Introductory Comments
August 1, 2023, Meeting of the
Medical Imaging Drugs Advisory Committee on
New PET Drug pre-IND and Phase 1 Dosimetry Data

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Why Are We Here?

To **discuss issues** involving pre-IND and Phase 1 radiation dosimetry data for certain groups of new positron emission tomography (PET) drugs*

- *Not:* product-, sponsor-, or application-specific matter
- *Not:* voting-type meeting

- *Issue*: stakeholder concern regarding burden of animal dosimetry data collection for certain groups of new PET drugs
- *Rationale*: available data often allows reasonable calculation of radiation risk for subjects prior to collection of Phase 1 dosimetry data

*Includes both PET biological and drug products (see also 21 CFR 601).

Where We Need Advice

Regarding new IND sponsors of certain groups of new PET drugs lacking drug-specific animal dosimetry data

- Discuss **sufficiency** of reviewed dosimetry data
- Discuss **reasonableness** of approach under consideration for investigational administration prior to Phase 1 dosimetry data
  - *Administered radioactivity* ≤ *X*: FDA may generally find administered activities safe-to-proceed from radiation safety perspective
  - *Administered radioactivity* > *X*: continued case-by-case review regarding reasonableness of available animal or human dosimetry data

Today's Agenda

12:20 p.m.	Guest Speakers	Hallett (Invicro) Zanotti-Fregonara (NIH)
1:10 p.m.	FDA presentations	Plyku (medical physics) Cohen (nonclinical) Cotter (OSE)
3:00 p.m.	Open Public Hearing & Questions to the Committee	

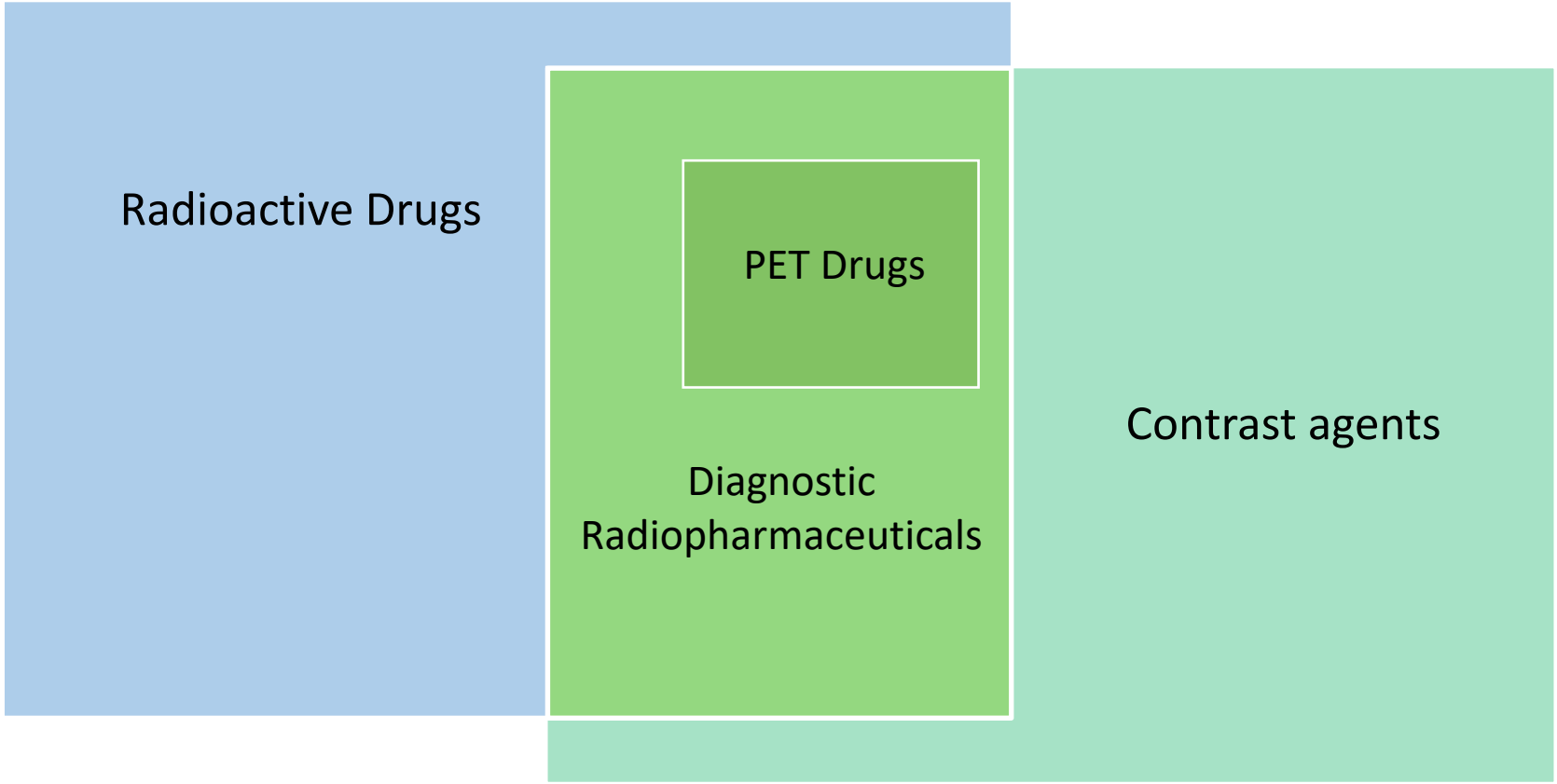
PET Drugs in Context: 1975–1997

Year	Act, Regulation, Guidance	For certain medical products:
1975	21 CFR 310.3, 310.503, 361.1, 600.3	• Defined "radioactive drug" as drug or biological product exhibiting spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons • Ended exception since 1963 for Nuclear Regulatory Commission oversight of investigational use • Provided certain new authority for oversight of basic research to FDA authorized Radioactive Drug Research Committees (RDRCs)
1987	21 CFR 312.23	• Rewrote IND regulation, including regarding radioactive drugs and data on radiation-absorbed dose from animal or human studies and Phase 1 studies for dosimetry calculations
1997	Modernization (FDAMA)	• Defined "PET drug" as one exhibiting spontaneous disintegration of unstable nuclei by the emission of positrons and used for providing dual photon PET diagnostic images • Defined "radiopharmaceutical" as an article intended for diagnosis or monitoring of disease and exhibiting spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons

PET Drugs in Context: 1999–2022

Year	Act, Reg, Guidance, or Approval	For certain products:
1999	21 CFR 315	• Specified scope, definition, general factors, indications, evaluation of effectiveness and safety for "diagnostic radiopharmaceuticals."
2004	Developing medical imaging drug and biological products	• Provided 3-part guidance for developers of medical imaging drugs and biological products (safety; clinical indications; design, analysis, and interpretation)
2017	Reauthorization (FDARA)	• Defined "contrast agent" as diagnostic radiopharmaceutical or other drug intended to improve the visualization of structure or function within the body by increasing the relative difference in signal intensity within target tissue, structure, or fluid. • For certain diagnostic imaging devices intended for use with approved contrast agents, permitted approval of certain new contrast agent uses under 510k, de novo, or PMA device marketing applications.
2022	Omnibus Reform (FDORA)	• Defined "contrast agent" as i) a diagnostic radiopharmaceutical or ii) a diagnostic agent that improves the visualization of structure or function within the body when used in conjunction with a medical imaging device. • Excepted implant or article similar to an implant and articles that apply radiation from outside of the body from definition of radioactive drug

PET Drugs in Context



21 CFR 312.23

Additional information. In certain applications, as described below, information on special topics may be needed. Such information shall be submitted as follows:

Radioactive drugs. If the drug is a radioactive drug,

- Sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject.
- Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

Discussion Points

- A) Discuss the sufficiency of reviewed data from animal or human studies involving F 18, C 11, Ga 68, Cu 64, Rb 82, or N 13 to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon first-in-human administration of a new PET drug containing one of these radionuclides

Discussion Points

- B) Discuss the reasonableness of the approach under consideration involving administered activity values for new PET drugs containing F 18, C 11, Ga 68, Cu 64, Rb 82, and N 13, such that Phase 1 studies that will both i) initially administer one or more activity levels ≤ value and ii) collect 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

Medical Physics Presentation
August 1, 2023
Meeting of the Medical Imaging Drugs Advisory Committee on New PET Drug Pre-IND and Phase 1 Dosimetry Data

