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Memorandum

To:	Discipline Reviewers – Division of Individual Health Science (DIHS), Division of Product Science (DPS), and Division of Nonclinical Science (DNCS)
From:	Division Immediate Offices of DIHS, DPS, and DNCS
Subject:	Clarification of PMTA Review Responsibilities Regarding HPHC Aerosol and Smoke Yields and Clinical BOE Data Among DIHS, DPS, and DNCS

Digitally signed by Kimberly R. Lindsey -S
Date: 2021.03.02 08:47:58 -05'00'

Digitally signed by Matthew J. Walters -S3
Date: 2021.03.04 09:28:44 -05'00'

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Date: 2021.03.04 10:40:16 -05'00'

Background

In the course of developing several scientific reviews for premarket tobacco product applications (PMTAs), the leadership and reviewers from DIHS, DPS, and DNCS have identified areas of overlap in scientific reviews between the behavioral and clinical pharmacology (BCP) discipline within DIHS, the chemistry discipline within DPS, and the toxicology discipline within DNCS. Specifically, overlap in the review of studies and data pertaining to machine-generated harmful and potentially harmful constituent (HPHC) aerosol and smoke yield[1] and clinical biomarkers of exposure (BOE) has led to the need for clarification of review roles and information transfer among scientific staff from BCP, chemistry, and toxicology who each evaluate, summarize, and analyze some of the same nicotine and non-nicotine HPHC yield and clinical BOE data, including relevant data regarding comparison products, reported in submitted PMTAs. In the interest of clarity and efficiency in completing scientific reviews, this memorandum delineates the review responsibilities and information transfer of respective disciplines within DIHS, DPS, and DNCS in the case of PMTAs that include studies and data on machine-generated HPHC yield and BOE.

Assessment

Studies and data pertaining to machine-generated HPHC yield and clinical BOE represent a potential area of overlap for BCP, chemistry, and toxicology. These overlapping data support each discipline's review and conclusions in distinct, yet complementary ways. For example, all three disciplines (BCP, chemistry, and toxicology) will review HPHC yield data of the new and comparison products: 1) chemistry will assess HPHC yields for new and comparison products to determine whether they are analytically equivalent, deferring analytically inequivalent data to toxicology, 2) toxicology will review analytically inequivalent HPHCs to determine their overall impact on product toxicity, if needed, and 3) BCP will review and compare nicotine yield data between the new and comparison products and use these comparisons to draw conclusions regarding the relative nicotine exposures and abuse liability of the new tobacco products. These complimentary discipline reviews allow the TPL to draw conclusions on

[1] This memo pertains to studies and machine generated HPHC aerosol and smoke yield data submitted in support of PMTAs for inhalable tobacco products including combusted and non-combusted tobacco products.

the potential toxicity and HPHC exposure of the new tobacco products compared to other comparison products, thereby facilitating the TPL's determination of whether the new tobacco products are appropriate for the protection of public health.

While each discipline brings its own perspective to the review of the same data, discipline-specific perspectives should be discussed in small group settings (i.e., comparison products and toxicant exposure small group meetings) during scientific review to facilitate information transfer between disciplines (see the PMTA Scientific Review Job Aid Section 3.8, Information flow between disciplines). Sharing discipline-specific perspectives in small group meetings during the scientific review process will permit BCP, chemistry, and toxicology to ensure that HPHC yield and clinical BOE information is evaluated by the appropriate discipline(s), that all relevant material is presented in the appropriate discipline's review, and that all applicable disciplines are represented in any HPHC- or BOE-related deficiencies. These small group meetings can also be used to facilitate chemistry's normalization of HPHC yields[2] and the transfer of information related to this process.

The areas of overlap and the delineation of review responsibilities with respect to HPHC yield and clinical BOE data (studies sponsored by the applicant and studies included in an applicant-submitted literature review) are listed below.

BCP will review the following:

- Clinical studies[3] examining potential BOE following actual use of the new and comparison products.
    - If nicotine BOE data or discussion is lacking, BCP could potentially issue a deficiency, depending on whether the totality of submitted data addresses user exposure to nicotine. (Note: OS will not be issuing deficiencies regarding the lack of non-nicotine BOEs.)
    - Study design strengths and weaknesses, study population
    - Significant differences in BOE between comparison product(s) and new tobacco product(s)
    - Impact of use behaviors on BOE (e.g., exclusive v. dual use)
    - Role of nicotine BOE to impact future use and addiction
    - Use BOE to help predict effects on cessation, complete switching, dual use
- The machine-generated HPHC aerosol and smoke yield testing regimen[4] to determine if the applicant's justification for the chosen regimen is representative of human use behavior (e.g., human puff topography study, published literature).

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[2] Normalization of HPHC Yields between new and comparison products in ENDS PMTAs (September 10, 2020)

[3] PubMed Clinical Study Definition: A work that reports on the results of a research study to evaluate interventions or exposures on biomedical or health-related outcomes. The two main types of clinical studies are intervention studies (clinical trials) and observational studies.

[4] Although BCP reviewers will review the applicant's overall HPHC testing regimen, reviewers will only evaluate nicotine yield data.

    - If BCP determines that justification to support the HPHC aerosol testing regimen is missing or insufficient, BCP could potentially issue a deficiency, depending on whether the totality of submitted data addresses user exposure to nicotine.
- Machine-generated nicotine yield data of the new and comparison products to determine its impact on abuse liability.[5]

Chemistry will review the following:

- Methodology of the HPHC regimen used to generate aerosol and smoke yields of the new and comparison products as well as the methodology used to detect specific analytes.
- Evaluation of the suitability of the methods for their intended purpose including validation of the methods and the quantification of expected variability of the method findings (separation of the analytical error from testing error and product to product variances, where provided). This analysis provides important information about the quality of the data and the degree to which decisions about HPHC yield should considered.
- The accreditation of laboratory, sampling (i.e., sample size, sample identification, number of batches), pass/fail criteria, and whether the information provided about the testing is adequate.
- HPHC yields for new and comparison products (as applicable).
    - Evaluation of HPHC yields will follow TOST: "Equivalence Testing for SE Evaluations" and "Addendum to February 24, 2017, Equivalence Testing for SE Evaluations Memo."
    - After reviewing the applicant's HPHC yields and conducting TOST analysis, analytically inequivalent HPHCs are referred to toxicology for further evaluation and the final decision on these differences is within the purview of toxicology for the HPHC yields. All tables are sent to toxicology and the chemist and toxicologist work together to address any differences in understanding.

Toxicology will review the following:

- Prioritize analytically inequivalent HPHCs referred to toxicology by chemistry and assess overall product toxicity relative to data from comparison products. In this evaluation, toxicology reviewers have the discretion to additionally review all HPHC aerosol and smoke yield data (including nicotine) to determine their impact on overall product toxicity if their evaluation requires it.
- All nonclinical BOE data from the new and comparison products. The most common such BOE is anticipated to be cotinine.
- Clinical studies[3] examining potential BOE following actual use of the new and comparison products.
    - Evaluate the potential impact of the BOE outcomes from the toxicology perspective.

Conclusion

DIHS, DPS, and DNCS seek to clarify and delimit the scope of discipline reviews to ensure consistency in content across reviews. In addition, a clearer delineation of review responsibilities pertaining to

[5] For ENDS, BCP will not review free nicotine yield because the buffering capacity of the lungs makes free nicotine inconsequential for BCP.

machine-generated HPHC yield and BOE outcomes will save time, making the process more efficient. BCP, chemistry, and toxicology should hold small group discussions on this topic throughout the review process to facilitate achievement of this goal.