Oncology Therapeutic Radiopharmaceuticals: Dosage Optimization During Clinical Development

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (OCE) OCE Guidances at OCE-Guidances@fda.hhs.gov, or (CDER) Will Maguire at William.Maguire@fda.hhs.gov.

U.S. Department of Health and Human Services
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Oncology Center of Excellence (OCE)
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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors in identifying an optimized dosage(s)[2] (administered activity and schedule) for radiopharmaceutical therapies (RPTs)[3] for oncology indications during clinical development and prior to submitting a marketing application for a new indication and usage.

This guidance should be considered along with the FDA guidance *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* (August 2024).[4] Some of the recommendations outlined in that guidance may be applicable to RPTs; however, this guidance is more specific to RPTs.

This guidance does not address selection of the initial RPT administered activity in first-in-human trials. For current FDA thinking regarding this topic, refer to the FDA guidance for industry *Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations* (August 2019).

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE) and the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purpose of this guidance, dosage refers to the administered activity and schedule (i.e., the recommended interval between administrations and number of administrations/cycles) and administered activity refers to the radiation dose of the radiopharmaceutical. An optimized dosage is the administered activity and schedule that can maximize the benefit/risk profile or provide the desired therapeutic effect while minimizing toxicity.

[3] For the purpose of this guidance, a radiopharmaceutical therapy, otherwise known as an oncology therapeutic radiopharmaceutical or RPT, is a radioactive drug or biological product that is used to treat cancer or palliate tumor-related symptoms (e.g., pain). In 21 CFR 310.3(n), such products are referred to as "radioactive drugs." Recommendations in this guidance are applicable to products that are administered systemically and undergo alpha, beta, and/or gamma decay.

[4] We update guidances periodically. For the most recent versions of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

This guidance does not address other aspects of the clinical development of RPTs, for example use of dosimetry software, use of fixed administered activity dosing for a population versus dosing determined by personalized dosimetry, and theranostic co-development.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in an FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

RPTs, typically administered systemically to treat cancer, share characteristics with both external beam radiation therapy (EBRT) (e.g., cell killing through ionizing radiation) and systemic drug therapy (e.g., systemic biodistribution and pharmacologic targeting). Administered activities of RPTs have historically been chosen to adhere to absorbed dose limits to critical organs derived from prior experience with EBRT. However, differences in physical properties and treatment delivery between RPTs and EBRT, such as dose rate and distribution of radiation, lessen the applicability of EBRT-derived organ absorbed dose limits to RPTs. Therefore, the optimized dosage of an RPT may be greater than or less than a dosage limited by EBRT organ tolerances. Furthermore, radiation absorbed dose limits may differ between different isotopes or RPTs based on their physical properties. Empiric determination of RPT-specific organ tolerances, or full assessment of dose-response relationships for a specific RPT, may not be possible if the evaluated dosages are limited based on EBRT organ tolerances.

A particular challenge for dose-escalation and dosage optimization of RPTs is that standard dose-escalation designs include a finite dose-limiting toxicity (DLT) window and emphasize detecting and limiting acute and subacute toxicities. However, RPTs have the potential to lead to persistent long-term or delayed onset toxicities that depend on cumulative administered activity received (e.g., renal toxicity, xerostomia, xerophthalmia, bone marrow failure). Long-term or delayed toxicities are unlikely to be fully characterized within the DLT window of a standard dose-escalation design, and therefore methods of overdose control in standard dose-escalation designs are not sufficient to prevent cumulative overdosing. Furthermore, selecting dosages for evaluation in subsequent larger trials without an adequate duration of safety follow-up may expose increasing numbers of participants to unacceptable long-term toxicity. Long-term toxicity may manifest through specific adverse reactions, inability to receive subsequent effective therapies, and detrimental effects on clinical endpoints such as overall survival.

A limit on cumulative exposure is a standard approach for cancer treatments with long-term, potentially irreversible toxicities that depend on cumulative dose, such as EBRT (e.g., various normal organ toxicities that correlate with distribution and radiation absorbed dose, as described by established normal tissue complication probability models), platinum chemotherapy (e.g., renal toxicity, peripheral neuropathy, and hearing loss), and anthracycline chemotherapy (e.g., cardiac toxicity). Administering RPTs for fixed durations that are supported by available evidence, in addition to dosage optimization strategies such as those detailed below, may help

obtain the additional data needed to define RPT-specific organ tolerances while managing the risk of long-term and/or cumulative toxicity.