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Center for Drug Evaluation and Research, FDA

Outline

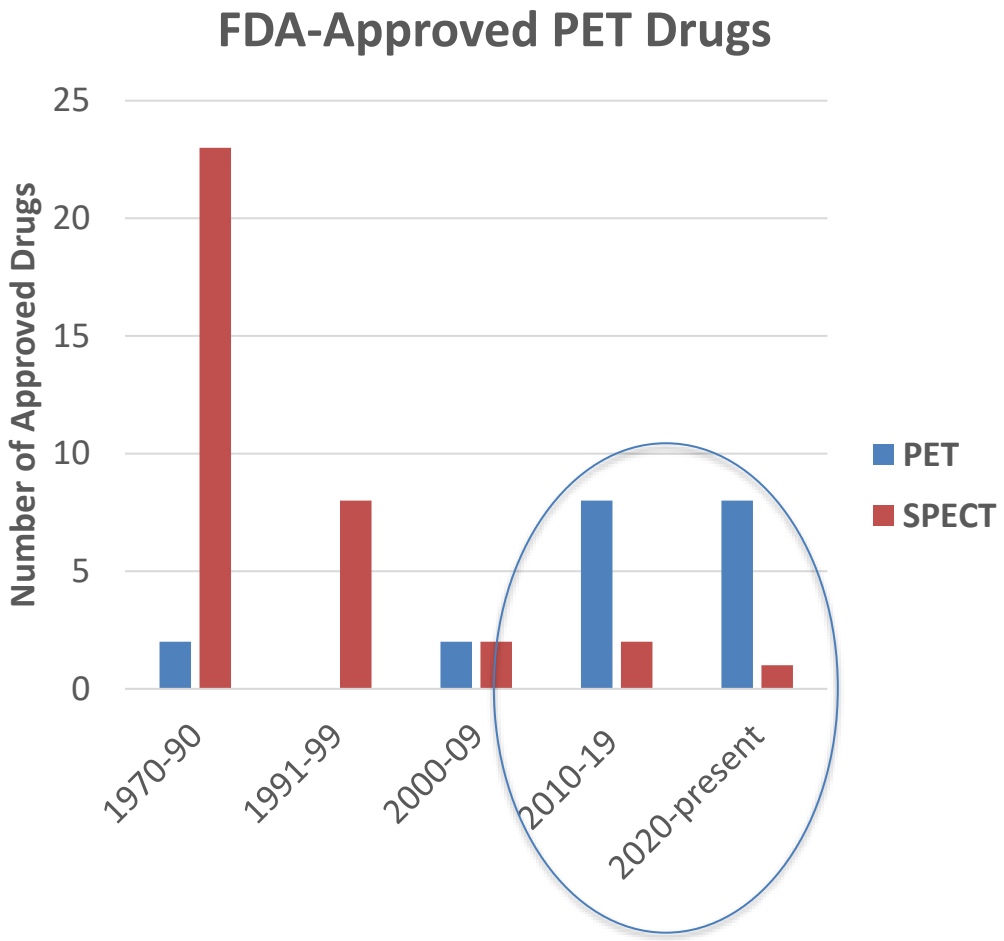
- Introduction
  - PET Imaging Drugs
  - Radiation Dosimetry and Regulatory Aspects
  - Value of Nonclinical Dosimetry Studies for Animal-to-Human Extrapolation
- Literature Review on Radiation Dosimetry Data of PET Drugs
- Recommendations for Designing First-in-Human (FIH) Studies to Evaluate Radiation Dosimetry of Certain New PET Drugs
- Other Considerations for Discussion

PET Imaging Drugs

- Some unique characteristics:
  - Short half-life, high energy radiation (511 keV)
  - Diagnostic agents used for therapy planning and evaluation
- Advancements in Cancer
  - Neuroendocrine diagnostics
  - Restaging and informing treatment planning of recurrent prostate cancer
  - Adjunctive detection in breast cancer
- Advancements in Alzheimer's, Parkinson's and Cardiac conditions
- PET/CT Imaging Innovations: Digital PET/CT, Total Body PET

Radioisotope	Phys. Half-Life	Positron Decay (%)
^{82}Rb	1.25 m	96
^{15}O	2.03 m	99.9
^{13}N	9.97 m	100
^{11}C	20.4 m	99.8
^{68}Ga	68.1 m	90
^{18}F	109.8 m	96.9
^{64}Cu	12.7 h	19.3
^{89}Zr	3.3 d	23
^{124}I	4.2 d	25

PET Imaging Drugs



- Currently 19 FDA-approved PET drugs (NDAs)
- 85 total abbreviated NDAs (ANDAs) for PET drugs in the US (including 38 ANDAs for ^{18}F-FDG)

Regulatory Aspects

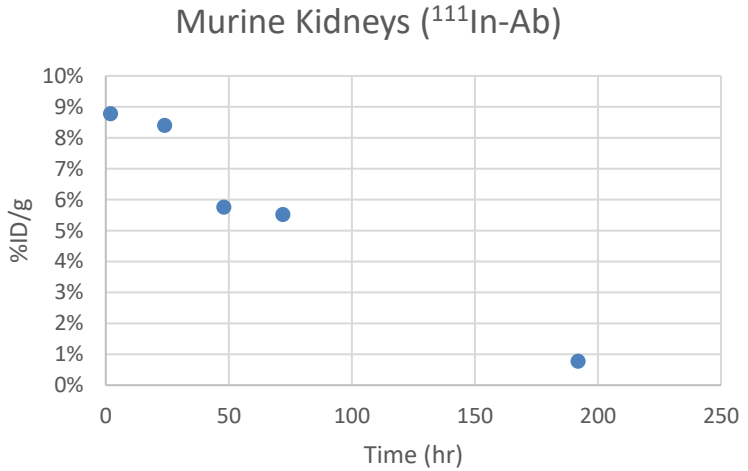
- For radioactive drugs, 21 CFR 312.23(a)(10)(ii) requires that IND submissions include "*sufficient data from animal or human studies to allow a reasonable estimation of absorbed-dose to the whole-body and critical organs upon administration to a human subject*".
- For FIH studies, IND submissions include absorbed dose (AD) estimates for humans that are often extrapolated from animal biodistribution data.
- Regulatory Considerations:
  - Tendency to underestimate human organ AD when extrapolated from animal data
  - Level of variation expected from this extrapolation

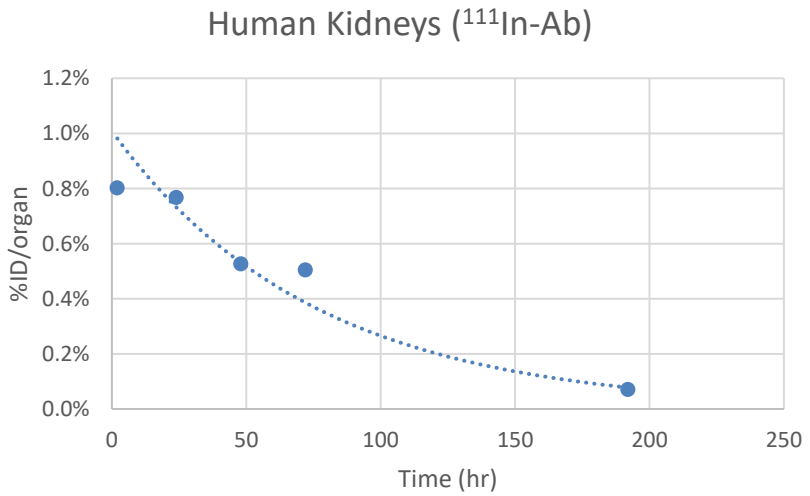
Animal to Human Conversion

Relative Organ-Mass Extrapolation

$$[\%ID/organ]_H = [\%ID/g]_A \cdot TBM_A \cdot \frac{OM_H}{TBM_H}$$

Assumption: *the metabolism is similar between animals and humans and varies only as a function of organ mass*





Nonclinical Biodistribution Studies

- Provide an estimate for human organ AD
- Could be used to identify unexpected high uptake in a particular organ

