

Editorial

Streamlining first-in-human PET radiopharmaceutical development: FDA's evolving stance on preclinical dosimetry

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Received June 18, 2025; Accepted June 21, 2025; Epub August 15, 2025; Published August 30, 2025

Abstract: The U.S. Food and Drug Administration (FDA) has proposed a regulatory shift in the early-phase development of positron emission tomography (PET) radiopharmaceuticals, specifically regarding the requirement for animal-based dosimetry in first-in-human (FIH) studies. This editorial discusses the implications of the FDA's recent Advisory Committee briefing, which supports the omission of pre-clinical dosimetry under defined conditions for radiopharmaceuticals labeled with ^{18}F , ^{11}C , ^{68}Ga , ^{64}Cu , ^{82}Rb , and ^{13}N . The proposed policy reflects a shift toward a more streamlined, evidence-based approach to FIH studies while maintaining stringent standards for patient safety.

Keywords: PET imaging, radiopharmaceuticals, FDA guidance, first-in-human study, dosimetry, administered activity, nuclear medicine, preclinical studies

Historically, the development of positron emission tomography (PET) radiopharmaceuticals has required preclinical animal dosimetry data prior to initiating first-in-human (FIH) clinical trials. While intended to ensure radiation safety, its requirement imposes substantial time, financial, and ethical burdens. Accumulating evidence indicates that animal-derived dosimetry predictions often have limited accuracy when extrapolated to human subjects [1, 2].

In its 2023 Advisory Committee briefing, the U.S. Food and Drug Administration (FDA) proposed a significant revision to pre-investigational new drug (IND) dosimetry requirements [3]. This proposal permits omission of pre-clinical animal dosimetry studies for radiopharmaceuticals labeled with six commonly used PET radionuclides [4, 5], including ^{18}F , ^{11}C , ^{68}Ga , ^{64}Cu , ^{82}Rb , and ^{13}N , under defined conditions. Specifically, this exemption applies when the planned administered activity (AA) for clinical studies does not exceed established average dosing levels derived from PET agents (e.g., 299 MBq [8 mCi] for ^{18}F , 555 MBq [15 mCi] for ^{11}C , 158 MBq [4.3 mCi] for ^{68}Ga , 148 MBq [4 mCi] for ^{64}Cu , 1440 MBq [39 mCi] for ^{82}Rb , and 552 MBq [15 mCi] for ^{13}N), and when the study population is not considered at elevated risk for radiation exposure (**Table 1**).

To support the proposed regulatory change, the US FDA conducted a comprehensive review of dosimetry data from 322 PET radiopharmaceuticals, both investigational and approved agents. This analysis encompassed effective dose (ED) and maximum organ absorbed dose (AD) values. Results showed that human-derived dosimetry estimates consistently remained within acceptable safety thresholds across all six radionuclides. For example,

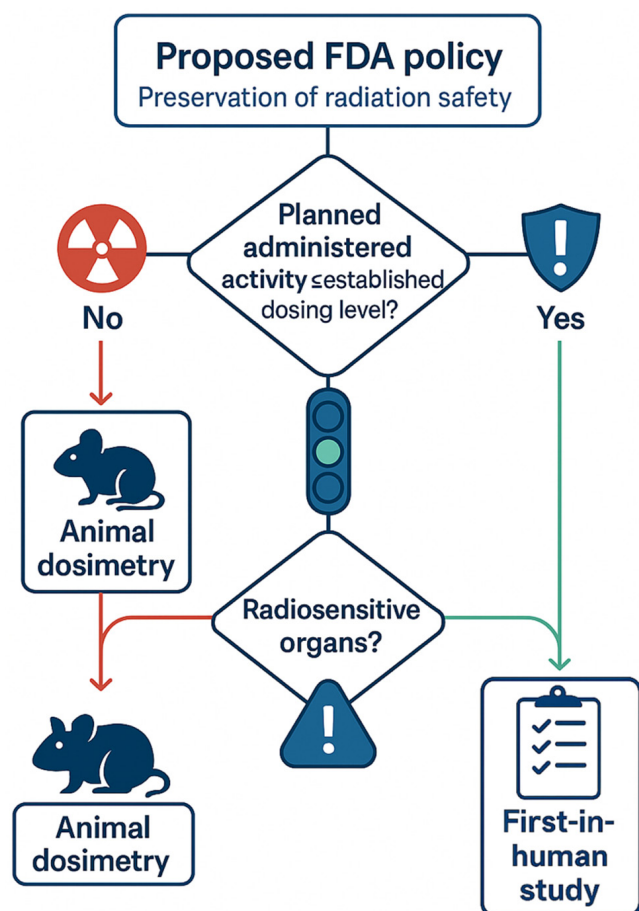
^{18}F -labeled compounds exhibited a mean ED of 0.021 mSv/MBq and a mean maximum organ AD of 0.161 mGy/MBq, corresponding to approximately 6.28 mSv and 48.1 mGy, respectively, at an administered activity of 299 MBq. Comparable safety profiles were observed for the other radionuclides, including notably low cumulative doses for ^{11}C (mean ED of 3.33 mSv at 555 MBq) and ^{82}Rb (mean ED of 2.88 mSv at 1440 MBq) [6, 7].

