a toxicology decision that is otherwise based on relative tobacco product data, but they represent a method of data evaluation that may otherwise be informative. They are not in themselves empirical data; instead, they rely on assumptions in the evaluation of adverse health outcomes. For example, assumptions can include exposure factors and lung function measurements for and in relevant populations, peer-reviewed reference values for a specific route of exposure, additivity, synergy, or antagonism of affects from different toxicants in complex mixtures, and considerations for carcinogenicity of a substance. All these elements reflect challenging uncertainties for establishing a comprehensive toxicology approach to assess the differences between tobacco products. Importantly, this uncertainty needs to be considered during any qualitative, semi-quantitative, and QRA evaluations of HPHCs, and in the assessment of the value that a QRA adds to submitted data and related conclusions within a review application.

This evaluation itself will be tiered, with certain parameters precluding further review of the QRA. The following items are necessary for a QRA to be useful, and if any of these items are not present or inadequately justified in a QRA, review of the QRA may not be necessary as the QRA will not be considered reliable:

1. Pertinent data:
   a. All raw data
   b. All equations
   c. All assumptions
   d. All parameters
   e. All outputs
   f. All references
   g. All statistics
   h. All summary results
i. Any other pertinent data and applicable information that the QRA depends on needs to be provided by the applicant and included in the assessment.

2. Qualitative and quantitative components of the risk assessment paradigm:
   a. Adequate problem formulation, to include scope of assessment, selection of assessment endpoints, identification of exposed populations and relevant routes of exposure, and development of a risk analysis plan
   b. Hazard assessment and identification, to include identification and evaluation of constituents/ingredients of concern and appropriateness of reference values used
   c. Dose-response assessment, to include accurate application of any toxicity values, route-to-route extrapolation, and for carcinogenic HPHCs, characterization of the risk across multiple/all cancer/tumor types relevant to humans
   d. Exposure assessment, to include steps to identify and evaluate exposure estimates and assumptions and whether they are appropriate (e.g., representative of tobacco product use), with supporting scientific evidence for the consumption rates for the new and predicate products
   e. Risk characterization, to include the probability of the exposed population experiencing an adverse effect (including cancer), with the toxicity and exposure assessments summarized and integrated into quantitative and qualitative risk expressions
   f. Accounting for uncertainty, to include differences in exposure and product use scenarios, populations, laboratory measurements, and effects of multiple stressors unique to tobacco products

If the QRA is complete, including data from all measured HPHCs, then further evaluation may be considered beginning with the problem formulation and hazard assessment, which establishes critical factors that have the potential to cause harm. If any step in the risk assessment paradigm is not complete, then the QRA unlikely is suitable for review and will not yield useful information.

Risk Characterization and Uncertainty:

In the context of any decision considering differential health risks resulting from HPHC changes between products, uncertainty must be considered and explained by both the applicant and the reviewer. The unique characteristics of tobacco products and the human smoking scenario, compared to that of chemicals in the ambient environment, present challenges for the understanding of risks between new and comparator products. For example, significant uncertainties may be expected in the amount of chemical measured in the tobacco product or tobacco smoke via analytical means (such as machine smoking) versus the actual amount/concentration reaching the end user. This may be due to several factors, including characterization of exposure scenarios, variability in human smoking behavior and product use (including dual use), effects in sensitive subpopulations as well as the full population at risk, multiple rounds of intense acute exposure versus sustained, controlled measurements in a laboratory, and the effects of multiple chemical agents/stressors (i.e., mixtures toxicity). Examples of considerations for uncertainty include:
Applicants need to correctly determine if a constituent or ingredient presents a hazard in a new versus a predicate product and ensure the impact of the entity on the product characteristics is discussed. The issue of the analytical variability of HPHCs and reliability of the measurement method, and if the applicant has adequately validated the method to ensure correct identification of the constituent based on its chemical/physical properties and accurate representation of the constituent’s level, also warrants consideration. HPHC measurements can inform exposure scenarios; acceptable analytical variability (upper vs. lower bound of measurement) may therefore reflect a range of toxicological risks. Current thinking considers that analytically equivalent measurements between a new and predicate product would represent a component of risk that would not change for a constituent. However, if an HPHC present in a new product is known to interact (additively, synergistically, or antagonistically) with other HPHCs not present in the predicate or comparator product, such needs to be taken into account.