MIRD Methodology

$\tilde{A}(r_S)$: Number of decays in ROI

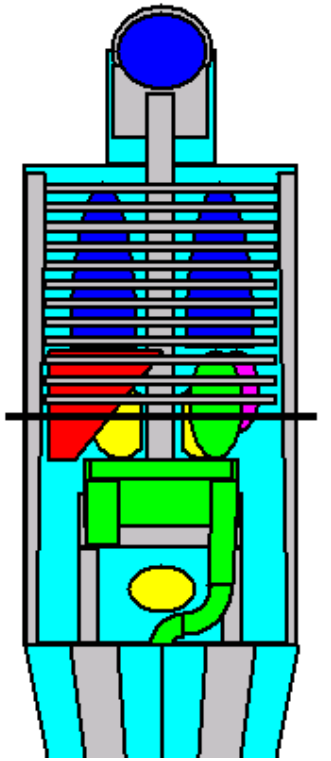
$$D(r_T) = \sum_{r_S} \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S)$$

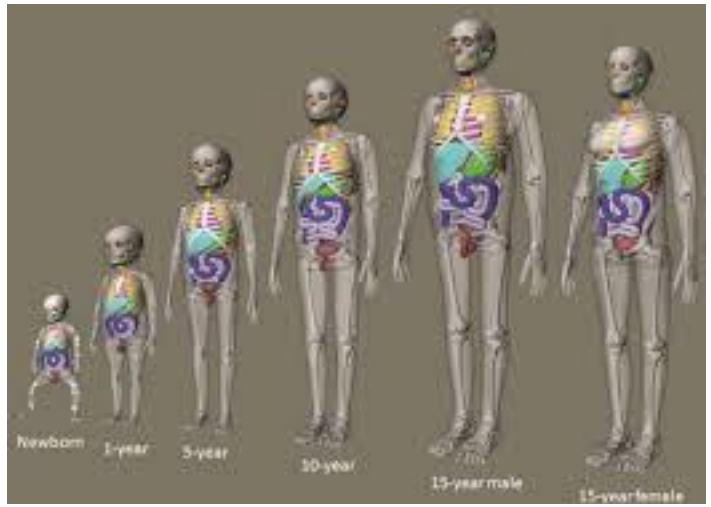
S-value: Pre-tabulated energy transfer coefficients:

- properties of the radionuclide
- organ anatomy
- organ mass

$D_t = \tilde{A}_{s1} \cdot S(t \leftarrow s1) + \tilde{A}_{s2} \cdot S(t \leftarrow s2) + \ldots.$

The Medical Internal Radiation Dose (MIRD) *S*-value schema (MIRD Pamphlet 21)





Digital anthropomorphic phantoms of varying size and anatomy, Uni. of Florida

FDA Recommendations on Nonclinical Dosimetry Studies for New PET Drug Development

Current State

1) Pre-IND submissions (Questions and Briefing Package) to obtain FDA feedback for planning an IND Opening Protocol
   - Plans to conduct or results from animal biodistribution and dosimetry studies
2) FDA reviews IND Opening Protocols
   - Results from animal biodistribution and dosimetry studies
   - Human organ dosimetry estimates

- **Review performed on a case-by-case basis**
- **Review issues generally include:**
  - Limitations of animal-to-human radiation dose extrapolation
  - Recommendations on planning and design of animal biodistribution and dosimetry studies
  - Recommendations on the design of clinical dosimetry studies

FDA Recommendations on Nonclinical Dosimetry Studies for New PET Drug Development

Future State

Approach under consideration involves administered activity (AA) values for new PET drugs containing:

- ^{18}F
- ^{11}C
- ^{68}Ga
- ^{64}Cu
- ^{82}Rb
- ^{13}N

in the absence of animal-to-human dosimetry estimates

Approach under consideration for investigational administration prior to Phase 1 dosimetry data

- *AA ≤ X*
  - *Recommendations?*
- *AA > X*
  - *Recommendations?*

Value of Nonclinical Dosimetry Studies

- Performance of commonly used extrapolation techniques to predict TIACs (aka: residence times) in humans using biodistribution data collected from animals for 33 RPs (including PET and SPECT imaging drugs)

  (1) no extrapolation,

  (2) relative organ-mass extrapolation (*assumption: the metabolism is similar between the two species and varies only as a function of organ mass*),

  (3) physiological time extrapolation (*assumption: many physiological functions across various animal species are related as a function of body mass*),

  (4) using a combination of mass and time methods.

- TIACs were calculated using animal and human data, and distributions of ratios (animal-derived/human-measured) were plotted for each extrapolation method.

Sparks, R. B., & Aydogan, B. (1999). *Comparison of the effectiveness of some common animal data scaling techniques in estimating human radiation dose* (No. ORISE-99-0164-Vol. 2; CONF-960536-PROC.-Vol. 2). Oak Ridge Associated Universities, TN (United States).
Abbreviations: TIAC, time-integrated activity coefficient; RP, radiopharmaceuticals); SPECT, single-photon emission computed tomography

Organ Residence Times Ratio (Animal-Derived/Human-Measured)

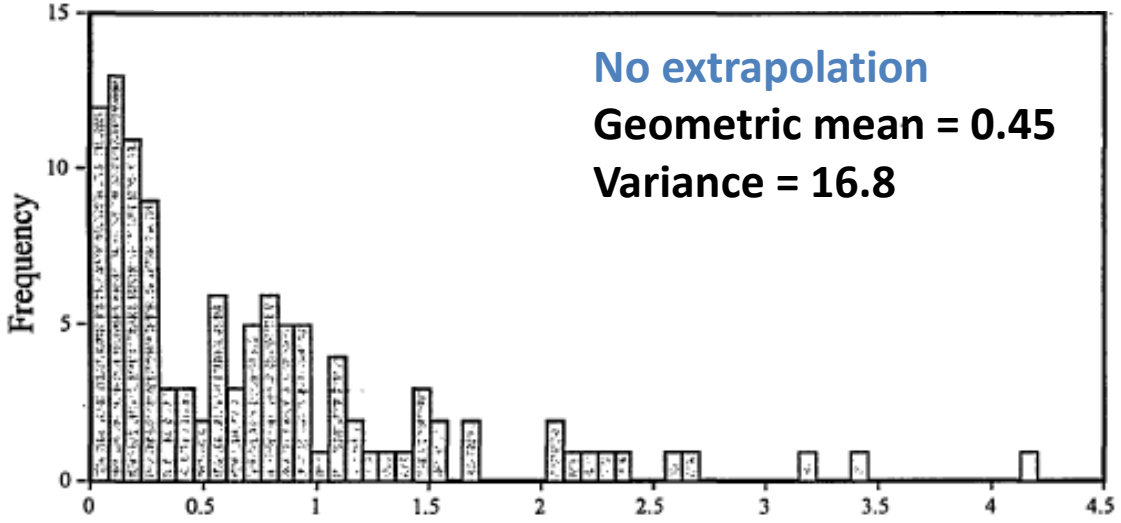


Figure 1. Frequency distribution of the ratio of the organ residence times found using the raw animal data to the residence times found using data from humans.

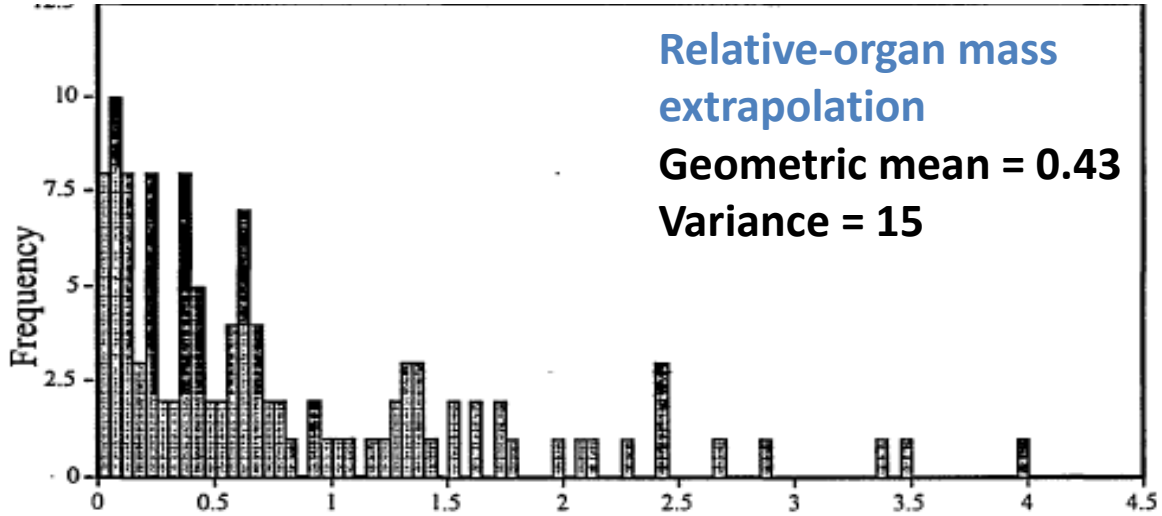


Figure 2. Frequency distribution of the ratio of the organ residence times found using the mass extrapolated animal data to the residence times found using data from humans.