The FDA guidance for industry *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* (August 2024) contrasts the historical dosage selection for cytotoxic chemotherapies, where the maximum tolerated dose (MTD) was identified in dose-finding trials and frequently administered in subsequent clinical trials, to that of modern targeted oncology drugs where dosages below the MTD may have similar efficacy to the MTD with fewer toxicities. RPTs share characteristics with both cytotoxic chemotherapies and modern targeted oncology drugs, and the MTD of many RPTs with respect to either acute or long-term toxicities has not been established at least in part due to prior adherence to EBRT organ tolerances. Therefore, it is not yet clear whether identifying an MTD (or dosing up to normal tissue tolerances) is the optimal approach for determining the recommended dosage for an RPT. Furthermore, the appropriateness of an MTD-based dosing strategy may be product- and situation-specific and could depend on numerous factors (e.g., target expression, ligand specificity, physical properties of the isotope and construct [stability, half-life, and decay scheme]; and slopes of the dose-response and dose-toxicity relationships for a given participant population). Although determination of the MTD may provide useful information, dosages selected for trials intended to support a future marketing application should be based on a totality of available data from a range of dosages, and not based solely on the MTD or normal organ tolerances.

III. CONSIDERATIONS FOR DOSAGE OPTIMIZATION

Administered activities per cycle and/or cumulative RPT administered activities that result in tissue absorbed doses that exceed EBRT organ tolerances or previously characterized RPT dosages may be studied in clinical trials of RPTs when there is adequate rationale that the optimized dose of an RPT may not be identified at lower dosages (i.e., dosages that do not exceed EBRT organ tolerances or previously characterized RPT dosages). Proposals to expose participants to RPT dosages that exceed EBRT organ tolerances or previously characterized RPT dosages could be justified based on existing clinical data or other approaches, as applicable, and should be discussed with FDA during formal meetings, including early in clinical development. Trials should include safeguards such as appropriate participant selection, trial design, safety monitoring, and radiation dosimetry evaluation.

A. Participant Population

- Trials that include an objective of defining the MTD of an RPT, or that include exceeding EBRT-defined dose limits or previously characterized RPT dosages, should be conducted in participants who have limited life expectancy due to cancer-related mortality and for whom the potential for delayed permanent organ failure is considered an acceptable risk. The exact participant population for which such studies are appropriate is disease-specific and should be discussed with the appropriate FDA review division.

- RPT dosages, and thus the corresponding organ absorbed doses delivered by RPT, in participants at lower risk of morbidity and/or death from their disease (e.g., earlier stage disease, diseases that may be curable, and diseases that have long natural history and expected survival times) should not exceed dosages that have been characterized in participants at greater risk for cancer-specific mortality (e.g., later stage advanced/metastatic disease, diseases with short expected survival times) with an adequate duration of follow-up. This is because participants with a lower risk of morbidity and/or death may have an increased risk of experiencing long-term toxicity from treatment compared to participants with more advanced disease. Dosages and delivered organ absorbed doses lower than those associated with serious and irreversible toxicities may be appropriate in earlier disease settings, and further dosage optimization may be needed in these participant populations.

- For participants treated previously with EBRT, eligibility for RPT trial enrollment should be determined by clinical variables such as pre-existing baseline toxicities and organ function. Receipt of prior EBRT should generally not be used to exclude participants from participation in RPT trials, except when there is a specific clinical concern about co-localization of toxicity from prior EBRT and RPTs.

- For participants treated previously with RPT, eligibility for RPT trial enrollment should be determined by clinical variables such as pre-existing baseline toxicities and organ function, in addition to consideration of prior radiation absorbed doses. Sponsors should prespecify a maximum cumulative radiation absorbed dose to critical organs from prior and current RPTs that is based on available data. Sponsors should provide justification for any proposal that exceeds these organ tolerances.

- Sponsors should consider evaluating participants who have received prior RPT in different cohorts from participants who have not received prior RPT, given that safety considerations may differ between these populations.

B. Trial Design

- RPTs should generally be administered for a fixed number of cycles to mitigate the risk of delayed or cumulative toxicity. Protocols should pre-specify a limit to the cumulative administered activity, and corresponding radiation absorbed doses to critical organs, that is justified based on available data on RPT-specific organ tolerances. The appropriate limit may be product- and indication-specific, and the appropriate limits may be revised based on emerging data. In situations where there is relatively high uncertainty (e.g., a novel product with no clinical data, alpha-emitter RPTs, RPTs that are predicted to have heterogeneous sub-organ distribution of radiation, or existence of uncertainties about additive toxicity from prior RPT treatment), a lower limit to cumulative activity delivered in a particular protocol may be appropriate as a starting point. In situations where there is less uncertainty (e.g., established product with substantial clinical data, high-energy beta-emitting isotopes, RPTs with relatively homogeneous sub-organ distribution of radiation,

participants with no prior RPT treatment), more flexibility in the upper limit may be appropriate.

