FDA Briefing Document

Drug name: **PET Diagnostic Radiopharmaceutical Drugs**

Medical Imaging Drugs Advisory Committee Meeting

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Division of Imaging and Radiation Medicine (DIRM), OSM, OND, CDER

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought "*Radiation Dosimetry for First in Human Studies of Investigational PET Radiopharmaceutical Drugs*" to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AA	administered activity
AC	Advisory Committee
AD	absorbed dose
CT	computed tomography
ED	effective dose
FDA	Food and Drug Administration
FIH	first-in-human
IND	investigational new drug
PET	positron emission tomography
PI	prescribing information

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the Advisory Committee Meeting

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss dosimetry data needed to support the initial clinical study in an original investigational new drug (IND) application for certain new positron emission tomography (PET) drugs used in diagnostic nuclear medicine.

1.2 Context for Issues to Be Discussed at the AC

PET drugs are medical products that exhibit spontaneous disintegration of unstable nuclei by the emission of positrons and are used for generating dual-photon PET diagnostic images . Because they are radioactive and administered for diagnostic purposes (i.e., low administered activities [AAs]), PET drug administration carries a stochastic radiation risk (e.g., probability of developing cancer later in life). To minimize this risk, dosage and administration instructions for PET drugs generally instruct prescribers to use AA levels that have been found to be the lowest adequate amounts based on premarket investigation; AA is a measure of decay events per time (measured in units of Becquerels and/or Curies). The science of linking AA to estimates of radiation absorbed dose (AD) delivered within the body is called dosimetry; AD is a measure of energy per unit mass (measured in units of Grays or rads) absorbed by an organ/tissue or volume within the body or by the whole body. Notably distinct from externally sourced radiation delivery, recommended AA plays a prominent role in dosing and administration instructions for PET drugs and other internally distributed radioactive products, meaning that the recommended AA is of primary interest to clinicians responsible for prescribing these products. In comparison, clinically derived and PET drug-specific AD estimates play a more limited and supplementary role in premarket safety review and PET drug labeling, a role generally akin to that of other clinical pharmacology information provided under standardized drug prescribing information (PI).

FDA's involvement in the development of a new PET drug typically begins when the drug's sponsor wants to initiate investigation in humans. Per IND dosimetry regulations, (i) PET drug INDs must contain sufficient data from animal or human studies to allow a reasonable calculation of AD to the whole body and critical organs upon administration to a human subject (pre-IND dosimetry); in addition, (ii) Phase 1 study protocols must include studies to obtain sufficient clinical data for dosimetry calculations (Phase 1 dosimetry). Accordingly, (i) FDA has generally reviewed the sufficiency of pre-IND dosimetry on a case-by-case basis and (ii) has found IND-opening study protocols unsafe to proceed if proposed Phase 1 methods for obtaining drug-specific clinical dosimetry data are lacking.

Certain stakeholders in new PET drug investigation and development have expressed concern that pre-IND animal dosimetry studies may be burdensome and unnecessary when human studies are available to allow a reasonable pre-IND dosimetry calculation, a calculation essentially limited in relevant scope to the small number of study subjects (pre-Phase 1-dosimetry cohort) investigated between the time of first-in-human (FIH) administration and the superseding collection of Phase 1 clinical dosimetry data, which must be obtained on a drug-specific basis per IND regulations, as summarized above.

In response to stakeholder comments and in accordance with applicable law, regulation, and guidance, FDA is considering whether the current approach to review pre-IND dosimetry data may be clarified and

streamlined. To support this objective, FDA is seeking to leverage findings of the safety of marketed PET drugs labeled with various radionuclides when administered at the AA levels specified under the dosing and administration instructions of approved PIs. Further, to explore the applicability and potential implications of this leveraging strategy, FDA conducted a systematic literature review and analysis of PET drugs (both investigational and approved) containing the six radionuclides used for positron emission among the currently marketed PET drugs (^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N).

1.3 Brief Description of Issues for Discussion at the AC

FDA's analysis suggests that an AA-based leveraging strategy is consistent with the flexibility provided under applicable pre-IND dosimetry regulations and may represent a safe and feasible approach toward increasing review transparency and, under appropriate circumstances, clarifying expectations around pre-IND dosimetry. For example, in the absence of animal dosimetry data (and assuming studies in the reviewed literature can be used to predict future protocol submissions), FDA anticipates that leveraged clinical data could be sufficient to support 67% and 69% of Phase 1 studies of new PET drugs containing ^{18}F and ^{11}C, respectively. In all cases (e.g., including under this example, the remaining 33% and 31%), given the flexibility provided under pre-IND dosimetry regulations, drug-specific (i.e., case-by-case) consideration remains an option for the FDA – in the absence of animal dosimetry data – to obtain clinical data sufficient to meet the reasonable calculation standard.

In summary, this general topic AC meeting is being convened to solicit advice on the circumstances under which FDA may consider human studies sufficient to allow reasonable radiation AD calculations for new PET drugs containing one of six radionuclides in the absence of drug-specific animal dosimetry data. In particular, for review of Phase 1 studies of new PET drugs, including Phase 1 IND-opening clinical study protocols:

- In the absence of drug-specific animal dosimetry data, if the maximum protocol-specified AA covering the pre-Phase 1-dosimetry cohort is less than or equal to the corresponding AA for PET drugs approved as of 08/01/2023 – and will involve a study population with a similar risk profile – clinical data to allow a reasonable calculation of AD may generally be considered sufficient to find the corresponding portions of the protocol safe to proceed from a radiation-safety perspective.
- Conversely, the sufficiency of drug-specific animal dosimetry should continue to be reviewed on a case-by-case basis if the maximum protocol-specified AA covering the pre-Phase 1-dosimetry cohort exceeds the corresponding AA for PET drugs approved as of 08/01/2023 – or if the study population is notably dissimilar in terms of radiation risk.

Notably, this proposed clarification of FDA's review approach is intended to encompass the spectrum of academic and commercial sponsors and the diversity of early-phase clinical study designs typically reviewed under IND for new PET drugs. As such, the proposed approach is intended to accommodate both single and multi-AA-cohort designs, the latter more responsive to standard FDA recommendations for sponsors to explore across a broad range of AA cohorts for identification of the lowest adequate dose. For example, the proposed review approach includes but is not limited to finding study protocols safe to proceed from the perspective of radiation safety if they involve absence of drug-specific animal dosimetry data, initial administration of lower AA levels intended to support collection of human dosimetry estimates, and then subsequent administration of higher AA levels according to acceptable protocol-specified escalation- and study-stopping rules.