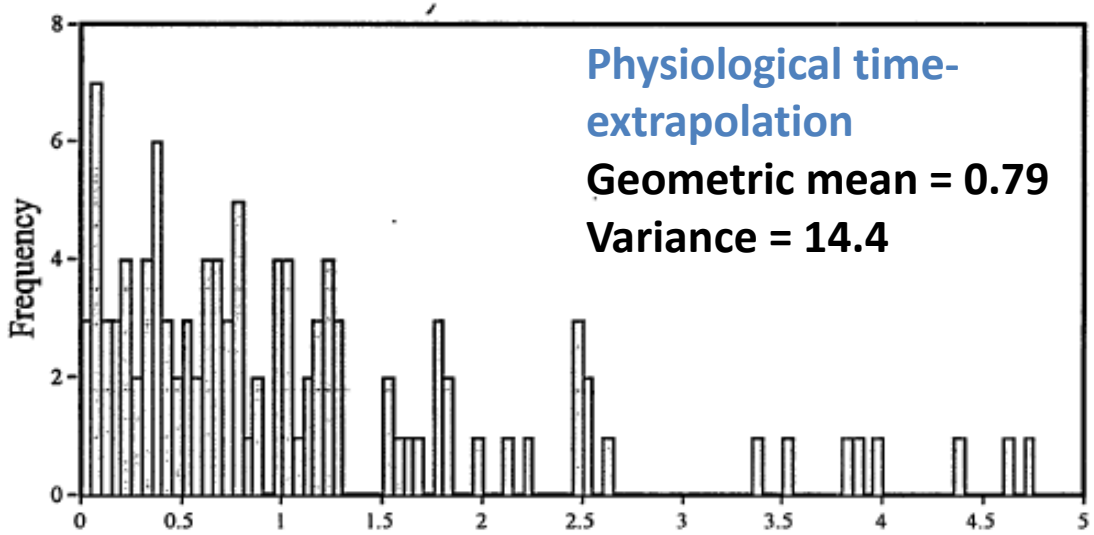


Figure 3. Frequency distribution of the ratio of the organ residence times found using the time extrapolated animal data to the residence times found using data from humans.

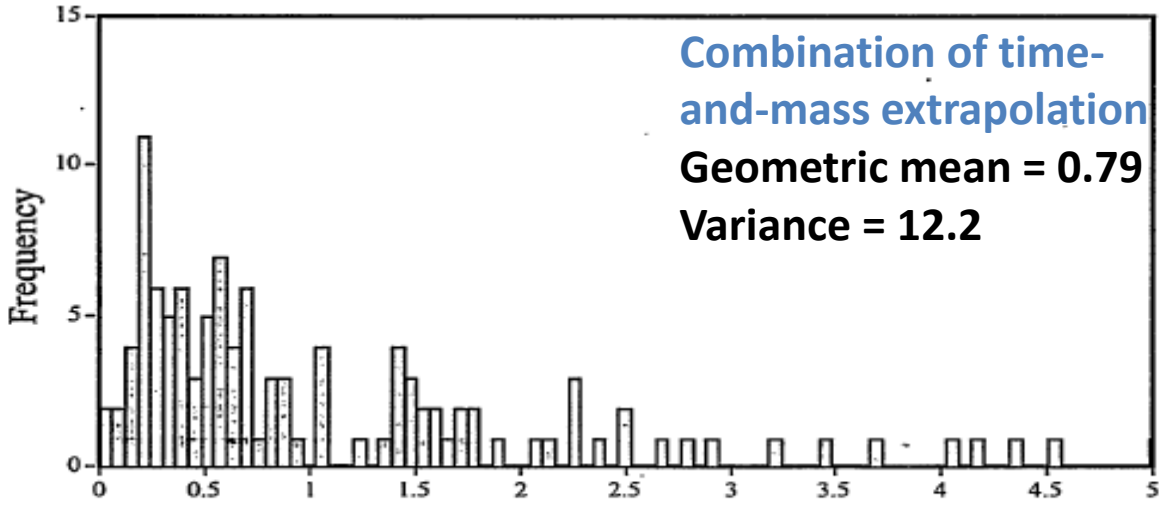
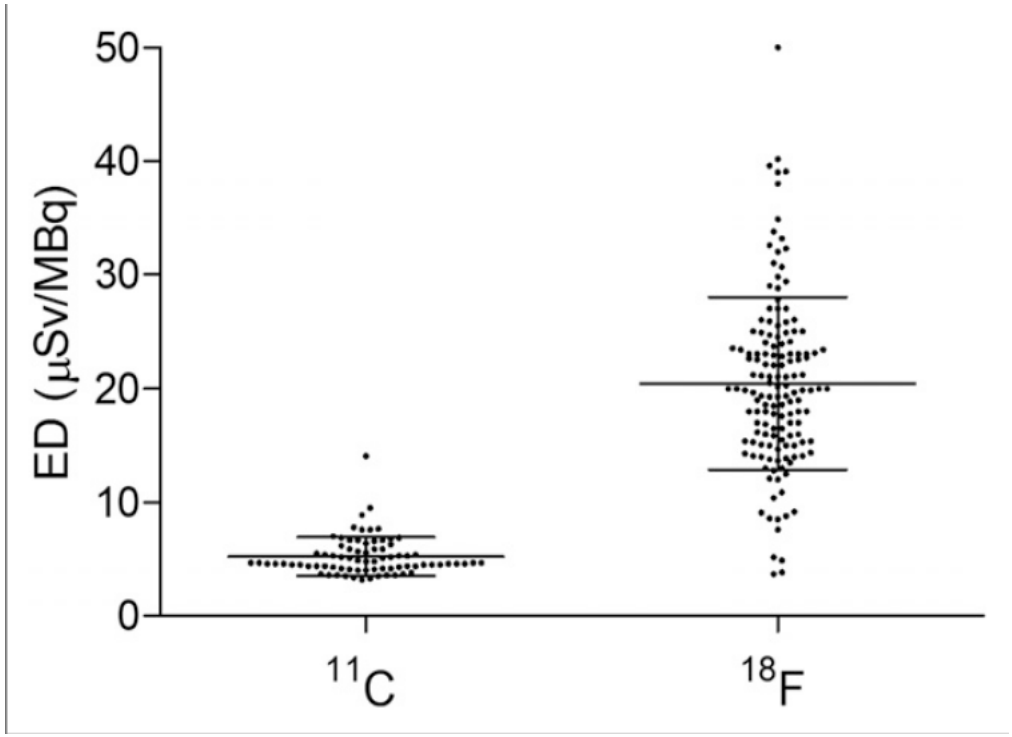


Figure 4. Frequency distribution of the ratio of the organ residence times found using the time and mass extrapolated animal data to the residence times found using data from humans.

Zanotti-Fregonara et al. (2012-2020)

Suggested Pathway to Assess Radiation Safety of 11C-labeled PET Tracers for FIH Studies, EJNMMI, (2012) 39: 544-547
Suggested Pathway to Assess Radiation Safety of 18F-labeled PET Tracers for FIH Studies, EJNMMI, (2013) 40: 1781-1783
11C Dosimetry Scans Should be Abandoned, JNM, (2020) 62: No.2



- ^{11}C whole-body effective dose (ED) values have a smaller variability compared to F-18 (4-fold diff.)
- Variations around the mean values largely methodological: choice of **dynamic bladder model** and **voiding time parameters** could have a 10-60% diff. in the calculated ED value.