- Consistent with the FDA guidance for industry *Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations* (August 2019), the EBRT literature should be used as a starting point for the dosage of RPTs, which means that the first dosage studied in humans (administered activity level per cycle summed across the number of cycles that is planned for therapeutic purposes) should generally not exceed EBRT limits.

- In situations where initial clinical data suggest limited toxicity at the prespecified maximum administered activity of a dose-escalation trial of RPTs, and preliminary efficacy data (tumor absorbed dose data and/or clinical data) suggest the optimized dosage has not been reached, sponsors should request a meeting with the appropriate FDA division to discuss protocol amendments allowing further dose-escalation. Detailed initial data, including safety, preliminary efficacy dosimetry, and pharmacokinetic data, should be provided in the meeting package to justify the higher administered activities.

- Dosages chosen for trials intended to support a future marketing application should be based on all relevant data, including but not limited to clinical data regarding safety, preliminary efficacy, pharmacokinetics and/or pharmacodynamics, and patient-reported outcomes; the MTD (if established); estimated organ tolerances; and tumor and normal organ radiation dosimetry.

  Additional considerations for selection of the optimized dosage(s) for trials intended to support a future marketing application include:

  - While a DLT period of one cycle may be sufficient to allow escalation to a higher dose in initial dose-finding trials, sponsors should incorporate longer-term safety and tolerability data into their decision-making to justify the recommended dosage(s) for subsequent trials. If multiple cycles of an RPT are intended, safety data obtained with one cycle will not be sufficient to support a dosage for future development; in this case, safety data from participants who received multiple cycles and from multiple dose levels should be provided to assess potential cumulative toxicity. The choice of a recommended dosage(s) for trials intended to support a future marketing application should be informed by a duration of safety follow-up that corresponds to the timeframe of the anticipated toxicities, and/or the median life expectancy of the participant population (if less than the timeframe of anticipated long-term toxicities).

  - Dose-escalation cohorts may lack a sufficient number of participants to identify dosages to be further explored. It may be useful to evaluate additional dose-level cohorts or add more participants to existing dose-level cohorts (i.e., backfill cohorts) in dose-finding trials to provide additional safety and activity data for dosages which are being considered for further development and to increase the

number of participants with longer-term follow-up available for determination of the optimized dose for trials intended to support a future marketing application.

- Sponsors should compare multiple dosages, including in randomized dose-response trials, prior to selecting a dosage(s) for trials intended to support a future marketing application, given that the optimized dosage may or may not correspond to the highest dose studied. Randomized dose-response trials may be particularly important when evaluating a dosage(s) that exceeds EBRT-defined organ tolerances, or a dosage(s) that corresponds to the MTD of an RPT. Randomized dose-response trials should be sized to allow for adequate assessment of activity, safety, and tolerability for each dosage. Refer to the FDA guidance for industry *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* (August 2024) for general information on randomized parallel dose-response trials. The dosage(s) selected for trials intended to support a future marketing application should be based both on data from randomized dose-response trials, including preliminary efficacy and shorter-term toxicity data, as well as longer-term toxicity data available from the initial dose-finding trial(s), including any backfilled cohorts.

- Sponsors should consider the cumulative administered activity received from any prior RPT when choosing levels of administered activity to study for an investigational RPT. Lower dosages (starting administered activity and maximum cumulative administered activity) of the investigational RPT may be appropriate in participants who have received prior RPT.

- The informed consent process and documents for dose-finding trials of RPTs should communicate appropriate information regarding the potential risks of long-term, late-onset, and cumulative radiation toxicity and that such information may not be well-characterized for a product during initial development stages.

C. Safety Monitoring

- Because the onset of radiation toxicity may be delayed by months to years, sponsors should perform monitoring against a pre-specified list of late radiation adverse events of special interest (rAESI) for at least 5 years after the last dose or until death in cases where life expectancy is typically expected to be less than 5 years. The rAESI list and monitoring schedule should explicitly reflect the drug-specific dosimetry results and a corresponding detailed critical radiation safety analysis plan. RPTs granted approval for cancer indications may be subject to a postmarketing requirement to provide such long-term safety follow-up data for FDA review.

