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U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	Discipline Reviewers -- Division of Population Health Science (DPHS) and Division of Individual Health Science (DIHS)
From:	DIHS and DPHS Immediate Offices
Date:	March 30, 2022
Subject:	Clarification of PMTA Review Responsibilities between DPHS and DIHS

Background

In past scientific reviews of Premarket Tobacco Applications (PMTAs), scientific reviewers from several disciplines each evaluated, summarized, and analyzed the same data from a PMTA leading to redundancy and potential confusion for the TPL. In the interest of clarity and efficiency, this memorandum delimits the review responsibilities of respective disciplines within DPHS and DIHS. Additional information can also be found in instructions in the PMTA review template.

Assessment

There are several areas of overlap within and between disciplines in the Division of Population Health Sciences (DPHS) and the Division of Individual Health Science (DIHS). When it is beneficial to the review team for several disciplines to review the same data, which are assessed to evaluate scientific outcomes and evidence, discipline-specific perspectives can be shared in small group meetings before moving to written reviews. The relevant disciplines will identify a primary discipline to conduct a full review of the study design, methods, outcomes, analysis, and limitations of the study; if there is not agreement on which discipline should be primary discipline, Division leadership or the TPL can weigh in. If the study's findings are necessary to support overall conclusions in another discipline's written review, reviewers from the non-primary discipline may incorporate a brief summary based on the primary reviewer analysis and refer to the primary discipline's review. The areas of overlap and the delineation of review responsibilities for the applicant sponsored submission are listed below.

1. Understanding Tobacco Use Behavior – A PMTA often includes studies which examine use behaviors and provide data to support the probability that current tobacco users would use the new product. These may be clinical studies in which current tobacco users are selected and assigned (possibly randomized) to tobacco use groups, (e.g., use new product, use current product, use no product) and may be followed over time (e.g., up to 6 weeks) to determine the proportion of current tobacco users who use the new product among other tobacco use behaviors. PMTAs may also include survey data and observational studies which record (retrospectively or prospectively) tobacco use behavior among current tobacco users or nonusers over time. In observational studies, participants are not assigned to use of a tobacco product, but rather the existing tobacco use behaviors among individuals in the study are observed and recorded. Additionally, quantitative tobacco product perception and intention studies describe precursors to tobacco use based on survey question responses, sometimes after viewing promotional, marketing, or other descriptive material. These data sources all address the larger issue of understanding tobacco use behaviors in the context of the new product.

Delineation of Review of Tobacco Use Behavior Studies:

a. Behavioral and Clinical Pharmacology (BCP) in DIHS will be the primary discipline to evaluate use behavior data collected from an experimental or actual use clinical study design where tobacco product use is assigned to participants. BCP reviewers will draft deficiencies related to abuse liability.

   BCP reviewers will not evaluate observational data or survey studies regarding tobacco use in the population. However, BCP reviewers may include a summary of the conclusions and limitations from observational or survey data (from Epidemiology) in their review to support an overall conclusion regarding use behavior in the population.

b. Epidemiology in DPHS will be the primary discipline to evaluate use behavior studies with observational designs (i.e., non-clinical studies). Epidemiology reviewers will draft deficiencies related to observational studies on tobacco use behavior including switching behavior, which may include likelihood of youth use from the Epidemiology or Social Science review.

   Epidemiology reviewers will not evaluate clinical studies of tobacco use behavior in which tobacco product use is assigned to participants. However, Epidemiology reviewers may include a summary of the conclusions and limitations from clinical use data (from BCP) in their review to support an overall conclusion regarding use behavior in the population.

c. Social Science in DPHS will be the primary discipline to evaluate precursors of use derived from studies investigating perceptions of or intentions to use the new product to inform likelihood of new product use. Social Science reviewers will draft deficiencies based upon submitted perception and intention studies related to likelihood of use of the new products among youth and never users, which may be incorporated in Epidemiology deficiencies.

   Social Science reviewers will not evaluate actual use behavior data, except in cases where the applicant has attempted to pair intentions to use data with actual use data to support an overall interpretation of the data (e.g., development or use of algorithms to predict use rates from intentions data).

2) Health Risk/Biomarker Studies – A PMTA may include studies of the potential health risk of new tobacco product use. Studies may directly estimate risk of disease such as the cardiovascular endpoint atherosclerosis or indirectly measure risk to human health through estimation of biomarkers of exposure (BOE) and biomarkers of potential harm (BOPH) in association with product use. Similarly, these studies may directly assign current tobacco users to use of new products, or they may be designed to observe and record direct or indirect health impacts of tobacco product use among participants selected from the population. Both experimental and observational studies may include reports of adverse events experienced by participations during the study. This information may also be relevant to review, especially when viewed in concert with other adverse exposure reports.