Other Studies on Animal-to-Human Radiation Dosimetry

Crawford et al. and Wegst et al. (1980) – Third International Radiopharmaceutical Dosimetry Symposium Proceedings

- Strengths and Weaknesses of various extrapolation methods proposed in the literature
- Factors Affecting Animal-to-Human Extrapolation: the ratio of organ to body weight

Gupta, A., et al. (2020). Preclinical voxel-based dosimetry in theranostics: a review. NMMI, 54, 86-97

- Factors (variation in size and anatomy, interspecies differences in PK, and methodological differences in biodistribution measurements) that cause discrepancies between mouse and human derived organ AD

Korde, A., et al. (2022). Practical considerations for navigating the regulatory landscape of non-clinical studies for clinical translation of radiopharmaceuticals. EJNMMI Radiopharmacy and Chemistry, 7(1), 1-29

- Need for standardization in reporting dosimetry methodology and data

Cicone, F., et al. (2022). Comparison of absorbed dose extrapolation methods for mouse-to-human translation of radiolabelled macromolecules. EJNMMI research, 12(1), 21

- Methodological implications, compared five extrapolation methods – Best approximation of the actual human dosimetry provided by the method applying a metabolic scaling to the mouse organ TIACs.

Summary of the Issues for the AC Meeting

In order to determine approach under consideration involving AA values for new PET drugs containing ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N, we followed this approach:

1) Leverage findings <u>for the safety of approved PET drugs</u> when administered at the AA levels specified on the drug label.

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)
^{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)

Summary of Issues for the AC Meeting

In order to determine approach under consideration involving AA values for new PET drugs containing F-18, C-11, Ga-68, Cu-64, Rb-82, and N-13, we followed this approach:

1) Leverage findings for the safety of approved PET drugs when administered at the AA levels specified on the drug label, and,

2) Analyze dosimetry data from published nonclinical and clinical studies of PET drugs (both investigational and approved drugs) through a systematic literature review.

Literature Review

Methods:

- Six literature searches on **^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N** labeled PET drugs publications since 1990 (investigational and approved drugs)
- Reported human-organ radiation dose estimates from animal and human studies calculated following MIRD or related methodology (i.e., whole-body effective dose (ED) and organ absorbed dose (AD) coefficients, etc.)
- **Animal-derived** and **human-measured** whole-body ED and max. organ AD
- Calculated proportion of published studies with reported AA values > the per-radionuclide mean AA from approved drug label

Literature Review Results

Total of **322 PET radiopharmaceuticals** (including both **investigational** and **approved**)

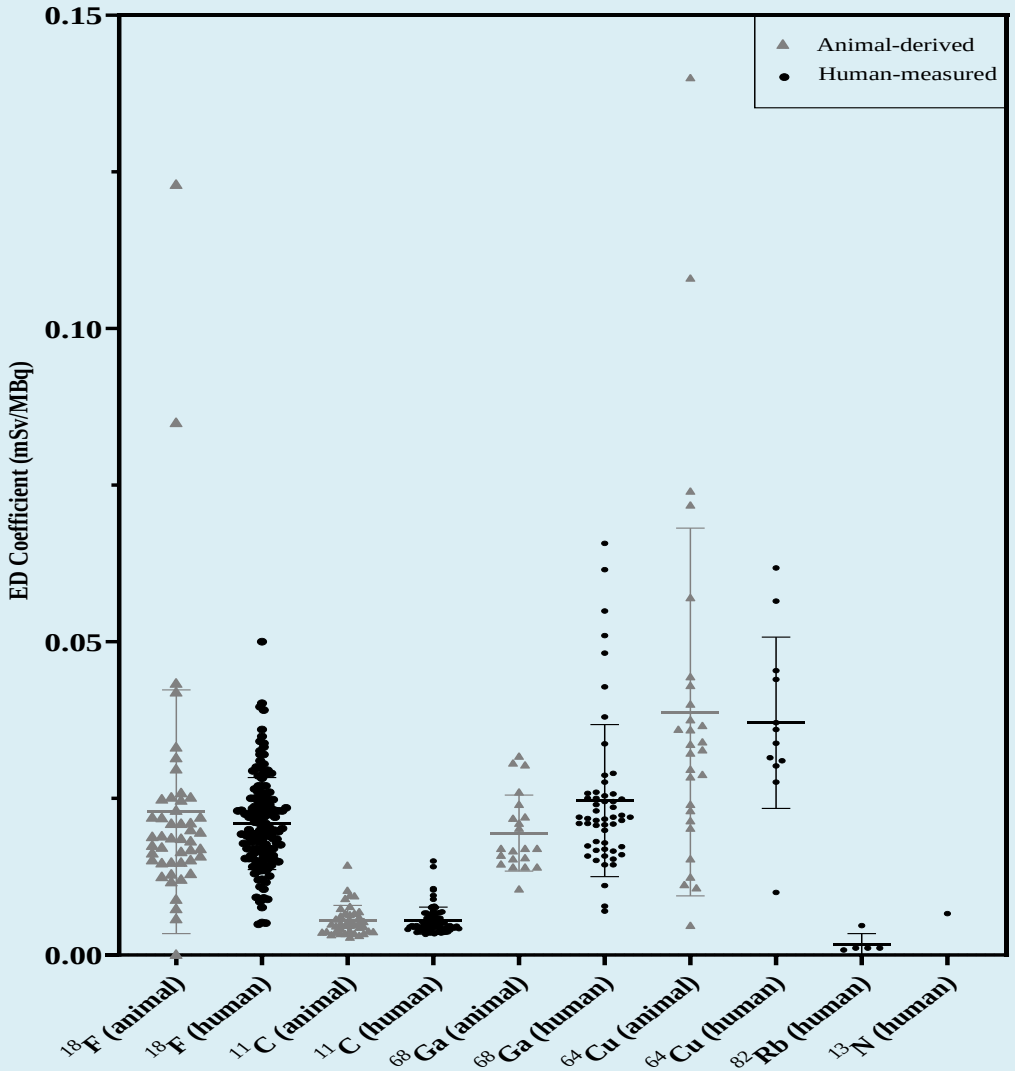


Fig. 1 Whole-Body ED Coefficients (mSv/MBq)

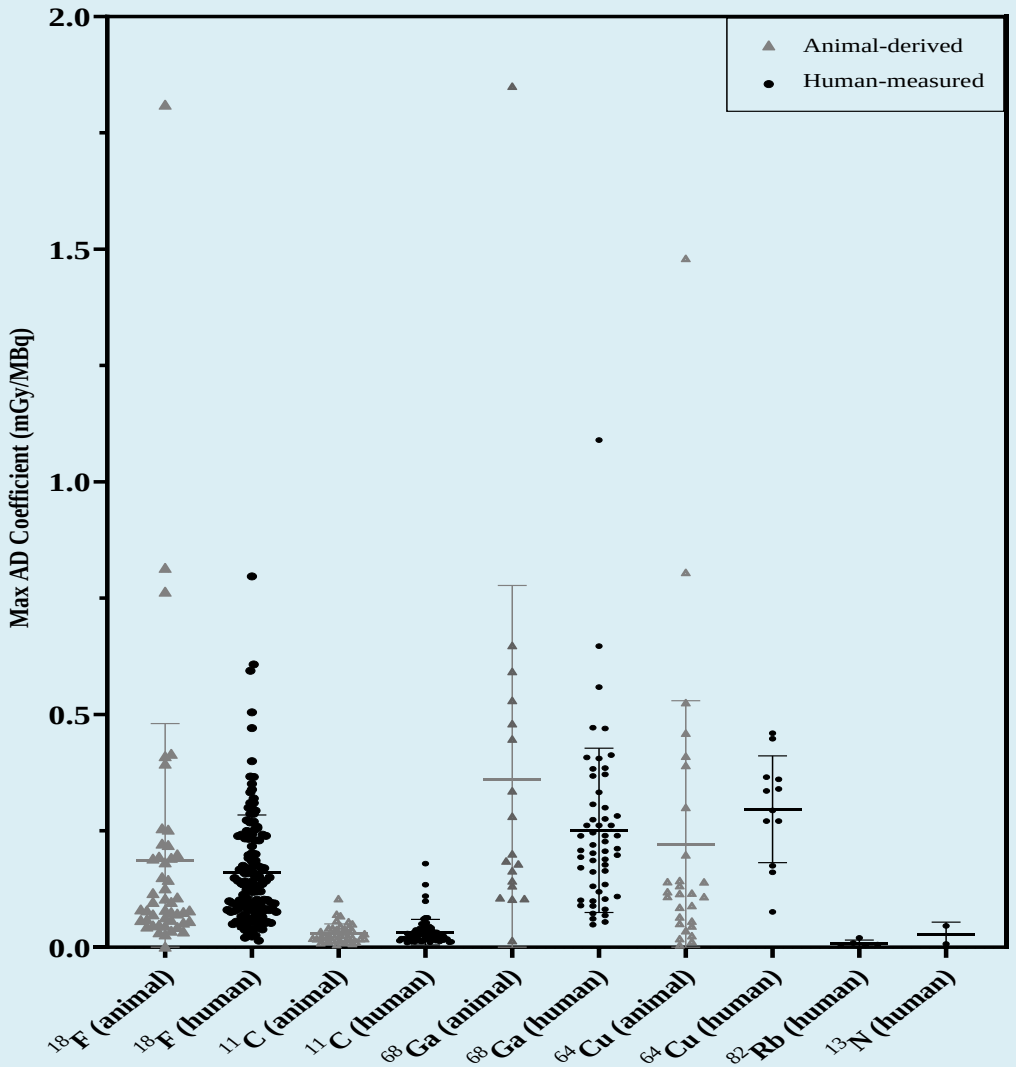


Fig. 2 Max. Organ AD Coefficients (mGy/MBq)