The proposed policy preserves radiation safety by prioritizing robust, human-derived data over less predictive animal-based estimates. This approach addresses well-documented limitations and interspecies variability associated with animal-to-human extrapolations, as discussed in previous studies (e.g., Zanotti-Fregonara et al.) [8]. The FDA's analysis revealed substantially lower variability in human dosimetry data, enhancing the reliability of safety assessments for first-in-human studies. The proposal also includes safeguards for scenarios involving elevated radiation risk. Radiopharmaceuticals targeting radiosensitive organs or administered at doses exceeding established limits will continue to undergo individualized review, which may include animal dosimetry experiments. Clinical trial protocols involving dose escalation or staged enrollment must incorporate clearly defined stopping criteria and radiation safety procedures to ensure participant protection (**Figure 1**).

Beyond regulatory simplification, this policy enables more efficient allocation of resources toward innovation, clinical validation, and radiopharmaceutical development. Investigators working with short-lived radionuclides, in particular, will benefit most as reduced regulatory barriers may accelerate clinical translation. This is especially advantageous in fields such as oncology, neurology, and car-

Table 1. Dosimetry summary for PET radionuclides (^{18}F , ^{11}C , ^{68}Ga , ^{64}Cu , ^{82}Rb , and ^{13}N)

Entry	Radionuclide	Mean Human ED Coefficient (mSv/MBq)	Mean Human Max Organ AD Coefficient (mGy/MBq)	Proposed Max AA for FIH Study (MBq)	$t_{1/2}$ (min)
1	^{18}F	0.021	0.161	299 (8 mCi)	109.8
2	^{11}C	0.006	0.032	555 (15 mCi)	20.3
3	^{68}Ga	0.025	0.251	158 (4.3 mCi)	67.7
4	^{64}Cu	0.037	0.297	148 (4 mCi)	762
5	^{82}Rb	0.002	0.009	1440 (39 mCi)	1.25
6	^{13}N	0.007	0.0071	552 (15 mCi)	9.96

**Figure 1.** Flowchart illustrating the FDA's proposed framework for omitting animal dosimetry in first-in-human studies of PET radiopharmaceuticals.

diology, where PET radiopharmaceuticals play a pivotal role in diagnosis, therapy monitoring, and biomarker evaluation.

In summary, the US FDA's recent proposal makes significant advancement in regulatory policy for PET radiopharmaceutical development. By emphasizing human-derived dosimetry data, the agency acknowledges the current limitations of traditional animal dosimetry methods and promotes a more efficient, scientifically rigorous, and patient-centered framework. This shift is expected to enhance safety, support innovation, and expedite the clinical availability of novel diagnostic imaging agents.

Acknowledgements

S.H.L. gratefully acknowledges the support provided, in part, by the NIH grants (MH128705, AG075444, AG083084, NS130128, AG081401, AG094161), Emory Radiology Chair Fund, and Emory School of Medicine Endowed Directorship.

Disclosure of conflict of interest

None.

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