Extrapolation between species. In cases where animal data or studies may inform toxicity in humans, in light of this source of uncertainty, scientific evidence and rationale may be needed to explain how the reference values allow for an adequate risk evaluation for exposures differences resulting from a smoking scenario, how differences in exposures between animal and human studies affect the accuracy of the subsequent biological response(s), and how variability in the human population vs. that of often inbred laboratory animals may impact any models of exposure extrapolation.

In the case of route-to-route extrapolations, for example, Rennen et al. states that route-to-route extrapolation is a two-step procedure: step 1, conversion of the external oral NOAEL to an internal systemic dose by correcting for the amount of the compound which did not enter the body during experimental exposure as the result of incomplete oral absorption, and step 2, transformation of the internal dose to an external dose for the exposure route of interest (for example, skin or inhalation) by taking into account the amount of incomplete dermal or inhalation absorption. In the absence of such a procedure, the introduction of a multiplicative uncertainty factor is a standard practice.

Mixtures. As tobacco products contain many potential chemical hazards, for example mainstream smoke and aerosols are complex mixtures with up to thousands of constituents, multiple chemical agents/stressors effects (i.e., mixture toxicity) warrant consideration when considering a product’s quantitative risk to an end user. When characterizing risk between new and predicate products, addition is often employed to create a composite (or combined) risk value for comparison between the new and predicate products regarding both carcinogens (ILCR) and non-carcinogens (HQ). The combined risk value may be assessed by reviewers if the applicant determines this value from HPHCs that share a common mechanism of action or chemical class. However, as the number of constituents increases in a complex mixture, the assumption of additivity becomes less reliable, likely introducing further uncertainty in risk. Furthermore, as discussed above, in a case where all HPHCs are analytically equivalent but
known chemical interactions may affect toxicity, a discussion is warranted about the potential impact upon the risk of the product, and whether there is cause for concern.

Conclusion:

The SE, PMT, and MRTP application pathways all rely on comparisons between tobacco products or product data to inform regulatory decisions. While DNCS has the most experience with product evaluations in the SE pathway, the applicability of this memorandum may extend to MRTPAs and PMTAs on a case-by-case basis for comparative evaluations and 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 a similar health risk or whether one of the two products presents greater risk. This memorandum records recent changes in DNCS thinking on frameworks for evaluating 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; DNCS will continue to develop more comprehensive approaches that enhance scientific evaluation within tobacco product reviews, specifically toxicological outcomes due to the use of a tobacco product, comparisons of the risks and hazards between tobacco products, and the management of tobacco product health risk information as reflected in the criteria and approaches that are used to evaluate product toxicology across review pathways. While this process takes into account previous approaches to risk assessment of complex mixtures, the majority of the work required to develop a 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 confirmed higher and lower HPHC yields between the new and predicate products, an understanding that HPHC measurements that are considered equivalent are, in fact, already accounted for in a risk evaluation, and use of qualitative or semi-quantitative analyses of HPHC data before QRAs are evaluated or employed by reviewers. DNCS reviewers should apply a qualitative approach first if possible, describing how potency of a chemical, the magnitude of the higher or lower mass, and the relative direction of change impact overall risk or hazard. This is achievable depending on how many HPHCs change and can be employed in evaluating HPHC comparisons between tobacco products. In this way, reviewers will only examine 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. This memorandum will be updated as the division gains additional experience and knowledge in evaluating adverse health outcomes due to HPHC (and ingredient) differences in scientific reviews, and as more scientific evidence becomes available.
REFERENCES


9. Services USDoHaH. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. Silver Spring, MD: US Food and Drug Administration, Center for Tobacco


Attachment D
Hi [Name] – I wanted to circle back with you on this. I’ve connected with CTP, and they are anticipating that both (3) and 5(a) below will be completed by June 1. In response to 5(b), Nate Sabel, who is the FDA Agency Intramural Research Integrity Officer (AIRIO), is the point of contact. The following language was added to the relevant Staff Manual Guide (SMG), and Nate responds to emails directed to that email address noted in the SMG:

The Office of Scientific Integrity within OC’s Office of the Chief Scientist will maintain an SDR POC to provide an agency-wide resource to assist with the application of the SDR policies and procedures described in this SMG. The SDR POC will be available to provide advice and recommendations related to the application of SDR-related policies and procedures, coordinate with Center ombudsman and other personnel on SDR matters, and serve as a knowledgeable contact point on SDR issues for all FDA employees with questions or concerns. Current contact information for the SDR POC may be found on the Office of Scientific Integrity website or obtained via email to SDR@fda.hhs.gov.