Literature Review Results

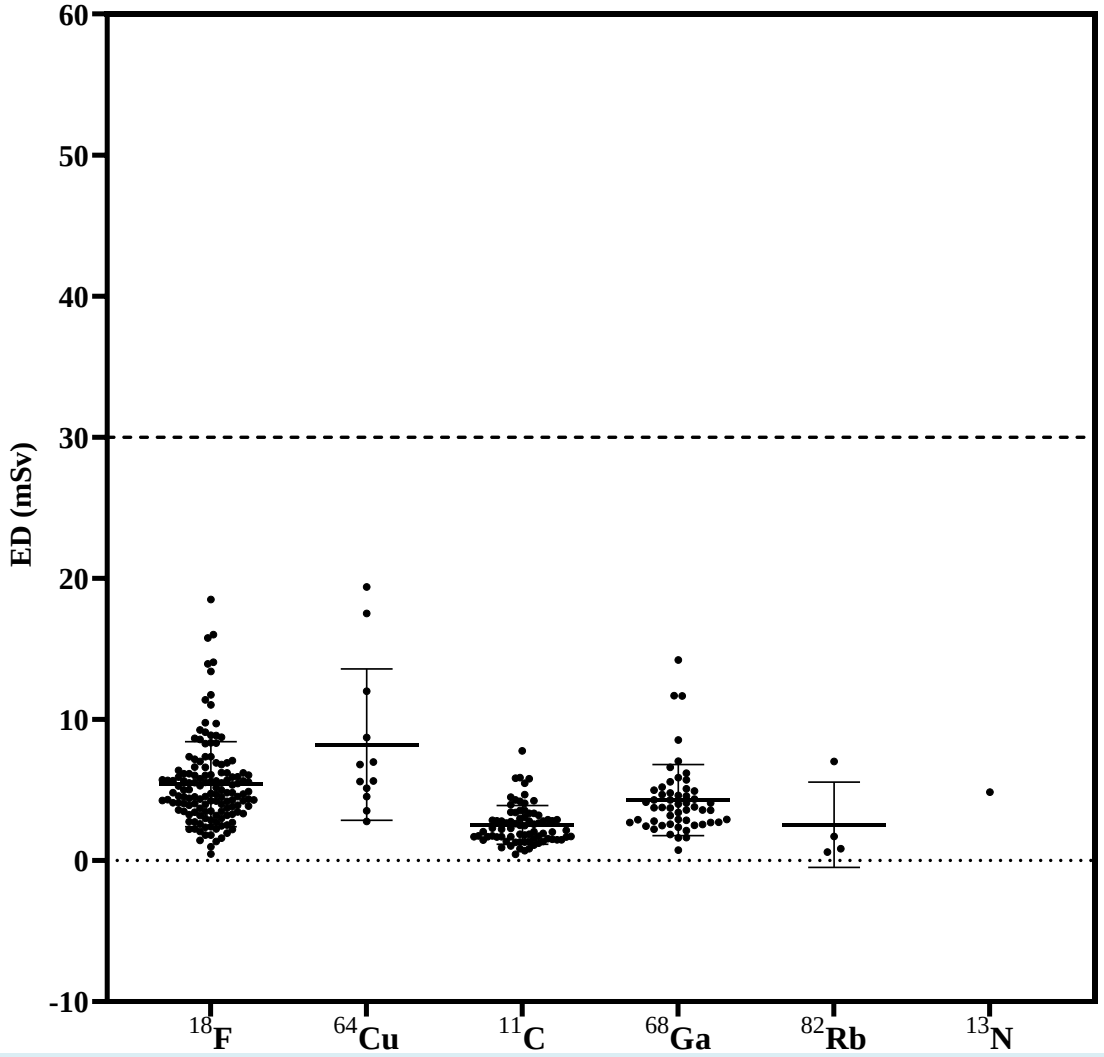


Fig. 3 Whole-Body ED (mSv) = ED coef. (mSv/MBq)*ave. AA

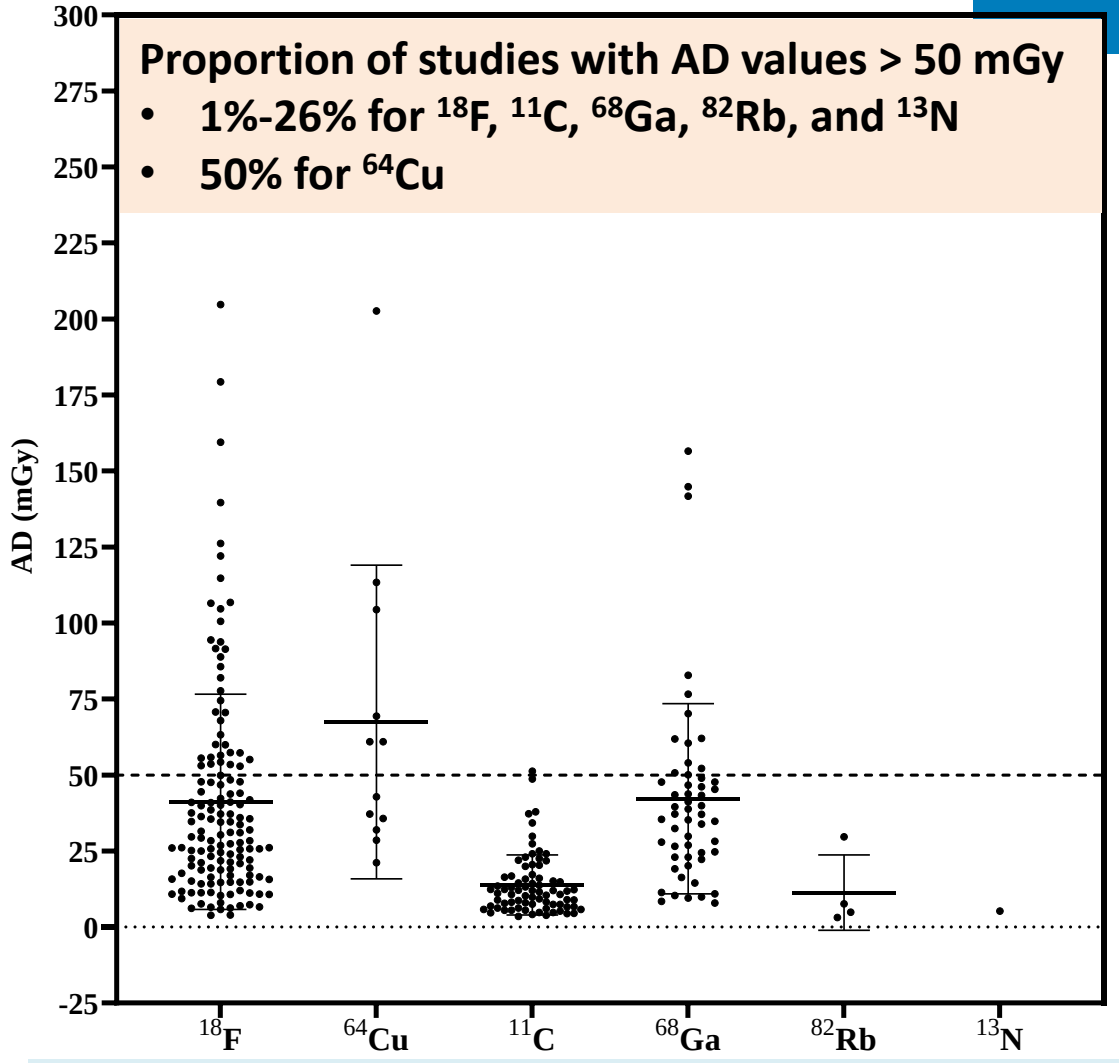
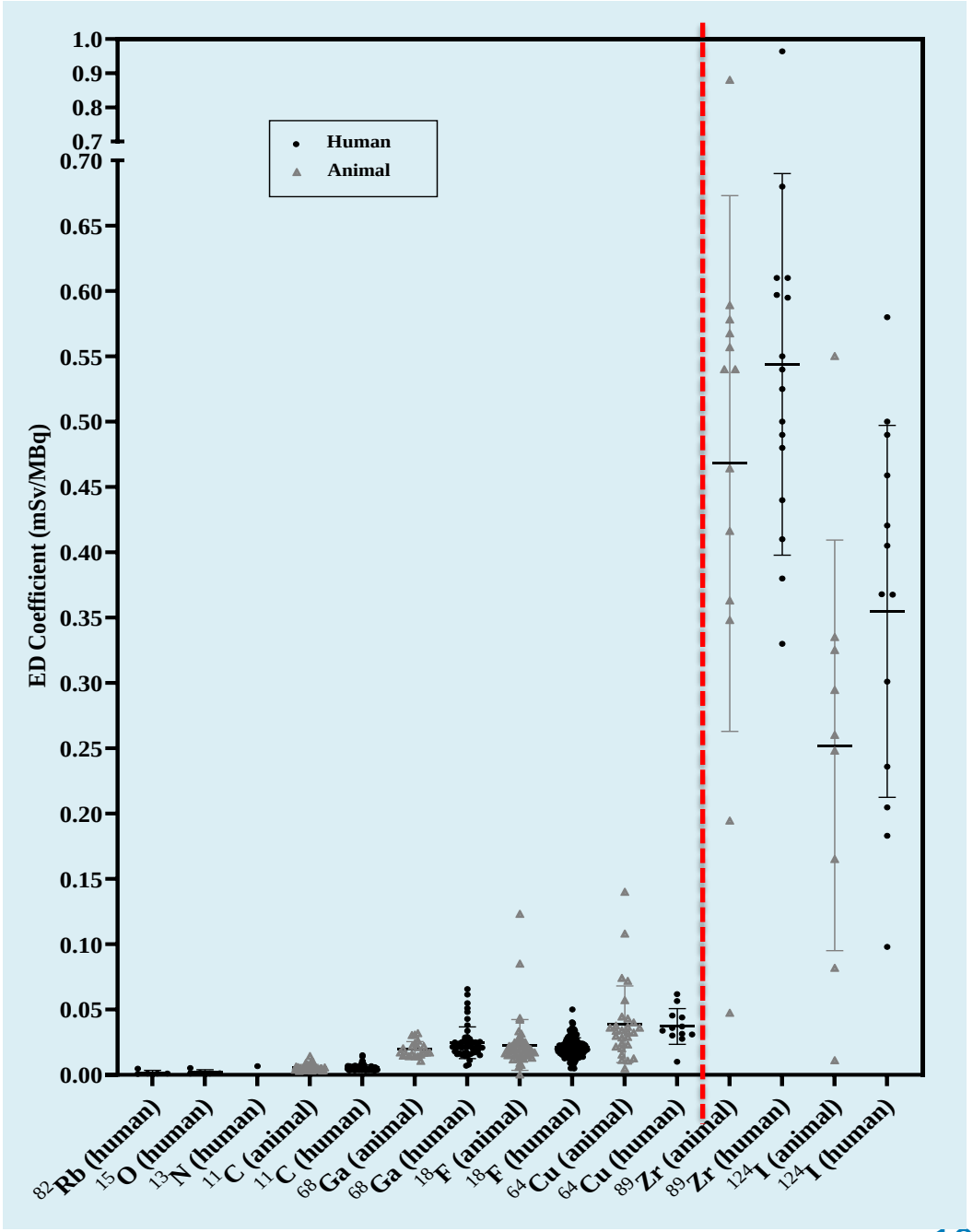


Fig. 4 Max. organ AD (mGy) = Max. organ AD coef. (mGy/MBq)* ave. AA

Effective Dose Comparison

- <u>^{89}Zr and ^{124}I radiopharmaceuticals:</u>
  - Mean ED coefficients of ^{124}I and ^{89}Zr are **~10x** and **~15x higher** than ^{64}Cu
  - Major differences in the radiation profiles and in the variability of ED estimates when compared to ^{82}Rb, ^{15}O, ^{13}N, ^{11}C, ^{68}Ga, ^{18}F and ^{64}Cu radiopharmaceuticals



Radiation Dose Limits

Radioactive Drug Research Committee (RDRC)

Radiation Dose Limits to Individual Organs and the Whole-Body

For radioactive drugs, 21 CFR 361.1 (b) the conditions under which use of radioactive drugs for research are considered safe and effective are:

1) Approval by RDRC.

2) Limit of Pharmacological Dose.

3) Limit on Radiation Dose

(i) Whole body, **active blood-forming organs**, **lens of the eye**, and **gonads**:

Single dose	**3 rem**
Annual and total dose commitment	**5 rem**
Other organs:	
Single Dose	**5 rem**
Annual and total dose commitment	**15 rem**

