Supplementary Table 4. Discussion Questions for Presenters and Panelists

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| **In the context of tobacco regulation and with respect to tobacco-related mortality and morbidity, including cancer, nonmalignant pulmonary disease, and cardiovascular disease:** |
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| 1. Can biomarkers of potential harm offer a valid scientific prediction of longer-term clinical outcomes?
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| 1. What criteria, such as biomarker characteristics and pathophysiology, should be considered when identifying, evaluating, and selecting biomarkers of potential harm?
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| 1. What are the currently well-established biomarkers of potential harm? What biomarkers have been identified as having the potential to be validated biomarkers of potential harm contingent upon future research and development?
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| 1. In clinical trials, surrogate endpoints are used when the clinical outcomes require a very long time to study or when the clinical benefit of improving the surrogate endpoint is well understood. However, rigorous testing is needed to show that these surrogate endpoints can reliably predict, or correlate with, clinical benefit. In other regulatory settings, what validated surrogate endpoints have been used to predict longer-term clinical outcomes? What are the lessons learned from the use of surrogate endpoints?
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| 1. What shorter-term clinical endpoints such as lung function tests could also serve as biomarkers of potential harm for longer-term clinical outcomes?
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| 1. Of the currently identified biomarkers of potential harm, what are their strengths and limitations in terms of their measurement?
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| 1. What factors (e.g., interindividual variation, potential confounders) should be considered in the data analysis and interpretation of biomarkers of potential harm?
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| 1. What considerations should be taken into account when selecting biomarkers of potential harm to compare potential health risks across different classes of tobacco products?
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| 1. What studies have been conducted using biomarkers of potential harm to compare potential health risks across different classes of tobacco products?
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| 1. What biomarkers of potential harm can be considered translational (i.e., might be useful to compare across clinical and nonclinical studies)?
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| 1. What are the strengths and weaknesses of using Mode of Action analysis of harmful and potentially harmful constituents (HPHCs) in identifying biomarkers of potential harm?
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| 1. How can advancements and findings from newer areas of research such as genomics, metabolomics, and proteomics be applied to the evaluation of the potential health risks of tobacco products in clinical and nonclinical studies? What are the challenges to interpreting and applying data from these newer technologies?
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