



Dockets Management  
U.S. Food and Drug Administration (FDA)  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

**Re: Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development (FDA-2025-D-1757)**

To Whom it May Concern:

Friends of Cancer Research (*Friends*) powers advances in science and policy that speed life-saving treatments to patients. *Friends* is committed to accelerating cutting-edge cancer care that extends and improves quality of life for patients. To accomplish this, we leverage groundbreaking collaborations, generate scientific evidence, and integrate patient input to shape public policy.

*Friends* appreciates the opportunity to provide comments on the draft guidance, “*Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development.*” This guidance represents an important step toward clarifying FDA’s expectations for radiopharmaceutical therapy (RPT) dosing strategies, balancing therapeutic benefit with patient safety and supporting the development of innovative RPTs. Throughout this document we use the term “dosage” to refer to the dose and schedule to align with FDA’s use of the term.

RPTs present unique challenges in dosage optimization due to their combination of pharmacologic targeting and systemic radiation delivery, potential for delayed or cumulative toxicities, and the evolving understanding of organ-specific tolerances. RPT dose optimization is still at an early stage of evidence generation, highlighting the need for harmonized data, long-term toxicity monitoring, validated biomarkers, and multidisciplinary collaboration.

We offer the following considerations in response to the draft guidance, with a focus on practical implementation, safety, and data-driven dose optimization.

**1. Dose Escalation Beyond External Beam Radiation Therapy (EBRT)-Derived Limits**

The draft guidance appropriately emphasizes the importance of incremental dose escalation and the need to account for cumulative radiation exposure. This framework establishes a valuable baseline for balancing therapeutic potential with patient safety. Additional clarification in certain areas, however, would help sponsors translate these principles into consistent, scientifically justified approaches across development programs.

We recommend that FDA:

- Clarify that organ-specific dose limits derived from EBRT may not be directly applicable for RPTs due to differences in radiation distribution, biological effects, and retention times. Clear expectations should specify when sponsors may justify alternative organ-specific dose thresholds based on preclinical data, early human evidence, or mechanistic modeling.
- Provide more detailed guidance on establishing cumulative dosage limits that account for patient-specific characteristics, including prior therapies, comorbidities, radiosensitivity, and expected survival. Flexible yet scientifically grounded boundaries would support adaptive and patient-centered dose escalation in monitored populations.
- Encourage structured, incremental dose-escalation frameworks that incorporate per-cycle activity, total cumulative activity, and inter-cycle timing. The FDA could clarify how emerging data from early cohorts may inform mid-trial dose adjustments under appropriate oversight.
- Encourage sponsors to engage early with FDA to justify proposed dose-escalation strategies using integrated preclinical, clinical, and modeling data. Outline expectations for documentation of dosage selection decisions, including how sponsors weigh potential efficacy against acute and delayed toxicities. Clear criteria for rationale documentation would support consistent regulatory review.

## **2. Safety Monitoring and Early Biomarkers**

We appreciate FDA's recognition of the importance of safety monitoring, long-term follow-up, and the identification of early toxicity indicators in RPT development. RPTs differ from conventional therapies in their timing and manifestation of toxicities, necessitating proactive, sustained monitoring to capture both acute and delayed events. Expanding guidance on how early biomarkers and longitudinal data should be incorporated into study design would enhance the utility and consistency of safety data across programs.

We recommend that FDA:

- Encourage the use of early biomarkers to predict delayed toxicities and guide adaptive dosing decisions. These biomarkers should be prospectively defined, with clear thresholds that prompt dose modification, temporary holds, or closer monitoring.
- Provide guidance on integrating acute toxicity data with cumulative or delayed toxicity signals to inform dose decisions across multiple treatment cycles. This integration should account for patient heterogeneity and prior therapies.
- Emphasize the need for long-term follow-up to capture delayed organ-specific toxicities, which may manifest months or years post-treatment. FDA could consider recommending minimum durations or intervals for follow-up assessments to ensure comprehensive toxicity characterization.