Note. These limits are not applicable if the agent is being used for therapy.

Recommendations for Designing FIH Studies to Evaluate Radiation Dosimetry With New PET Drugs

Table 2. Administered Activity (AA) From Clinical Studies and Mean of the Recommended AA From Current Drug Labels (Prescribing Information)

		Clinical Studies			Drug Labels	Comparison
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%)

Approach under consideration - AA values for FIH studies

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

Table 3. ED Values (mSv) for Approved Drugs and for Studies with AA > the Mean AA From Drug Labels

	Approved Drugs			Studies With AA > Mean AA From PI		
RN	N	Mean ED±SD (mSv)	Range (mSv)	N	Mean ED±SD (mSv)	Range (mSv)
^{18}F	8	6.0±1.5	4.3–8.9	47 (33%) >299 MBq	7.8±3.7	1.6–18.5
^{11}C	1	1.9	-	24 (31%) >555 MBq	3.5±1.0	2.5–5.8
^{68}Ga	3	3.1±1.1	2.4–4.4	33 (61%) >158 MBq	5.1±2.6	1.8–14.2
^{64}Cu	1	5.6	-	9 (75%) >148 MBq	9.5±5.7	2.8–19.4
^{82}Rb	1	1.9	-	2 (50%) >1440 MBq	1.8±0.1	1.7–1.9
^{13}N	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

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

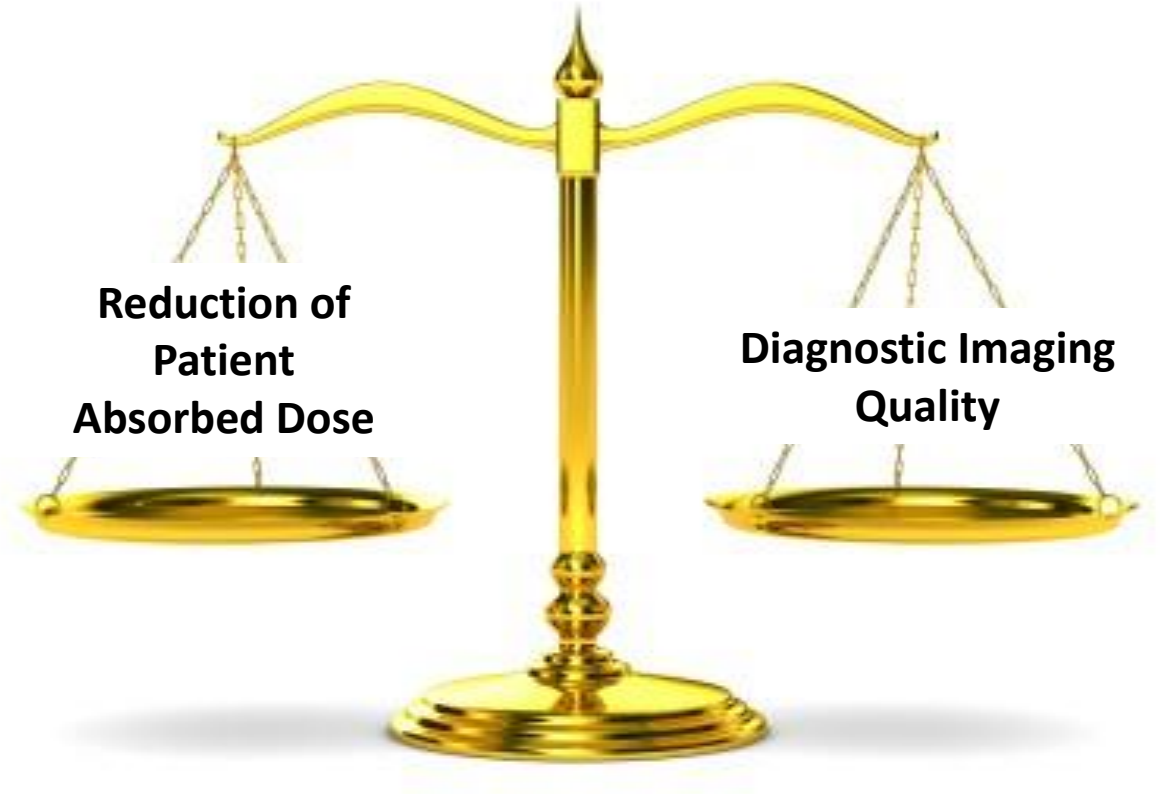
Table 4. Max. Organ AD Values (mGy) for Approved Drugs and for Studies with AA > the Mean AA From Drug Labels