1.4 Draft Points for Consideration

- Discuss the sufficiency of reviewed data from animal or human studies involving ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon first-in-human (FIH) administration of a new PET drug containing these radionuclides.
- Discuss the reasonableness of the proposed list of numerical guidelines for new PET drugs containing ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N, such that Phase 1 studies that will both i) initially administer one or more activity levels ≤ guidelines and ii) obtain sufficient human data for dosimetry calculations may generally be found safe-to-proceed from a radiation safety perspective in the absence of dosimetry data based on prior animal administration of the new PET drug under investigation.

2 Introduction and Background

2.1 Background

FIH studies of diagnostic radiopharmaceuticals may be supported by preclinical dosimetry to estimate the radiation AD in various human organs. CFR Title 21 Section 312.23(a)(10)(ii) [1] requires that IND applications include sufficient data from animal or human studies to allow a reasonable estimation of AD to the whole body and critical organs upon administration to a human subject. Animal studies are conducted to evaluate toxicology and pharmacology (including biodistribution, stability, and metabolism) and to obtain an initial estimate of human radiation doses of a new diagnostic imaging drug to inform the safety evaluation of a FIH study. Thus, original IND submissions include human-dose estimates that are often extrapolated from preclinical dosimetry studies. The extrapolation methods make assumptions about differences in metabolism, anatomy, and biodistribution between animals and humans. These assumptions contribute to uncertainties in predicting radiation dose to human organs [2].

In diagnostic nuclear medicine, dosimetry is used primarily to evaluate the stochastic risk (e.g., development of cancer) associated with radiation exposure. In this context, the mean organ AD to a well-defined anatomical model is needed, as risk data are expressed in terms of mean organ AD to a model that is representative of the exposed (or imaged) population [3]. Dosimetry and other early-phase study results are used to support dosing and administration instructions that can provide good image quality while maintaining an acceptable organ AD and effective dose (ED) to the patient [4]. These quantities are considered to select the lowest adequate AA, where adequacy is evaluated in terms of pharmacodynamic and/or imaging-reader assessments. Increasing the AA above the lowest adequate amount violates the principle of as low as reasonably achievable, which is designed to minimize exposure to radiation.

The effective dose was developed primarily for radiation protection of occupationally exposed persons and is important for standardization and comparison of patient exposure from different radiation sources [5]. The ED attributes weighting factors w_T to organs or tissues, representing fraction of the stochastic risk resulting from the irradiation of that organ or tissue T when the whole body is irradiated uniformly [6]. The ED is calculated by adding the weighted organ or tissue mean dose equivalents in a target organ or tissue, based on the relative radiation sensitivity (w_T) of that organ or tissue. The mean

equivalent dose is obtained by summing each product term of the mean AD from the radiation *R* of a particular organ or tissue with the radiation weighting factor w_R. The ED is an important component of the multiple considerations involved in estimating the sex- and age-averaged risk of stochastic effects to populations of patients.

Dosimetry for therapeutic radioactive products involves additional consideration of AD and derivative estimates to the therapeutic target, deterministic off-target risks, and how to balance the two. Questions involving therapeutic dosimetry are of active interest to FDA but fall outside the scope of this AC meeting.

It has been proposed that for ^{11}C- and ^{18}F-labeled radiopharmaceuticals, upper limits of AA for FIH studies could be derived from published clinical dosimetry data , rather than from estimates extrapolated from preclinical dosimetry studies [7-9]. This approach led Zanotti-Fregonara et al. to propose AA amounts that could be safely used in FIH studies with new ^{11}C- and ^{18}F- labeled radiopharmaceuticals, in part by considering the maximum reported whole-body ED and maximum organ AD coefficients from clinical studies and using 30 and 50 mSv whole-body and organ radiation AD thresholds, respectively [10].

The FDA does not have defined thresholds that limit the organ AD or whole-body ED for diagnostic radiopharmaceuticals studied under an IND application. However, the CFR Title 21 Part 361.1(b)(i) outlines upper radiation dose limits to individual organs and the whole body for radioactive drugs studied under an institutional Radioactive Drug Research Committee [10] for adult subjects and limits the radiation dose from a single or cumulative number of studies conducted within 1 year to 30 mSv for the whole body and organs with the highest radiosensitivity (blood-forming organs, lens of the eye, gonads), and to 50 mSv for all other organs.

These considerations prompted FDA to re-evaluate the utility of preclinical dosimetry studies for the assessment of the radiation safety of a range of PET drugs. The objectives were to conduct a systematic review of clinical dosimetry estimates of PET drugs derived from preclinical and clinical dosimetry studies, to determine AA amounts that could be used to safely conduct FIH studies of new PET drugs without prior animal dosimetry studies. The focus of this AC meeting is on dosimetry for FIH studies of PET drugs radiolabeled with ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N. A similar consideration for FIH studies of diagnostic radiopharmaceuticals involving single-photon emitters could be discussed in future, but these studies are generally less common and outside the scope of this AC meeting.

2.2 Pertinent Drug Development and Regulatory History

CFR Title 21 Section 312.23(a)(10)(ii) requires that IND applications for radioactive drugs include sufficient data from animal or human studies to allow a reasonable estimation of AD to the whole body and critical organs upon administration to a human subject. Animal studies of radioactive drugs may be conducted, among other reasons, to obtain an initial estimate of human radiation doses to inform the safety evaluation of a FIH study protocol.

When a radioactive drug is approved for marketing after a new drug application or biologics license application, clinical radiation dosimetry data are included in the Radiation Dosimetry subsection of Section 2 of the PI (21 CFR 201.57(c)(3)(iii)). These data include estimated organ AD and whole-body ED per unit of AA expressed in units of mGy/MBq and mSv/MBq or µGy/MBq and µSv/MBq, respectively. Information on specific organ AD and ED resulting from a given AA may also be included in mGy or mSv.