   Human health risk data are often derived from clinical studies in which tobacco product use is assigned and participants are followed for a period (e.g., up to 6 weeks). Health outcomes are ascertained or biological samples and clinical measurements (e.g., urine, blood, spirometry, blood pressure) are taken from participants during the study and compared by tobacco use category or by pre- and post-clinical study completion. BOE measured may include nicotine and nicotine metabolites, polycyclic aromatic hydrocarbons such a 1-hydroxypyrene, volatile organic compounds such as 2-cyanoethylmercapturic

acid, and heavy metals like lead or nickel. BOPH may include markers of inflammation or oxidative stress like C-reactive protein and fibrinogen and isoprostanes. Clinical measurements such as heart rate, blood pressure, and forced expiratory volume (measure of lung function) may also be informative and measured in these types of clinical studies.

Similarly, observational and survey studies may sample tobacco product users from the population and directly measure health outcomes or clinical or pre-clinical disease states or infer potential human health effects using biomarkers. For example, although data are limited, applicants may submit observational studies of new product use (e.g., ENDS) and adverse health outcomes such as cardiovascular disease and respiratory health. Observational studies (e.g., PATH, NHANES) of the human health effect of new product use may also measure BOE or BOPH and compare by tobacco user group. These data also inform the potential toxicity and risk to human health upon use of the new product.

Delineation of Review of Biomarker Studies:

a. Behavioral and Clinical Pharmacology (BCP) in DIHS will evaluate BOE data derived from clinical studies in which tobacco product use is assigned to participants (i.e., actual use/ experimental switching studies). BCP reviewers will draft deficiencies related to abuse liability.

b. Medical in DIHS will evaluate direct measures of clinical or pre-clinical disease states or BOPH data derived from clinical studies in which tobacco product use is assigned to participants (i.e., actual use/experimental switching studies). Medical will also evaluate all adverse events reports included in either experimental (clinical) or observational studies submitted by the applicant. Medical reviewers will draft deficiencies related to adverse events and clinical effects in study data.
c. Epidemiology in DPHS will
    i. evaluate BOE and BOPH data derived from observational studies in which new product use is not assigned. For BOE and BOPH data from observational studies, Epidemiology reviewers will draft deficiencies related to the potential health impact of new tobacco product use, including switching.
    ii. evaluate studies of pre-clinical or clinical disease states derived from observational studies in which new product use is not assigned. For pre-clinical or clinical disease states derived from observational studies, Epidemiology reviewers will draft deficiencies related to the potential health impact of new tobacco product use, including switching.

3) Public Health Impact Models (PHI Models) PMTAs may include a mathematical model of the potential influence the introduction of the new product may have on population health as a whole. Population health models include certain underlying data on prevalence of tobacco use, assumptions regarding the proportion of current and new tobacco users who would begin to use the new product under different scenarios, the rates of tobacco related disease and death, and the time period over which the new product may influence the population. OS reviewers consider the validity of the underlying data, particularly PHI model data that are derived from studies included in the PMTA, the assumptions, and the overall results or conclusions of the model.

Delineation of Review of Public Health Impact Models*:*

a. Epidemiology in DPHS will evaluate the underlying data, assumptions, and results of the PHI Models.

i. The Epidemiology reviewer may consult with other discipline reviewers regarding the quality and overall results of applicant provided data, or consult on resources used as inputs (e.g., Social Science) to the PHI model.

b. Statistics in DPHS[1] may be asked to consult regarding the underlying mathematical procedures and construct when requested by the Epidemiology reviewer.

Conclusion

DPHS and DIHS endeavor to clarify and delimit the scope of review for respective division discipline reviews to ensure consistency in scope and content across reviews and reduce redundancy and possible confusion for the TPL integration. The PMTA review process is designed to be open and collaborative and discipline reviewers are encouraged to discuss their respective review pieces to support the most scientifically well-grounded conclusions and to ensure all information is presented across the respective reviews without significant duplication. Small group discussions throughout the review process will facilitate achievement of this goal, and targeted written evaluations by the primary review discipline referenced by other disciplines will save time for the review team.

[1] Statistics in DPHS may also provide statistical consulting on review issues other than Public Health Impact Models to other disciplines as requested.