Also, I will be on leave next week. I will check email once a day, but if I am delayed in responding, you will know why. Have a great weekend and enjoy this fabulous weather.

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Great, thank you.

Attorney, Retaliation and Disclosure Unit
U.S. Office of Special Counsel
1730 M Street, N.W. Suite 1000
Washington, D.C. 20036
CAUTION: EXTERNAL EMAIL Do not click on links, open attachments, or provide information unless you are sure
the message is legitimate and the content is safe.

Will check and circle back.

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you
recognize the sender and know the content is safe.

Can you provide more concrete anticipated completion dates for items (3) and (5)(a) below? Also, can
you identify the person or position that FDA has established in response to (5)(b)?

Thank you,

Attorney, Retaliation and Disclosure Unit
U.S. Office of Special Counsel
1730 M Street, N.W. Suite
Washington, D.C. 20036
202-653-5161 (fax)
Hi [redacted] – FDA is happy to provide the following information on our progress to address the goals articulated in the agency’s report transmitted to OSC on Jan 8, 2021. We used the framework that provided in August 10, 2021 (at the bottom of the email trail). Please let us know if you have any additional questions.

**Progress on corrective actions**

**Goals 1 and 2:** Revision of the HPHC Memo to clarify (a) the three tiers of the new investigative method, (b) the methodology and criteria, (c) how CTP will resolve scientific uncertainty, and (c) that toxicologists have discretion to evaluate a quantitative assessment submitted with an application but that it is unlikely to produce a different outcome.

**STATUS:** Complete, as per the attached, revised HPHC memo. As previously noted, the whistleblower participated in the revision of the HPHC Memo.

**Goal 3:** Development of a decision tree to clearly lay out steps for SE/NSE determinations.

**STATUS:** A flowchart has been created but is still being verified to ensure that it comports graphically to the content and decision-tree process described in the updated HPHC memo.

**Goal 4:** Continue work to evaluate and revise the tiered qualitative/semi-quantitative process set out in the HPHC Memo.

**STATUS:** Ongoing. As this is an emerging area of regulatory science, FDA/CTP intends to continue to evaluate and refine the process discussed in this memo as it gains additional insight and experience into HPHC evaluation.

**Goal 5a:** Eliminate the ambiguity in CTP’s internal scientific dispute resolution policy and procedures (SDR-ToPP) by clarifying the circumstances under which CTP staff may initiate the SDR process.

**STATUS:** Anticipated in 2022. CTP intends to revise this ToPP as part of a larger effort to update and refine their procedures. Training on the purpose and process of the SDR ToPP (described below) has helped to address any immediate concerns about ambiguity in the meantime.

**Goal 5b:** Creating an institutionally knowledgeable point of contact for SDR issues at the agency level.

**STATUS:** Complete. FDA created such a point of contact, added that resource information to its agency-level SDR SMG, and has advertised the existence of the point of contact within CTP using the training effort described below.

**Goal 5c:** Providing substantial education and training to CTP staff involved in scientific decision-making.

**STATUS:** Complete. FDA’s review of the whistleblower allegations cited a lack of familiarity with FDA’s existing scientific dispute resolution (SDR) policies as one of the areas where remedial action was needed. To ensure that all staff at CTP who are engaged in scientific decision-making were aware of the SDR process, FDA’s Office of Scientific Integrity partnered


with CTP’s Ombudsman’s Office, and CTP’s Office of Science to design, create, and deliver a training program to improve SDR policy and process awareness among CTP staff involved in scientific decision-making. Structurally, the training consisted of two parts. The online portion had a voice-directed discussion that walked participants through the purpose and importance of both informal and formal SDR at FDA and CTP, explained the procedural pathways available to all CTP employees in detail, and provided resources and contact information (including for FDA’s new agency-wide SDR point of contact) to assist employees navigating the SDR process. The first training component is available here https://360.articulate.com/review/content/64c7a2c5-4032-4a6d-9b29-b6e35cfa8ec6/review. Questions and feedback solicited during this first portion formed the starting point for a second, live session that included a discussion of hypothetical SDR examples, clarified and refined concepts from the first session in response to questions, and offered an opportunity for CTP staff to get to know the FDA personnel who are available to them to work through SDR issues (i.e. the Agency Intramural Research Integrity Officer, the CTP Ombudsman, and the Associate CTP Ombudsman). The first section was mandatory and cataloged participation from five hundred and fifty-six CTP Office of Science staff at last count, including division directors, managers, and other supervisors as well as staff-level reviewers. The voluntary second session drew participation from over two hundred CTP scientists and review staff across two separate hour-long sessions. Feedback from participants of the training as a whole was positive and viewed as a successful effort to improve staff familiarity with the SDR process at FDA/CTP. FDA plans to use this training program as a model for expanding its SDR education to other agency components in the future.