If the PET imaging procedure includes computed tomography (CT), effective dose estimates from CT scanning and total radiation exposure from administration of the radiopharmaceutical and CT imaging may also be included.

Nonclinical dosimetry studies are conducted to evaluate radioactivity over time in organs and tissues, typically by counting the radioactivity in excised tissues of animals or by imaging at preplanned timepoints after the administration of the radioactive drug.

3 Summary of Issues for the AC

In order to determine thresholds for administered activities in FIH studies of PET drugs in the absence of animal-to-human dosimetry extrapolation, the proposed approach included: 1) leveraging findings of substantial evidence for the safety of approved PET drugs when administered at the AA levels specified under the dosing and administration instructions of PIs, , and, 2) analyzing dosimetry data from published clinical studies of PET drugs (inclusive of investigational and approved PET drugs) through a systematic literature review.

3.1 FDA-Approved PET Drugs

Table 1 lists FDA-approved PET drugs, along with their approved indication(s) and a summary of dosing and administration information from the most recent version of the corresponding PI.

Table 1. FDA-Approved PET Drugs

Radionuclide (Half-Life)	Approved Indication(s) in Adults	FDA-Approved RPs	Recommended Dosing and Administration From PI, AA[a] (MBq (mCi))
^{18}F (0.076 days)	Abnormal glucose metabolism in suspected or existing diagnosis of cancer, coronary artery disease (CAD), left ventricular dysfunction, and foci of epileptic seizures	^{18}F-fludeoxyglucose	278 (8)
	Altered osteogenic activity in bone	^{18}F-sodium fluoride	-
	β-Amyloid plaque density in patients evaluated for Alzheimer's disease (AD) and other causes of cognitive decline	^{18}F-florbetapir	370 (10)
		^{18}F-flutemetamol	185 (5)
		^{18}F-florbetaben	300 (8)
	Prostate cancer recurrence based on elevated prostate-specific antigen levels following prior treatment	^{18}F-fluciclovine	370 (10)
	Striatal dopaminergic nerve terminal visualization in patients with suspected Parkinsonian syndromes	^{18}F-fluorodopa	185 (5)
	Detection of estrogen receptor-positive lesions of recurrent or metastatic breast cancer	^{18}F-fluoroestradiol	222 (6)
	Tau neurofibrillary tangle density and distribution in patients evaluated for AD	^{18}F-flortaucipir	370 (10)
	Prostate-specific membrane antigen (PSMA) positive lesions of prostate cancer	^{18}F-piflufolastat	333 (9)
		^{18}F-flotufolastat	296 (8)

Radionuclide (Half-Life)	Approved Indication(s) in Adults	FDA-Approved RPs	Recommended Dosing and Administration From PI, AA[a] (MBq (mCi))
^{11}C (0.014 days)	Prostate cancer recurrence for subsequent histologic confirmation	^{11}C-choline	555 (15)
^{68}Ga (0.047 days)	Somatostatin receptor-positive neuroendocrine tumors (NETs)	^{68}Ga-DOTATATE	140 (4)[b]
		^{68}Ga-DOTATOC	148 (4)
	PSMA-positive lesions of prostate cancer	^{68}Ga-gozetotide	185 (5)
^{64}Cu (0.53 days)	Somatostatin receptor-positive NETs	^{64}Cu-DOTATATE	148 (4)
^{82}Rb (1.25 min)	Myocardial perfusion in patients with suspected or existing CAD	^{82}Rb-rubidium	1480 (40)
		^{82}Rb-rubidium	1400 (38)[b]
^{13}N (9.97 min)		^{13}N-ammonia	552 (15)

Source: FDA summary of approved PI.

[a] Median AA used for cases when dosing and administration instructions in the PI are given as a range.

[b] AA calculated for a 70 kg adult human for cases when dosing and administration instructions in the PI are given in terms of MBq/kg or mCi/kg.

Abbreviations: AA, administered activity; PI, prescribing information; RP, radiopharmaceutical

3.2 Literature Review – Radiation Dosimetry of PET Drugs

3.2.1 Methods

Six literature searches were conducted from January to June 2021 using the bibliographic databases PubMed, Embase, SciFinder, Web of Science, and Google Scholar to compile available radiation dosimetry data from full-text articles published since 1990 in English for ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N labeled PET drugs (including investigational and approved drugs) [11]. The search strategy included the key terms: dosimetry, fluorine-18, carbon-11, gallium-68, copper-64, rubidium-82, and nitrogen-13. Studies were selected after excluding publications lacking sufficient dosimetry data. Studies referenced in review articles were also selected. Articles that were selected reported human-organ radiation dose estimates from animal and human studies calculated according to the Medical Internal Radiation Dose [12] or related methodology and included human maximum organ AD and whole-body ED per unit AA in mGy/MBq and mSv/MBq (i.e., organ AD coefficients and whole-body ED coefficients, respectively). Information was also collected from the approved PIs listed in Table 1.

The human dose values derived from animals are referred to as animal-derived AD and ED, and estimates based on clinical data are referred to as human-measured AD and ED throughout this literature review. The animal-derived and human-measured ED and maximum AD coefficients reported in each study were collected. The mean, median, and range of the published data for each radionuclide were tabulated.

ED values (mSv) for each clinical study were calculated by multiplying the reported ED coefficient by the average AA (of all subjects) reported in that study. Similarly, the maximum AD values (mGy) for each clinical study were calculated by multiplying the maximum reported AD coefficient by the average value of the activity administered to the specific study subjects. The proportion of studies with AA values above the per-radionuclide mean of Table 1 was also calculated.

3.2.2 Results

The literature searches yielded 175 (^{18}F), 100 (^{11}C), 68 (^{68}Ga), 40 (^{64}Cu), 6 (^{82}Rb), and 2 (^{13}N) publications for 141, 87, 59, 32, 1, and 1 different PET drugs (i.e., unique chemical or biological entities independent

of manufacturer), respectively, totaling 322 PET drugs. The results of the literature search and selection of publications are presented in Table 2. Preclinical studies were not available for PET drugs containing ^{82}Rb and ^{13}N.

