American Association for Cancer Research®
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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-1757 — "Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development"**

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 advancing cancer research, prevention, and treatment, we appreciate the opportunity to comment on the U.S. Food and Drug Administration (FDA) draft guidance, "Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development."

AACR has frequently partnered with FDA to advance novel approaches to dosage optimization in oncology drug development and commends the Agency for issuing this timely guidance to bring clarity and consistency to radiopharmaceutical therapy (RPT) development. The draft appropriately underscores the need for multidisciplinary, fit-for-purpose strategies to define optimal dosing that maximize efficacy while minimizing toxicity. It also builds on insights from the 2024 FDA–AACR Workshop on *Optimizing Dosages for Oncology Drug Products*, which focused on targeted therapies and immunotherapies, while acknowledging the additional complexities and uncertainties unique to RPTs.

AACR remains committed to collaborating with FDA to advance rational dosing strategies in oncology. The comments below, reflecting perspectives from academia, industry, and patient advocacy, provide additional considerations to strengthen the guidance's clarity, scientific rigor, and feasibility.

1. Considerations for Exceeding EBRT Organ-Tolerance Limits
AACR agrees that evaluating dosages exceeding established external beam radiation therapy (EBRT) organ-tolerance limits may be appropriate in specific contexts, provided such proposals are supported by robust data and oversight. To enhance transparency and efficiency, FDA could describe additional data types (i.e., beyond clinical safety and efficacy results) that may justify such dosing, including model-based predictions or translational findings.

AACR also recommends acknowledging that the benefit–risk calculus may differ across curative-intent and palliative settings, and even among individual patients. Some early-stage populations may accept greater risks for potential therapeutic benefit. While AACR supports limiting such dose-escalation trials primarily to patients with limited life expectancy, flexibility should remain for scientifically justified exceptions. Explicit informed-consent language addressing potential delayed or cumulative organ toxicity, paired with independent data monitoring committee oversight, would safeguard participants while enabling exploration of therapeutic windows and individualized benefit–risk assessment

2. Expand Guidance on Long-Term Toxicity Monitoring and Post-Marketing Follow-Up
AACR commends FDA's emphasis on evaluating delayed and cumulative toxicities associated with RPTs. The final guidance could further strengthen implementation by highlighting opportunities to integrate patient-reported outcomes and real-world evidence to assess long-term functional and quality-of-life effects beyond traditional clinical measures.

Clarifying expectations for the duration and scope of long-term safety monitoring would also be valuable. Completing full follow-up before proceeding to subsequent trial phases could unnecessarily delay development; therefore, FDA might consider outlining criteria for determining appropriate follow-up durations and the use of validated early clinical surrogates of late toxicity. Routine pharmacovigilance, registry-based studies, and long-term observational efforts remain critical tools for detecting delayed adverse events and ensuring sustained patient safety.

3. Clarify Dose-Escalation Approaches in Early-Phase Studies
AACR agrees that dose-escalation design is critical to patient safety and data quality in early-phase RPT studies. The guidance appropriately notes that "methods of overdose control in standard dose-escalation designs are not sufficient to prevent cumulative overdosing." To enhance implementation, FDA could provide examples of acceptable alternative designs (e.g., adaptive, Bayesian, or model-based approaches) that explicitly account for cumulative radiation exposure and delayed toxicities. Clearer direction on these designs would help sponsors align early-phase strategies with the unique pharmacologic and radiobiologic characteristics of RPTs.

4. Support Site Competency and Infrastructure for RPT Trials
Given the complexity of RPT administration and monitoring, AACR encourages FDA to emphasize investigator training and institutional readiness. Standardized readiness checklists and educational resources could help ensure sites maintain appropriate infrastructure, radiologic safety procedures, regulatory compliance, isotope-handling protocols, and imaging capabilities. Partnering with professional societies and academic institutions to disseminate such tools would support consistent study quality and participant protection across diverse research environments.

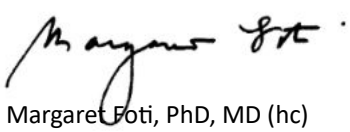
5. Expand on the Role of Dosimetry and Other Data in Dosage Decision-making
AACR agrees that radiation dosimetry provides an essential data point for dose optimization but cautions that inherent variability across methods may limit comparability. The final guidance could underscore that dosing decisions should consider dosimetric results in the context of all available evidence. AACR supports FDA's recommendation that sponsors submit detailed dosimetry protocols and justifications for administered-activity levels. Establishing minimum reporting standards for parameters such as imaging acquisition, reconstruction, segmentation, calibration, and model assumptions would promote reproducibility and data harmonization. Flexibility in approach is also key: implementation feasibility will vary depending on isotope characteristics and available imaging technology. FDA could clarify that the use of scientifically justified surrogate analogs is acceptable when direct imaging is technically infeasible. Furthermore, while micro-scale dosimetry and molecular imaging biomarkers remain emerging tools, FDA's support for developing validated, standardized methodologies will accelerate their incorporation into clinical research and patient-specific dosing paradigms.

6. Consider the Role of Incomplete Absorbed Dose Data
AACR agrees that sponsors should make every reasonable effort to document previous radiation exposure to critical organs for participants who have received previous EBRT or RPT, as such data can inform cumulative-dose assessments. However, complete historical records are often unavailable or inconsistent, particularly for patients treated at multiple centers, and mandating their documentation could complicate trial conduct. In these cases, incomplete dose information should not preclude enrollment when clinical organ-function assessments confirm eligibility. Clinical evaluation of organ function remains a more practical and reliable indicator of safety than theoretical cumulative-dose estimates and should guide eligibility and ongoing safety monitoring when prior dose data are limited.

Conclusion
AACR commends FDA's leadership in advancing the science of dose optimization for radiopharmaceutical therapies. By refining expectations in key areas, such as follow-up duration, dose-escalation methodology, site readiness, and use of diverse data sources, the Agency can promote both innovation and patient protection. AACR looks forward to continued collaboration with FDA and other stakeholders to ensure that radiopharmaceutical development proceeds with scientific rigor, transparency, and patient-centered focus.

Sincerely,

Lillian Siu, MD, FRCPC
President



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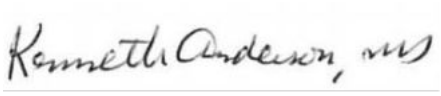

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Chair, Regulatory Science and Policy Subcommittee