- For participants who have received prior radiotherapy (EBRT and/or RPT), sponsors should record the dose to critical organs from the previous radiotherapy to further inform whether cumulative radiation absorbed dose from previous radiotherapy and the investigational product could cause added toxicity where co-localized. Organ-specific safety data for the participant should be correlated with their prior radiotherapy dose as

well as cumulative radiation absorbed dose (prior radiation dose plus the absorbed dose to be delivered as part of study treatment).

- Sponsors designing clinical trials for RPTs should consider including exploratory early biomarkers of delayed radiation toxicity. The choice of biomarker(s) should be guided by best available data. Sponsors should consider banking samples of blood, urine, and any other relevant tissues for potential future biomarker validation studies.

D. Dosimetry for Dosage Optimization Trials

- Per 21 CFR 312.23(a)(10)(ii), phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations. Each novel molecular entity should have dosimetry studies performed early in its clinical development program to provide measurements of potential toxicity/efficacy associated with exposure to radiation (e.g., delivered organ absorbed dose and related dosimetric quantities). Dosimetry studies provide a radiobiological context for the clinical efficacy and safety data and support dosage optimization. Given that the properties (e.g., physical and effective half-life, decay products and associated energies) of different radioisotopes vary widely, the appropriate design of the dosimetry studies may be isotope- or product-specific. Direct imaging of the therapeutic product is preferred, when possible, although this may be supplemented by dosimetry data from surrogate analogs when direct imaging is not possible or has substantial limitations.

- If an Investigational New Drug (IND) submission is supported by data obtained from studies that were not conducted under an IND and did not obtain dosimetry data, FDA expects that dosimetry data will be obtained during the trial included in the original IND submission to verify assumptions made in dosage selection. This could be accomplished via a dedicated imaging study or a lead-in cohort. In these situations, sponsors should request a meeting with the appropriate FDA division to discuss the dosimetry data prior to enrolling a large number of participants in a trial intended to support a future marketing application.

- Sponsors should implement a direct imaging approach of alpha-emitters when possible. Alternatively, sponsors may consider a combination of surrogate-imaging based dosimetry and pharmacokinetic modeling. The preferred imaging approach may depend on the specific alpha-emitter and current available imaging technology. Sponsors should submit their proposed dosimetry approach and any supporting data for FDA review. Sponsors should consider performing micro-scale dosimetry for alpha-emitters to account for the short range and highly heterogenous dose deposition in order to obtain sub-organ level absorbed dose estimates.

- Sponsors should provide radiation dosimetry protocols that include sufficient description of the imaging acquisition methods and image processing (e.g., reconstruction, corrections, etc.) for dosimetry calculations. Radiation dosimetry protocols should include detailed information of all steps taken to produce estimated organ absorbed dose results: camera and administered activity calibration procedures, organ and tumor

segmentation methods during image analysis, time-activity data fitting methods, radiation dosimetry software used when applicable, and any specific models, assumptions, or modifications to the default software settings used for dosimetry calculations. Sponsors should follow appropriate radiation dosimetry methodology for bone marrow dosimetry (e.g., based on expert consensus recommendations[5]), supported by product-specific measured activity distribution. Sponsors should describe radiation dosimetry methodology for activity uptake in small organs (e.g., salivary, lacrimal, and pituitary glands) in the dosimetry report, and, if dedicated (e.g., model-based) calculations are performed in addition to the software-based calculations, these methodologies should be included in the report.

- In general, estimated organ absorbed doses should be accompanied by estimated uncertainties accounting for all assumptions made in dosimetry calculations or other systematic uncertainties and statistical uncertainties.

- Sponsors should provide, as applicable, justifications for dose-escalation portions of the dose-finding trial, including estimates of upper limits for cumulative administered activity. Estimates of upper limits may include radiation biological considerations, including consideration of biological effective dose (BED) estimates corresponding to a well-defined effect of clinical interest from study across a range of radiation delivery methods. Sponsors should submit supporting data, including explanation of applicability and modeling details and assumptions, for FDA review.

- Regardless of the primary method used for estimating an upper limit for cumulative administered activity, sponsors should consider including both absorbed dose and derivative BED calculations when reporting dosimetry study results. BED-based dose-response analysis may aid with aggregation and analysis across studies as part of ongoing efforts to better define RPT-specific organ tolerances.

[5] Hindorf C, Glatting G, Chiesa C, Lindén O, Flux G, EANM Dosimetry Committee. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. Eur J Nucl Med Mol Imaging, 2010 Jun;37(6):1238-50.