Table 2. Summary of Study Selection Process

Radionuclide (Physical Half-Life)	Studies Identified by Database Searches and Additional Sources[a]	Studies Included	PET Drugs Identified by Data Type			
^{18}F (0.076 days)	219	175	Animal	Human	Both	Total
			42	121	22	141
^{11}C (0.014 days)	186	100	Animal	Human	Both	Total
			35	74	22	87
^{68}Ga (0.047 days)	97	68	Animal	Human	Both	Total
			18	46	5	59
^{64}Cu (0.53 days)	133	40	Animal	Human	Both	Total
			25	9	2	32
^{82}Rb (1.25 min)	13	6	Animal	Human	Both	Total
			-	1	-	1
^{13}N (9.97 min)	13	1	Animal	Human	Both	Total
			-	1	-	1

Source: FDA analysis of published dosimetry data.

[a] Manual search of references from review articles.

Table 3 shows the human ED coefficients extrapolated from animal studies (animal-derived) and clinically derived human ED coefficients (human-measured) for each radionuclide.

Table 3. Summary of Reported ED Coefficients

	Animal-Derived			Human-Measured		
RN	N	Mean ED±SD (mSv/MBq)	Median (Range) (mSv/MBq)	N	Mean ED±SD (mSv/MBq)	Median (Range) (mSv/MBq)
^{18}F	47	0.023±0.020	0.019 (0.0001–0.123)	143	0.021±0.007	0.020 (0.005–0.050)
^{11}C	39	0.006±0.002	0.005 (0.003–0.014)	78	0.006±0.002	0.005 (0.003–0.015)
^{68}Ga	21	0.020±0.006	0.017 (0.011–0.032)	54	0.025±0.012	0.022 (0.007–0.066)
^{64}Cu	28	0.039±0.029	0.033 (0.005–0.140)	12	0.037±0.014	0.035 (0.010–0.062)
^{82}Rb	-	-	-	5	0.002±0.002	0.001 (0.001–0.005)
^{13}N	-	-	-	1	0.007	0.007

Source: FDA analysis of published dosimetry data.

Abbreviations: ED, effective dose; RN, radionuclide; N, number of studies

Table 4 shows the mean and median maximum organ AD coefficients from published studies.

Table 4. Summary of Maximum Reported Organ AD Coefficients

	Animal-Derived			Human-Measured		
RN	N	Mean AD±SD (mGy/MBq)	Median (Range) (mGy/MBq)	N	Mean AD±SD (mGy/MBq)	Median (Range) (mGy/MBq)
^{18}F	47	0.186±0.294	0.081 (0.001–1.810)	141	0.161±0.123	0.135 (0.014–0.797)
^{11}C	39	0.030±0.021	0.025 (0.005–0.104)	77	0.032±0.027	0.025 (0.010–0.180)
^{68}Ga	18	0.361±0.417	0.193 (0.014–1.850)	54	0.251±0.177	0.216 (0.048–1.090)
^{64}Cu	28	0.221±0.309	0.116 (0.005–1.480)	12	0.297±0.115	0.315 (0.076–0.460)
^{82}Rb	-	-	-	5	0.009±0.006	0.006 (0.005–0.020)
^{13}N	-	-	-	1	0.0071	0.0071

Source: FDA analysis of published dosimetry data.
Abbreviations: AD, absorbed dose; RN, radionuclide; N, number of studies

These results (Table 3 and Table 4) demonstrate overlap in the distribution of radiation dose estimates derived from animal compared to human studies. However, the standard deviations and ranges calculated from animal compared to human data generally appear higher. These results therefore seem to support both the flexibility and precedence of human in relation to animal dosimetry requirements specified under IND dosimetry regulations.

The mean human-measured ED coefficient (mSv/MBq) for each radionuclide was 0.021±0.007 (^{18}F) (n=143 PET drugs), 0.006±0.002 (^{11}C) (n=78), 0.025±0.012 (^{68}Ga) (n=54), 0.037±0.014 (^{64}Cu) (n=12), 0.002±0.002 (^{82}Rb) (n=5), and 0.007 (^{13}N) (n=1) (Table 3). Table 4 shows the maximum reported mean AD coefficients in mGy/MBq. The mean human ED and AD coefficient for each radionuclide did not account for sex-specific differences and reflect sex-averaged values for each included study. The heterogenous reporting of data consisted of studies that reported dosimetry as sex-averaged values as well as sex-specific values (AD and ED values calculated with male and female adult phantoms using activity-time data from male and female patients, respectively). For studies where male and female dosimetry data were reported separately, there was generally a minimal difference between the sexes.

Whole-body ED values (mSv, calculated using the reported ED coefficients and the average AA for the study subjects) were less than 10 mSv for ^{11}C, ^{82}Rb, ^{13}N studies and less than 20 mSv for ^{18}F, ^{68}Ga, and ^{64}Cu studies. The organs exhibiting maximum organ AD coefficients were identified to be organs other than the blood-forming organs, lens of the eye, and gonads (organs for which the Radioactive Drug Research Committee radiation dose limit is 30 mSv (mGy) for a single-dose administration). The proportion of studies with maximum organ AD values above 50 mGy or mSv ranged from 1% to 26% of the studies with ^{18F}, ^{11}C, ^{68}Ga, ^{82}Rb, and ^{13}N-labeled radiopharmaceuticals, and 50% for ^{64}Cu studies.

3.2.2.1 Comparison of FDA-Approved PET Drugs and Literature Review Results: Administered Activity

The mean AA values from the approved PET drug PIs (Table 1) and from the published clinical studies were compared (Table 5).

Table 5. Administered Activities From Current PIs and Upper Limits on AA for FIH Studies

RN	N	Mean (MBq (mCi)) Clinical Studies	Median (MBq (mCi)) Clinical Studies	Range (MBq (mCi)) Clinical Studies	Mean of the Recommended AA (MBq (mCi)) From PI[a]	Proportion of Studies With AA Exceeding Values in Left Column
^{18}F	143	259±103 (7.0±2.8)	247 (6.7)	90–606 (2.4–16.4)	299 (8)	47/143 (33%)
^{11}C	77	471±206 (12.7±5.6)	428 (11.6)	106–1190 (2.9–32.2)	555 (15)	24/77 (31%)
^{68}Ga	54	175±49 (4.7±1.3)	168 (4.5)	101–263 (2.7–7.1)	158 (4.3)	33/54 (61%)
^{64}Cu	12	226±106 (6.1±2.9)	215 (5.8)	83–441 (2.2–11.9)	148 (4)	9/12 (75%)
^{82}Rb	4	1129±459 (30.5±12.4)	1240 (33.5)	536–1502 (14.5–40.6)	1440 (39)	2/4 (50%)
^{13}N	1	736 (19.9)	736 (19.9)	736 (19.9)	552 (15)	1/1 (100%)

Source: FDA analysis of drug PIs and published dosimetry data.