- Clarify how prospectively defined early biomarkers may be used as exploratory safety endpoints in early-phase studies to enable safe, data-driven dose escalation and support adaptive trial designs.
- Recommend that sponsors engage early with FDA, such as during pre-IND or other early-stage meetings, to discuss the validation and use of biomarkers as predictors of toxicity, including the evidentiary standards that would support their inclusion in regulatory decision-making.

### **3. Dosimetry Standards and Data Collection**

*Friends* commends FDA for highlighting the role of dosimetry as a foundational element of RPT development. Establishing standardized approaches to dosimetry and data collection will be essential to building a reliable evidence base, enabling cross-trial comparison, and improving dose-response modeling. While robust dosimetry practices are critical to advancing the field, the current variability in methods and reporting underscores the need for continued harmonization and validation efforts. Further clarity on practical expectations, minimum data elements, and acceptable methodologies would help sponsors generate consistent, high-quality data that can support regulatory decision-making and post-approval learning.

We recommend that FDA:

- Encourage adoption of robust, quantitative dosimetry methods in early-phase trials while allowing scientifically justified alternative methods in settings where resource constraints exist.
- Standardize key data elements—including administered activity, absorbed dose, imaging, toxicity, and patient-reported outcomes (PROs)—to enable cross-trial comparability, robust dose-response modeling, and regulatory confidence in dose selection decisions.
- Emphasize iterative data collection and integration throughout development. Sponsors should be encouraged to leverage emerging data from early cohorts to refine dosing, adjust cumulative limits, and inform subsequent trials.
- Emphasize the integration of dosimetry results with observed clinical safety and efficacy data. Exploratory dosimetry paired with clinical outcomes can help clarify long-term organ tolerances and refine safe exposure ranges for future trials.

### **4. Trial Design and Multidisciplinary Collaboration**

The guidance notes safety considerations but provides limited discussion of multidisciplinary collaboration. *Friends* recommends highlighting approaches that integrate pharmacologists, radiation physicists, clinicians, and other stakeholders early in trial design.

We recommend that FDA:

- Encourage sponsors to consider randomized dose-response trials where feasible, while allowing adaptive or backfill designs to accelerate learning in rare or heavily pre-treated populations.
- Recommend early involvement of multidisciplinary teams to integrate safety, dosimetry, and clinical feasibility considerations into trial protocols.
- Clarify when protocol amendments are acceptable in response to emerging safety or efficacy signals, balancing flexibility with regulatory oversight.
- Provide guidance on managing patient heterogeneity, including differences in radiosensitivity, prior radiotherapy exposure, tumor biology, and isotopic characteristics, when determining optimal dosing strategies.

## **5. Patient-Centered Considerations**

*Friends* appreciates FDA's focus on patient safety and encourages further integration of patient experience and quality –of life data into dose optimization. Collecting PROs and prioritizing patient education can enhance adherence, reduce preventable toxicities, and strengthen the relevance of trial findings.

We recommend that FDA:

- Encourage integration of PROs alongside traditional endpoints to capture treatment impact on quality of life, adherence, and tolerability.
- Recommend proactive patient education on supportive care measures to minimize preventable adverse events and improve real-world adherence.
- Clarify that cumulative and delayed toxicity assessments should consider individual patient characteristics and clinical benefit, allowing continued therapy when appropriate.
- Support inclusion of PROs and patient education in both early-phase and curative-intent studies to improve safety, data quality, and real-world applicability.
- Continue incorporating patients in conversations related to potential approaches for dosage optimization in RPT trials.

*Friends* appreciates FDA's leadership in advancing this draft guidance, which represents a significant step toward more systematic, evidence-based RPT dose optimization. We look forward to continued collaboration with FDA and other stakeholders to refine dose optimization strategies, integrate multidisciplinary perspectives, and ensure that patient-centered considerations are incorporated throughout clinical development.

Sincerely,

Mark Stewart  
Vice President, Science Policy  
Friends of Cancer Research