Additional Question: whether the agency will be developing regular training for toxicology staff to facilitate standardization in evaluating SE applications.

STATUS: The ongoing evaluation of the HPHC scientific method is part of the daily work of CTP OS staff and is intended to be iterative, focused on working in teams to continue to improve FDA’s understanding of HPHCs within this novel regulatory framework. CTP continues to encourage its toxicology staff to remain engaged with these scientific issues as part of the daily duties in evaluating applications and intends for the HPHC memo to continue to evolve as CTP’s scientific understanding continues to improve.
Attachment E
Hazard Identification
All HPHC data included in marketing application and Chemistry review confirms that:
(a) HPHC data are valid
(b) HPHC data address changes in product characteristics

Relative to predicate products, are all HPHCs in new products analytically inequivalent in one direction (all higher or lower), or all analytically equivalent?

Are there analytically inequivalent HPHCs but in different directions - some higher & most lower?

Are many HPHCs analytically inequivalent in different directions with most higher?

Note: If any of the HPHCs whose levels are higher (in new vs predicate product) is a known driver of tobacco-related health risk(s), consult with your secondary reviewer before proceeding

Tier 1 Approach
Evaluation of QRA Not Necessary
Qualitative assessment of HPHC data is feasible

Tier 2 Approach
Evaluation of QRA optional;
Qualitative/Semi-Quantitative assessment of HPHC data may be feasible

Tier 3 Approach
Evaluation of QRA necessary to examine any differential risk of products under review

Is a QRA necessary for submission review?

Are all inputs & parameters appropriate (e.g. follow National Academies recommendation)?

Perform QRA assessment

Assessment sufficient?

Can other information in application address HPHC differences?

No deficiency

No deficiency

Deficiency for insufficient data to support HPHC differences

Deficiency for insufficient data to support HPHC differences
ToPP: Internal Scientific Dispute Resolution (SDR) in Regulatory Decision Making

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A. Purpose

This Tobacco Policy and Procedure (TOPP) Guide describes and defines the policies and procedures for the Center for Tobacco Products (CTP) with respect to the process of internal Scientific Dispute Resolution (SDR) at the Food and Drug Administration (FDA) is a two-tiered approach:

- Each Center is to have a Standard Operating Procedure on resolving internal scientific disputes to include requirements to ensure robust processes.
- 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 the Center-level.

This document sets forth the Tobacco Policy and Procedure (ToPP) for internal SDR processes at CTP. FDA Staff Manual Guide (SMG) 9010.1 on SDR, sets forth the Agency-level appeals process. SMG 9010.1 mandates that each Center implement certain requirements and minimum standards for SDR processes.

Center processes should foster the principle of dispute resolution at the working levels within the organization and encourage employees to start with their managers or supervisors. The Center Director must provide a written opinion on a dispute that has reached their level before it will be addressed on appeal to the Agency level. These requirements ensure that disputes will be eligible for the Agency-level appeals process. This ToPP and the Agency’s SMG 9010.1 support and facilitate diversity of opinion which is important in a science-led agency like FDA. Through these processes, eligible scientific disputes can receive a full and fair hearing at all levels of the Agency, including the Commissioner’s level.

The intent of this ToPP is to promote thoughtful and independent scientific work products; effective communication among staff, managers, and supervisors; and good relationships in reaching institutional decisions. It is also important to have a record of individual accountability
ToPP: Internal Scientific Dispute Resolution (SDR) in Regulatory Decision Making

in institutional decision-making. When differences of opinion and disputes arise, discussion is to be handled in the spirit of open communication, trust, respect and without personal animosity.

All employees and supervisors have an obligation to identify and bring to management's attention any 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. Effective informal communication throughout the regulatory decision process (e.g., while a review is being drafted) is the best approach to avoiding and resolving differences. The mere act of discussing the SDR process or initiating or being involved in the processes described in this ToPP, will not adversely affect any employee’s performance rating.

B. Coverage

This ToPP covers 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 managers or supervisors. The recommendations may subsequently be reviewed by a supervisor, Division Director, Office Director, and if applicable, the Center Director for final approval and action.