[a] Mean values in this column correspond to proposed guidelines for streamlined review of pre-IND dosimetry data.

Abbreviations: PI, prescribing information; AA, administered activity; FIH, first-in-human; IND, investigational new drug; RN, radionuclide; N, number of studies

The proportions of ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N published clinical studies with reported AA values higher than the PI-derived values ranged from 31% to 75% (Table 5), with the highest percentage corresponding to the ^{64}Cu studies (excluding ^{13}N since there is only one published clinical study and one approved ^{13}N radiopharmaceutical). We are proposing the mean AA from approved dosing and administration instructions (i.e., mean of the recommended AA) as AA guidelines for FIH studies with new investigational PET drugs that would generally allow the investigator to forego animal radiation dosimetry studies.

3.2.2.2 Comparison of FDA-Approved PET Drugs and Literature Review Results: Radiation Dose

Comparisons of radiation dose, whole-body ED and organ AD for published clinical studies with AA above and below the proposed thresholds on AA for FIH studies (mean of the recommended AA from PI, Table 5) are shown in Table 6 and Table 7, respectively.

Table 6. Summary of ED Values and Proportion of Studies Above and Below the Mean AA From PIs

	All Studies			Approved Drugs			Studies With AA > Mean AA From PI			Studies With AA ≤ Mean AA From PI		
RN	N	Mean ED±SD (mSv)	Range (mSv)	N	Mean ED±SD (mSv)	Range (mSv)	N	Mean ED±SD (mSv)	Range (mSv)	N	Mean ED±SD (mSv)	Range (mSv)
^{18}F	142	5.4±3.0	0.5–18.5	8	6.0±1.5	4.3–8.9	47 (33%) >299 MBq	7.8±3.7	1.6–18.5	95 (67%) ≤299 MBq	4.2±1.5	0.5–9.1
^{11}C	77	2.5±1.4	0.4–7.8	1	1.9	-	24 (31%) >555 MBq	3.5±1.0	2.5–5.8	53 (69%) ≤555 MBq	2.1±1.3	0.4–7.8
^{68}Ga	54	4.3±2.5	0.7–14.2	3	3.1±1.1	2.4–4.4	33 (61%) >158 MBq	5.1±2.6	1.8–14.2	21 (39%) ≤158 MBq	3.1±1.8	0.7–8.5
^{64}Cu	12	8.2±5.4	2.8–19.4	1	5.6	-	9 (75%) >148 MBq	9.5±5.7	2.8–19.4	3 (25%) ≤148 MBq	4.4±0.8	3.5–5.1
^{82}Rb	4	1.3±0.6	0.6–1.9	1	1.9	-	2 (50%) >1440 MBq	1.8±0.1	1.7–1.9	2 (50%) ≤1440 MBq	0.7±0.2	0.6–0.8
^{13}N	1	4.8	-	1	4.8	-			-			-

Source: FDA analysis of drug PIs and published dosimetry data.

Abbreviations: ED, effective dose; AA, administered activity; PI, prescribing information; RN, radionuclide; N, number of studies

Table 7. Summary of Maximum Organ AD Values and Proportion of Studies Above and Below the Mean AA From PIs

	All Studies			Approved Drugs			Studies With AA > Mean AA From PI			Studies With AA ≤ Mean AA From PI		
RN	N	Mean AD±SD (mGy)	Range (mGy)	N	Mean AD±SD (mGy)	Range (mGy)	N	Mean AD±SD (mGy)	Range (mGy)	N	Mean AD±SD (mGy)	Range (mGy)
^{18}F	141	40.8±35.1	3.8–204.8	9	40.0±12.6	24.0-55.5	46 (33%) >299 MBq	58.6±43.8	6.2–204.8	95 (67%) ≤299 MBq	32.2±26.2	3.8–179.3
^{11}C	76	14.4±10.5	3.5–51.3	1	12.4	-	24 (32%) >555 MBq	17.8±10.4	6.6–48.7	52 (68%) ≤555 MBq	12.8±10.3	3.5–51.3
^{68}Ga	54	43.6±31.4	7.9–156.6	3	41.0±47.8	12.6-96.2	33 (61%) >158 MBq	48.2±31.8	11.4–156.6	21 (39%) ≤158 MBq	36.4±30.2	7.9–141.7
^{64}Cu	12	67.4±51.6	21.1–202.6	1	28.6	-	9 (75%) >148 MBq	77.4±56.6	21.1–202.6	3 (25%) ≤148 MBq	37.3±5.5	31.9–42.8
^{82}Rb	4	5.9±2.3	3.1–8.0	1	8.0	-	2 (50%) >1440 MBq	7.8±0.3	7.6–8.0	2 (50%) ≤1440 MBq	4.0±1.2	3.1–4.9
^{13}N	1	5.3	-	1	5.3	-			-			-

Source: FDA analysis of drug PIs and published dosimetry data.
Abbreviations: AD, absorbed dose; AA, administered activity; PI, prescribing information; RN, radionuclide; N, number of studies

Comparing radiation dose estimates under the AA > Mean and AA ≤ Mean columns (Table 6 and Table 7) shows that reducing administered activity along the lines of the proposed AA-leveraging approach generally serves to reduce radiation dose and may allow for reasonable calculation to ensure the safety of FIH subjects pending availability of required drug-specific clinical dosimetry estimates.

3.3 Additional Considerations

In general, an optimal AA for diagnostic imaging should be selected to provide diagnostic image quality with the lowest achievable radiation-induced risk. Optimization of dose and image quality should thus be considered independently of the question of whether animal dosimetry data are a necessary component of an IND submission.

