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Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2025-D-3217, "Use of Bayesian Methodology in Clinical Trials of Drugs and Biological Products; Draft Guidance for Industry"

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the world's oldest and largest scientific organization dedicated to cancer research, education, and collaboration, we appreciate the opportunity to provide comments on FDA's draft guidance entitled "Use of Bayesian Methodology in Clinical Trials of Drugs and Biological Products." We commend the Agency for issuing this comprehensive guidance, which represents an important step toward enhancing clarity and consistency in the regulatory evaluation of Bayesian designs and analyses.

Bayesian methods are increasingly used in oncology drug development, including adaptive trial designs, borrowing of external data, pediatric extrapolation, dose optimization, and rare disease research. The AACR supports FDA's efforts to provide structured guidance that promotes methodological rigor while maintaining appropriate flexibility to foster innovation and patient-centered development strategies.

As a consortium of academic clinical investigators, industry professionals, and patient advocates committed to advancing cancer research, we respectfully offer the following comments and recommendations to strengthen the draft guidance:

1. Clarification on When Bayesian Approaches Are Appropriate for Primary Efficacy Analyses
The AACR appreciates the guidance's recognition of the expanding role of Bayesian methods in clinical development. Additional clarification surrounding the role of Bayesian approaches in confirmatory clinical trials may enhance transparency and predictability. We believe greater clarity about the relationship between posterior probability–based decision rules and traditional frequentist operating characteristics would help ensure consistent interpretation across development programs. Additionally, clarifying relevant considerations, such as disease rarity, unmet medical need, ethical constraints, and the strength and relevance of external evidence, may enhance predictability while maintaining high evidentiary standards.

2. Calibration to Type I Error and Success Criteria
The AACR appreciates that the guidance clearly distinguishes between Bayesian designs calibrated to control Type I error and those that are not. Given the importance of Type I error control in confirmatory trials, additional clarification regarding when calibration is expected, when direct interpretation of posterior probability may be appropriate, and considerations for establishing posterior probability thresholds at interim versus final analyses would be helpful. It would also be beneficial to have more discussion about multiplicity across several primary or key secondary endpoints, especially when Bayesian decision rules are in use.

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3. Borrowing External or Nonconcurrent Data
The AACR appreciates the discussion concerning how to perform dynamic borrowing. However, it would be helpful to receive additional clarification on the distinction between external concurrent and nonconcurrent controls, expectations for addressing temporal drift in platform trials, and whether borrowing is being applied to treatment effects or to individual study arms.

As real-world evidence and hybrid control arms are increasingly seen in oncology, the AACR would also encourage additional discussion on methods for adjusting for covariates, such as propensity score approaches, in addition to Bayesian discounting when patient-level external data exists. Furthermore, we would welcome further elaboration on the REBYOTA example included in the guidance, which relied on a Bayesian model that utilized data from a previous Phase 2 placebo-controlled study to support efficacy claims in a subsequent Phase 3 study. Further context regarding the rationale for this approach, such as the similarity of the trial designs, whether the identical control population was employed, the understanding of disease progression, the robustness and quality of the earlier evidence, and the comparability of the study populations, would be especially beneficial.

The AACR would also appreciate more information regarding the specific parameters influenced by the prior. For example, whether the prior was constructed on the treatment effect parameter or on one or more treatment arms separately would offer valuable insight. This added detail would increase transparency and support improved Bayesian borrowing methods in cancer drug development.

4. Time-to-Event Endpoints in Oncology
The AACR appreciates the broad applicability of guidance across therapeutic areas. The AACR believes that including additional discussion on specific time-to-event endpoints, such as model selection, prior specification for hazard ratios, cure fraction considerations, and simulation across plausible accrual scenarios, would strengthen its relevance to oncology development.

5. Prior Specification and Discounting Methods
The AACR appreciates the discussion of various discounting approaches. However, it would be useful if the guidance provided a structured framework for selecting an appropriate borrowing approach. The AACR recommends that the guidance provide decision principles based on the number and similarity of external data sources; clarify expectations regarding pre-specification of mixture weights; and encourage comparative operating characteristic assessments when multiple approaches are plausible.

Further clarification regarding effective sample size estimation methods would also be beneficial, particularly when robust mixture priors are used. We also suggest clarifying terminology when discussing prior Type I error conflict. In sections addressing potential inflation of Type I error when borrowing on the effect, it may be helpful to specify “treatment effect” to avoid ambiguity.

6. Expert Elicitation
The AACR appreciates the inclusion of expert elicitation as a consideration in Bayesian analysis. However, when empirical data are limited, expert-informed priors may be critical. Additional guidance on elicitation practices, documentation standards, translation of elicited beliefs into statistical priors, and

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management of expert disagreement may enhance rigor and transparency.

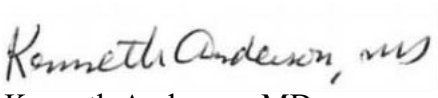
7. Operating Characteristics and Simulation Expectations
The AACR commends the Agency for emphasizing the importance of simulation. However, it would be helpful if the guidance defined minimum expectations. Additional clarity would be helpful regarding minimum scenario exploration, including prior–data conflict and temporal drift; required summary metrics, such as decision rates, bias, mean squared error, and coverage; diagnostic assessments for dynamic borrowing calibration; and clarification of conditional versus unconditional operating characteristics.

8. Computational Diagnostics and Reporting
The emphasis on algorithm reliability and convergence is appreciated. Specifying minimum expectations for convergence diagnostics, posterior predictive checks, and reproducibility documentation would promote consistency across submissions and strengthen regulatory confidence in Bayesian analyses.

Finally, the AACR appreciates the detailed expectations for documentation when Bayesian methods are used. Additional clarification regarding which documentation elements are most critical for regulatory review, particularly when well-established models and standard priors are used, may help support consistent and proportional implementation while maintaining scientific rigor.

Conclusion
The AACR appreciates FDA's thoughtful approach to this important guidance. Bayesian methodologies are central to advancing innovative and efficient oncology drug development. We support the Agency's efforts to clarify regulatory expectations and encourage continued refinement of the guidance to enhance transparency, predictability, and methodological rigor. We thank FDA for its continued leadership in regulatory science and look forward to ongoing collaboration.

Sincerely,



Kenneth Anderson, MD
Chair, Regulatory Science and Policy Subcommittee
The American Association for Cancer Research

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