Disputes addressed through this ToPP must be scientific in nature, arise during the regulatory decision 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. Relevant to determining if a dispute is consequential to a decision is whether a different decision may have a significant impact on public health, positive or negative.

This ToPP is primarily for disputes between a CTP employee and their managers or supervisor within a particular Office. However, it could also be used, with appropriate modification by the CTP Ombuds Team on a case-by-case basis, in disputes of scientific nature 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.

All disputes that arise during decision making are not necessarily eligible for resolution under this ToPP; rather employees are encouraged to address most disputes through informal procedures for documenting and responding to different scientific and regulatory viewpoints. In
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the process of developing consensus, many scientific views may be expressed and most disagreements can be resolved quickly as the issue(s) is discussed. A memo would be included in the administrative record documenting the difference in scientific viewpoint and resolution, although it is not necessary to document every such discussion as a team works together.

The following kinds of disputes are not eligible for resolution under this ToPP: non-scientific disputes; human resource issues related to personnel disputes such as EEO, labor and employment disputes; disputes related to the rulemaking process; disputes related to CTP enforcement policy; or scientific disputes that relate to non-regulatory activities. Other pathways are available to resolve these kinds of disputes.

C. Policy

CTP managers and supervisors shall foster an atmosphere in which open discussion on evolving scientific findings and opposing views 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 encouraged that reviewers, managers, and supervisors 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 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 scientific decision, 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 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.
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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 Ombuds will maintain the administrative files on formal internal scientific disputes that are not associated with Office- or Center-level administrative files.

3. In the event of a difference of opinion or informal dispute, the managers or supervisors will advise an employee to maintain the original draft, or final document. A supervisor who does not concur with, and thus overturns, a staff-level review memorandum or recommendation must document their decision in a separate document. Both the staff and supervisory documents should be included, and remain, in the administrative file for that scientific decision. These documents do not trigger a formal dispute as per this ToPP unless the staff-level employee (not the manager or supervisor) decides to become the initiator of a formal internal SDR.

4. Written documents in an administrative file should avoid irrelevant remarks or personal comments about individuals. Once completed and archived, the documents in the file may not be edited or removed.

5. The administrative file is an electronic file. As electronic policies and procedures change, CTP will ensure that administrative files conform with, and support, the requirements of this ToPP.

The Resolution Process:

1. In the process of reaching a science-based regulatory decision, differences of opinion or disputes may arise between staff members and their managers or supervisors. When this occurs, the parties should make every effort to resolve these differences through informal means, with open and respectful discussions.
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2. If efforts to resolve differences of opinion or disputes through informal means fail, or an employee cannot accept a science-based regulatory decision because they believe it could result in significant harm to the public health, the employee may choose to become the initiator of the formal SDR process. Once an employee decides to be an initiator, they 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 their managers or supervisor and provide a copy to the CTP Ombuds Team.

4. The initiation memorandum must explain the nature of the dispute, the basis of the initiator’s position on each issue raised, additional information or evaluations, if any, that would be needed to resolve each issue raised, the initiator’s recommendation on each issue raised and the basis for each recommendation, and possible negative consequences to public health. Scientific assertions in the initiation memorandum should be supported by scientific evidence. The initiation memorandum must be added to the administrative file.

5. The CTP Ombuds 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) calendar days after receiving a complete memorandum.

6. Dispute resolution should be addressed at successively higher organizational levels, 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, or Center Director. All discussions held and decisions reached in this process will be appropriately documented in the administrative file. If the initiator is not satisfied with the decision at a particular level and chooses to continue the dispute resolution process up the chain of command, they have ten (10) calendar days after receipt of the decision to continue the process and submit an updated initiation memorandum.

7. Managers or supervisors at each successively higher level may turn to scientific, technical, and other appropriate resources to gain a better understanding of the issue(s) in dispute and to aid in addressing them. Relevant resources may be other Center, Agency, or appropriate federal government staff with related expertise, Special Government Employee (SGE), journal articles, etc. Relevant resources should rely on scientific evidence to support any conclusions and recommendations.

8. After review, discussion, and consideration of all documents and points of view from all parties to the dispute and any relevant resources they may have consulted, the managers or
supervisors at the level where the dispute is currently being reviewed must issue a decision memorandum. The decision memorandum should document the efforts made to resolve the dispute at this level of the supervisory chain and their decision(s) on the issue(s) raised and the basis for each decision. Scientific assertions in the decision memorandum should be supported by scientific evidence. The managers or supervisors will send a copy of the decision memorandum to the initiator and CTP Ombuds, no later than thirty (30) calendar days after receipt of initiation memorandum. If the manager or supervisor consulted with other individuals which are not involved in the disagreement, the manager and supervisor should issue the decision memorandum no later than forty-five (45) calendar days after receipt of the complete and eligible initiation memorandum. The decision memorandum must be added to the administrative file.