In addition to the radiation risk due to administration of a PET drug, one should consider the added radiation dose from the CT component if a PET/CT scan is acquired. Data from the literature [13] indicate a mean CT and total ED of 5.0±1.0 mSv and 14±1.3 mSv for standard (attenuation CT) ^{18}F-FDG PET/CT imaging; and a mean CT and total ED of 15.4±5.0 mSv and 24.4±4.3 mSv for diagnostic ^{18}F-FDG PET/CT imaging.

In addition to reporting the recommended AA or calculating the mean recommended AA from PIs of PET drugs, we evaluated the maximum AA value from PIs and at published studies with AA exceeding this maximum value (Table 8). For certain radionuclides (e.g., ^{64}Cu) there is no difference between the mean versus maximum AA from PI approach when comparing the proportion of studies with AA exceeding mean AA or maximum AA from PI. However, for the majority of the cases in Table 8, following the mean recommended AA from PI to determine AA thresholds/upper limits for FIH studies appears to be more appropriate and safer when considering the comparison between mean and maximum AA values from PI and corresponding proportions of clinical studies with AA exceeding these values, because less than 10% of published studies have AA values higher than the maximum AA from PI.

Table 8. Mean and Maximum Administered Activities From Current PIs and Clinical Studies Comparison

RN	N	Mean of the Recommended AA (MBq (mCi)) From PI	Proportion of Studies With AA Exceeding Values in Left Column	Maximum of the Recommended AA (MBq (mCi)) From PI	Proportion of Studies With AA Exceeding Values in Left Column
^{18}F	143	299 (8)	47/143 (33%)	375 (10.1)	13/143 (9%)
^{11}C	77	555 (15)	24/77 (31%)	740 (20)	5/77 (6%)
^{68}Ga	54	158 (4.3)	33/54 (61%)	259 (7)	1/54 (2%)
^{64}Cu	12	148 (4)	9/12 (75%)	148 (4)	9/12 (75%)
^{82}Rb	4	1440 (39)	2/4 (50%)	2220 (60)	0/4 (0%)
^{13}N	1	552 (15)	1/1 (100%)	736 (20)	0/1 (0%)

Source: FDA analysis of drug PIs and published dosimetry data.
Abbreviations: AA, administered activity; PI, prescribing information; RN, radionuclide; N, number of studies

3.3.1 Limitations

Many dosimetry studies lacked descriptions of extrapolation methods, which further challenges the assessment of the data due to the inconsistency with the reported values. There are many other variables to consider in the dosimetry calculations and the comparison of dosimetry estimates presented here does not necessarily reflect all assumptions and methods used. For example, the software used for dose calculation and the incorporated models may be different between studies. Many studies lacked information on utilization of the bladder model or specification of a voiding interval. Without a standardized bladder voiding interval, the void times used across preclinical and clinical studies vary greatly (0.5 to 6 hours); depending on the interval used, the bladder dose and whole-body ED can be meaningfully affected. The PIs for currently approved PET radiopharmaceuticals primarily instruct patients to void as often as possible during the first hour after completing the imaging study to reduce radiation exposure.

In this review, we decided to focus on FDA-approved PET drugs and associated PIs as the basis for more transparent guidelines for investigators who may wish to forego performing animal dosimetry studies. The AA of approved drugs in the drug labeling has been selected as a result of a comprehensive marketing application assessment that includes radiation dosimetry data. However, there are limitations in the drug labeling approach to derive AA guidelines for studies with new PET drugs. This approach tends to assume that the biodistribution of new PET drugs is informed by the biodistributions of previously investigated PET drugs and that biodistributions with unprecedented radiation safety implications will be rare. We provide more discussion below on so-called worst-case scenarios, e.g., unusual radioactivity uptake in a radiosensitive organ.

3.3.2 Worst-Case and Other Scenario Considerations

Gatley [14] performed simulation studies to estimate an intravenously injected quantity of several ^{11}C-labeled compounds that would not exceed a regulatory limit of 50 mSv on absorbed doses for individual organs [10]. Upper limits on organ cumulative activities were estimated by assuming that ^{11}C-labeled compounds are instantaneously distributed in the plasma and then transferred only and irreversibly to a single organ. This approach allows the assessment of the worst-case estimate, in order to conservatively plan initial human PET studies. Using an organ radiation dose limit of 50 mSv, Gatley showed that a

preliminary study with up to 130 MBq (3.5 mCi) of ^{11}C could be performed in humans without reaching this limit.

As an example of conservatively determining the maximum AA for human studies with a new radiopharmaceutical based on maximum reported human radiation dose values and upper dose limits, here we consider the 50 mSv RDRC limit for a single administration of ^{11}C and ^{18}F radiopharmaceuticals. In Zanotti-Fregonara et al. [8], a similar calculation is reported using this upper limit of ED in radiation research studies as defined by the National Institutes of Health (50 mSv). For ^{11}C radiopharmaceuticals, the highest reported ED in human studies was with ^{11}C-WAY100,635 [15] (study-reported AA: 243 MBq [6.6 mCi]) (0.0160 mSv/MBq) corresponding to a maximum AA of 3125 MBq (~84 mCi). However, since the dose to a particular organ can be higher than the ED in general, it is important to consider the organ AD values for the same radiopharmaceutical. Considering the maximum reported AD would be a more restrictive approach. For ^{11}C-WAY100,635, the urinary bladder was the organ with maximum AD (0.0194 mGy/MBq), limiting the AA to 2577 MBq (~70 mCi). The highest reported organ AD for ^{11}C radiopharmaceuticals was with ^{11}C-CSar [16] (AA: 114 MBq [3.1 mCi]) and the gallbladder was the organ with maximum AD (0.1799 mGy/MBq), restricting the AA to 278 MBq (~7.5 mCi).

Zanotti-Fregonara et al. [7] noted that an activity of 370 MBq (10 mCi) would be sufficient to perform a study with an acceptable image quality, i.e., 370 MBq of any ^{11}C-labeled radiopharmaceutical can be safely used for FIH studies. Higher injected activities (e.g., 20 mCi) are necessary for brain imaging to facilitate measurements in subregions of the brain, and to enable measurements of rapidly declining concentrations of radioligand in plasma, suggesting a pathway to safely perform FIH studies of new ^{11}C-labeled radiopharmaceuticals.