9. If the dispute has progressed up the chain of command to the Office Director, and the Office Director is unable to resolve the formal dispute, the initiator may elect to bring the matter to the next highest manager, the Center Director. The Center Director will render a decision as quickly as possible (normally within sixty (60) calendar days) after the initiator has submitted the dispute, 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 decision on the matter to the initiator, with copies to the lower-level managers or supervisors, and the CTP Ombuds. The decision memorandum must be added to the administrative file. If the initiator decides not to appeal to the Agency-level, then the Center Director’s decision is final.

10. If the parties resolve their differences at any stage of the process or the initiator chooses to withdraw the dispute, a withdrawal memorandum to this effect written by the initiator will be added to the administrative file. The initiator will provide a copy of the withdrawal memorandum to the official at the level where the dispute is currently pending and the CTP Ombuds.

11. The formal SDR process should consider any pertinent regulatory review time frames to help ensure that timelines are not exceeded unnecessarily. When a pending dispute has the potential to impact the outcome of an Agency decision or other significant Agency action, the manager or supervisor will notify the Center Director and the CTP Ombuds. As required by the Agency SMG 9010.1, while the SDR process is pending, work on a final regulatory decision will continue up to and including the actual issuance of the regulatory decision 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.

12. Regardless of an ongoing SDR process, the Center Director may decide to move forward with a decision, including issuance of a final regulatory decision that is subject of the dispute. The memorandum including a decision and rationale will be placed in the
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administrative file. If an accelerated timeline is needed for dispute resolution because of a significant action due date or imminent public health concern, all parties should be notified and the CTP Ombuds should determine if the dispute resolution process could be accelerated. At the discretion of the Center Director, the CTP Ombuds may notify an affected company if a final regulatory action related to that company’s submission will be delayed because of a pending dispute.

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 factors, an initiator may go directly to the Center Director to request expedited review of the dispute, rather than moving through each successive level of managers or supervisors review, so that the Center Director may decide within a condensed timeframe.

Appeal to the Agency-Level:

If the initiator is not satisfied with the Center Director’s decision, and the Center-level process is thus exhausted, the initiator may appeal to the Agency-level Dispute Resolution Process. The Agency SMG 9010.1 requires that this be done within ten (10) calendar days of receiving the Center Director’s written decision.

E. Guidelines

This ToPP describes procedures for the documentation and resolution of internal scientific disputes among CTP employees, managers, or supervisors, who review, analyze, consult on, or otherwise provide input associated with science-based regulatory decisions that are related to both Center- and Agency-level missions. 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.) All CTP employees involved in a dispute and its resolution are to document their position and how it differs from the Center. This ToPP is intended to address serious internal scientific disputes that could have a significant negative impact on public health.

This process is for internal CTP use to address disputes in the scientific process; it is not applicable, for example, to scientific disputes between CTP and external stakeholders, such as the tobacco industry or public health advocates.

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, are 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 Ombuds.

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 (Ombuds) evaluates 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. They should notify the initiator and supervisor whether or not the memorandum is complete and eligible. The CTP Ombuds is also responsible for being knowledgeable about the two-tiered (CTP and Agency) SDR processes in order to confidentially counsel potential initiators who approach the Ombuds, and to help filter out personnel-related issues. At any point in the dispute process, the Ombuds may be approached by the initiator, or any other persons involved in the dispute, for consultation. Once the formal CTP process is initiated, the Ombuds will maintain the administrative file of the dispute.

Managers or Supervisors: CTP managers or supervisors are responsible for implementing both informal and formal internal 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 managers or supervisors 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.
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**Center Director:** The CTP Center Director 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 decisions on disputes that have advanced 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**

This section will define any special or unusual terms if applicable.

**H. References**

SMG 9010.1 FDA Staff Manual Guides, Volume IV – Agency Program Directives – Scientific Dispute Resolution at FDA: https://www.fda.gov/media/79659/download

21CFR10.70: Documentation of Significant Decisions in Administrative File:


**I. Appendix**

This section will include forms, samples, or checklists if applicable.

**J. Summary of Changes**

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