For ^{18}F radiopharmaceuticals, the highest reported ED in human studies was with ^{18}F-TFB [17] (AA: 370 MBq [10 mCi]) (0.0442 mSv/MBq), corresponding to a maximum AA of 1131 MBq (~31 mCi); the thyroid was the organ with maximum AD (0.3100 mGy/MBq), limiting the AA to 161.3 MBq (~4.4 mCi). The highest reported organ AD was with ^{18}F-4FMFES [18] (AA: 174 MBq [4.7 mCi]), and the gallbladder was the organ with maximum AD (0.7970 mGy/MBq), restricting the AA to 62.7 MBq (~1.7 mCi) based on the 50 mSv single administration limit.

Zanotti-Fregonara et al. [8] suggested an approach for FIH studies with a new ^{18}F radiopharmaceutical, namely beginning with whole-body scanning in a single human subject using an AA of about 74 MBq (2 mCi), which is less than one-third of the safe activity of the most irradiating ^{18}F radiopharmaceuticals in terms of ED. The aim of this first scan is to detect a radiopharmaceutical that disproportionately accumulates in a single radiosensitive organ. If this first scan confirms that the radioactivity is fairly widely distributed in the body, higher activities may be injected. To increase the count rates from this low injected activity, a slower whole-body scan may be acquired.

3.3.2.1 Estimation of Cancer Risk Due to Radiation Exposure in Diagnostic PET Imaging with ^{18}F, ^{11}C, ^{68}Ga, and ^{64}Cu

Calculated organ AD can be used to estimate cancer risk associated with a particular diagnostic radiopharmaceutical. This stochastic endpoint (i.e., cancer risk) was used as a measure to calculate risk associated with a hypothetical scenario of high absorbed dose delivered to a particular organ from activity accumulation in one organ only upon administration of a PET drug, and, to evaluate relative risk between different PET radionuclides. Specifically, the cancer risk due to radiation exposure from an imaging scan involving these PET radionuclides was estimated using the National Cancer Institute's

Radiation Risk Assessment Tool [19] assuming the following case scenario: 1) a typical AA of 100 MBq (2.7 mCi) taken up by one particular organ (kidneys); and 2) clearance by physical decay only. The target-organ cancer risks to kidneys only and to all sites including kidneys were estimated for an 18-year-old female using the AD calculated for this hypothetical scenario for each radionuclide, independent of pharmacophore. To compare with a real scenario, cancer risk was also estimated for a commonly used PET radiopharmaceutical, ^{18}F-FDG (AA = 370 MBq [10 mCi]), considering activity accumulation in all organs of activity uptake with both physical decay and biological clearance. In both scenarios, the risk was compared to the baseline lifetime risk for developing cancer not associated with radiation exposure. The risk was then used to calculate a risk index for each radionuclide and ^{18}F-FDG as introduced in [20]:

$$Risk\ Index\ (\%) = \frac{Estimated\ Radiation\ Induced\ Cancer\ Risk}{Natural\ Incidence\ of\ Cancer} \times 100 \qquad \text{Eq. 1}$$

The estimated lifetime cancer risk and natural incidence of cancer are the radiation induced risks from imaging studies and from an unexposed population, respectively, per 100,000 patients as a function of subject age and gender [19].

The risk index from exposure to kidneys and other target organs for an 18-year-old female was estimated respective to each of these radionuclides in increasing physical half-life order: ^{11}C, ^{18}F, ^{68}Ga, and ^{64}Cu (^{82}Rb and ^{13}N were not considered here given the much shorter physical half-lives). The higher kidney cancer risk compared to all sites risk is due to the assumption of activity uptake in kidneys only, therefore self-dose to kidneys and kidney cancer risk is high. In a real-case scenario when activity is distributed throughout the body, the self-dose would be the largest contribution to the dose to a particular organ compared to dose from other sources, but still lower than the self-dose in this hypothetical scenario when activity accumulates only in one organ. The lifetime risk (chances in 100,000) of developing cancer to kidneys due to radiation exposure from a hypothetical scenario of diagnostic imaging with a ^{11}C radiopharmaceutical is >3× smaller than the risk from a ^{18}F-FDG real diagnostic scan scenario. The kidney risk indices for the hypothetical cases with any ^{18}F, ^{68}Ga and ^{64}Cu were ~1.3×, ~2×, and ~4× higher than the risk index for ^{18}F-FDG, respectively.

3.4 Summary and Conclusions

In this briefing document, we presented a review of human organ AD and whole-body ED estimates extrapolated from animal dosimetry studies, and, also calculated based on human dosimetry studies from a total of 322 PET drugs containing ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N, including FDA-approved PET drugs. Our aim was to perform a systemic review of dosimetry data with PET drugs and determine if sufficient data might be available from animal or human studies to allow reasonable calculations of radiation-absorbed dose to the whole body and critical organs upon administration of a new PET drug to a human subject in FIH studies. Recommended AAs from PI of the approved PET drugs were analyzed to determine AA guidelines for FIH studies with new PET drugs for specific radionuclides. This study provides a comprehensive review of dosimetry data on PET radiopharmaceuticals, which adds data to the previous analyses by Zanotti-Fregonara et al. for ^{11}C- and ^{18}F-labeled PET drugs [7-9], and presents analyses of dosimetry data on radiopharmaceuticals labeled with other radionuclides used in PET imaging.

Other authors have noted that the animal data poorly predict human dosimetry [2, 7, 8, 21, 22]. In our study, we observed good agreement between animal-derived and human-measured dosimetry, especially in studies with PET radiopharmaceuticals labeled with shorter-lived radionuclides.

Analysis of the recommended AA values (mean AA from PI) of FDA-approved PET drugs and published clinical dosimetry data suggest that if the planned AA of a FIH study with a new PET drug radiolabeled with ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N is less than or equal to 299 MBq (8 mCi), 555 MBq (15 mCi), 158 MBq (4.3 mCi), 148 MBq (4 mCi), 1440 MBq (39 mCi), and 552 MBq (15 mCi), respectively, sufficient data may generally be available to justify omission of preclinical dosimetry studies and proceed to the required Phase 1 human dosimetry investigation to establish radiation safety. Although this review did not identify any studies that found the maximum absorbed dose to be colocalized with radiation-sensitive organs, the results of this review do not apply to exceptional cases in which animal dosimetry would still be necessary or required, such as a PET drug intended to target radiosensitive organs or patients.

The results of this review also show that ^{18}F-, ^{11}C-, ^{68}Ga-, ^{64}Cu-, ^{82}Rb-, and ^{13}N-labeled PET drugs in clinical studies conducted to date have a safe radiation profile when considering the current established Radioactive Drug Research Committee radiation-dose thresholds as a frame of reference. ^{18}F-, ^{11}C-, ^{68}Ga-, ^{64}Cu-, ^{82}Rb-, and ^{13}N-labeled radiopharmaceuticals are well below the whole-body ED limit of 30 mSv, and the same radiation profile applies with respect to the organ AD limit of 50 mGy with a lower (<30%) proportion of studies over this threshold, with the exception of ^{64}Cu (50% of studies over this threshold). Additionally, it must be noted that the maximal AAs for the very short-lived radionuclides ^{82}Rb and ^{13}N were derived from a significantly limited number of available published clinical data with no available preclinical data at the time of the search.

Zanotti-Fregonara et al. [7, 8] have proposed foregoing animal dosimetry to predict human doses and suggested pathways to safely perform FIH studies by beginning with whole-body imaging in a single human subject using 370 MBq (10 mCi) for novel ^{11}C-labeled radiopharmaceuticals and 74 MBq (2 mCi) for novel ^{18}F-labeled radiopharmaceuticals. The purpose is to confirm that the novel drug is widely distributed in the body, that no organ is likely to receive a theoretical maximal radiation dose, and that the radioactivity does not disproportionately accumulate in a single radiosensitive organ. A human dosimetry study could then be performed, provided that the biodistribution of the new compound is reasonable and that no organ is likely to have an abnormally high uptake. The results of this review generally support and extend the recommendations of Zanotti-Fregonara et al. [7, 8] based on the larger corpus of dosimetry data analyzed herein and with the aim of accommodating the full range of early-phase studies and study aims conducted under PET drug INDs.

In addition to the six PET radionuclides of focus in these recommendations, we also analyzed dosimetry data from published studies with other PET radionuclides (^{15}O, ^{89}Zr, and ^{124}I). Relevant results of this analysis for discussion, including comparison of dosimetry profiles and animal-to-human dosimetry assessment between PET radionuclides with varying physical half-lives, are provided in Section 5.

3.4.1 Conclusions

Recommended activity amounts for FIH studies with new PET drugs based on published human dosimetry data and regulatory experience depend on the radiation dosimetry profile of a given radiopharmaceutical (i.e., both physical and biological properties) and on the observed variability of estimated doses and AA values. In this review, we observed good agreement between animal-derived

and human-measured dosimetry, especially in studies with PET drugs labeled with relatively short-lived radionuclides. Given the increased amount of clinical data available and the lower variability in dose estimates derived from clinical studies, we relied on data from PIs of FDA-approved drugs and published clinical studies to derive AA guidelines that can be used prior to performing dosimetry in a FIH study of an investigational PET drug labeled with ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N. The proposed upper limits on AA for FIH studies with new PET drugs provide flexibility on the need to perform animal dosimetry studies for developing new radiopharmaceuticals labeled with one of these six PET radionuclides ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N.

4 References

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5 Appendix

A literature review was performed to collect dosimetry data for positron emission tomography (PET) radiopharmaceuticals with ^{15}O, and the longer-lived PET radionuclides, ^{89}Zr and ^{124}I, in addition to the PET radionuclides pertinent to the issues discussed at this Advisory Committee meeting. Similar analysis of the animal-derived and human-measured and reported human radiation dose estimates was performed as discussed in the methodology above.

For the purpose of comparing relative dosimetry profiles of the various PET radiopharmaceuticals, in this section the PET radionuclides are listed in increasing physical half-life order: ^{82}Rb, ^{15}O, ^{13}N, ^{11}C, ^{68}Ga, ^{18}F, ^{64}Cu, ^{89}Zr and ^{124}I. Lower variability was observed in radiation dose estimates from human studies compared to animal studies with ^{11}C-, ^{68}Ga-, ^{18}F-, and ^{64}Cu-labeled radiopharmaceuticals, when compared to radiopharmaceuticals labeled with the longer-lived PET radionuclides, ^{89}Zr and ^{124}I.

The mean effective dose (ED) coefficients of ^{89}Zr and ^{124}I are ~10× and ~15× higher than the mean ED coefficient of ^{64}Cu-labeled radiopharmaceuticals, and the variability in clinical whole-body ED estimates for ^{82}Rb, ^{13}N, ^{11}C, ^{68}Ga, ^{18}F, and ^{64}Cu is lower than for ^{89}Zr and ^{124}I, highlighting major differences in the radiation profiles and radiation risk of ^{82}Rb-, ^{15}O-, ^{13}N-, ^{11}C-, ^{68}Ga-, ^{18}F-, and ^{64}Cu-labeled radiopharmaceuticals compared to ^{89}Zr and ^{124}I in this group of radionuclides used for PET imaging. We thus focused on the former seven radionuclides to determine activity amounts for administration in first-in-human studies with novel ^{82}Rb-, ^{15}O-, ^{13}N-, ^{11}C-, ^{68}Ga-, ^{18}F-, and ^{64}Cu-labeled radiopharmaceuticals based on available clinical dosimetry data. ^{15}O was excluded because there are no approved ^{15}O-labeled PET drugs.

A similar calculation of the radiation risk index as described in Section 3.2.2.1 for ^{89}Zr and ^{124}I resulted in calculated kidney risk indices for the hypothetical cases (unusual activity accumulation in one organ (kidney) only post-administration and clearance by physical decay only) with ^{89}Zr and ^{124}I to be ~37× and ~72× higher than the risk index for ^{18}F-FDG, respectively.

For PET radionuclides with higher radiation risks, namely ^{89}Zr and ^{124}I, available ED and organ administered dose data were generally not found to meet the reasonable calculation standard for informing a decision about the unknown biodistribution of a novel radioactive drug. Even though there is large variability in animal-derived dosimetry, there is still value in estimating human radiation doses from animals given the large variability in the collected clinical dosimetry data and the relatively higher radiation doses of radiopharmaceuticals labeled with longer-lived compared to shorter-lived radionuclides. In addition, there are no approved ^{89}Zr or ^{124}I PET drugs.