	Approved Drugs			Studies With AA > Mean AA From PI		
RN	N	Mean AD±SD (mGy)	Range (mGy)	N	Mean AD±SD (mGy)	Range (mGy)
^{18}F	9	40.0±12.6	24.0-55.5	46 (33%) >299 MBq	58.6±43.8	6.2–204.8
^{11}C	1	12.4	-	24 (32%) >555 MBq	17.8±10.4	6.6–48.7
^{68}Ga	3	41.0±47.8	12.6-96.2	33 (61%) >158 MBq	48.2±31.8	11.4–156.6
^{64}Cu	1	28.6	-	9 (75%) >148 MBq	77.4±56.6	21.1–202.6
^{82}Rb	1	8.0	-	2 (50%) >1440 MBq	7.8±0.3	7.6–8.0
^{13}N	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

Other Considerations: Dosimetry in Diagnostic Nuclear Medicine



Balance Image Quality With Risk

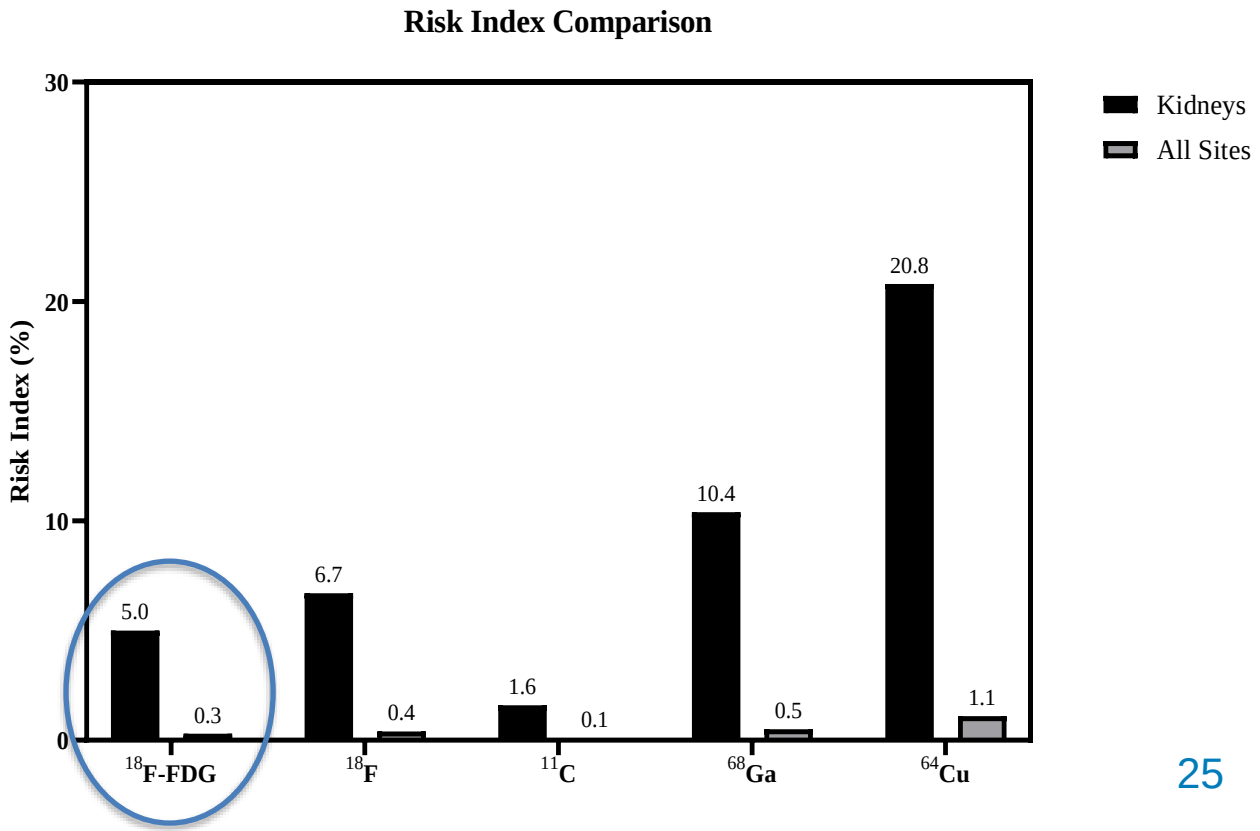
- **Endpoint -> <u>Cancer, other health risks</u>** (stochastic, prob. of cancer)
- **Input ->** Time-activity in ref. source organs
- **Dose Calculation ->** Ref. phantom-based MIRD dose calculation
- **Radiobiology ->** BEIR VII, ICRP, NCRP, EPA risk, models that relate equivalent or effective organ dose to risk
- Consider **added dose from CT scanning** (e.g., mean CT dose of 15.4±5.0 mSv for diagnostic ^{18}F-FDG PET/CT)

Abbreviations: BEIR, biological effects of ionizing radiation; ICRP, International Commission on Radiological Protection; NCRP, National Council on Radiation Protection; EPA, Environmental Protection Agency

Radiation Risk Comparison

- Case scenario: High AD to an individual organ
  - Accumulation of 100 MBq (2.7 mCi) in one organ (kidneys) post administration, and clearance by physical decay only
- 18-year-old female using the AD calculated for this hypothetical scenario for each radionuclide
- Radiation induced cancer risk estimated using **NCI's RadRAT tool**
  https://radiationcalculators.cancer.gov/radrat/
- Risk index definition (O'Reilly, et al., PMB, 2016. 61(6): p. 2319-32)
- Compare to risk for ^{18}F-FDG (AA = 370 MBq [10 mCi]).

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



Conservative Approaches to Determine Upper AA Limits for Human Dosimetry Studies

- **For ^{11}C:** Simulation studies performed by Gatley (Gatley, S.J., *JNM*, 1993. **34**(12): p. 2208-15) to estimate AA that would not exceed **50 mSv (5 rem)** individual organ AD, showed that **130 MBq (3.5 mCi)** can be used to perform a preliminary study in humans without reaching this organ AD limit.
- Consider the **50 mSv RDRC dose limit** for a single administration of ^{11}C and ^{18}F drugs:
  - **For ^{11}C**, the max. AA would be **3125 MBq (~84 mCi)** based on the highest reported WB ED (^{11}C-WAY100,635) in human studies; and **278 MBq (~7.5 mCi)** based on the highest reported organ AD (^{11}C-Csar).
  - **For ^{18}F**, the max. AA would be **1131 MBq (~31 mCi)** based on the highest reported ED in human studies was with (^{18}F-TFB); and **62.7 MBq (~1.7 mCi)** based on the highest reported organ AD (^{18}F-4FMFES).

Nonclinical Dosimetry Studies for New PET Drug Development

Current State

Collect Animal Dosimetry Data

Leverage Available Dosimetry

↓

Case-by-Case IND Review

↓

Collect Phase 1 Clinical Dosimetry Data

Future State

Collect Animal Dosimetry Data

Leverage Available Dosimetry

AA > approach under consideration, or if Patients notably dissimilar in terms of radiation risk

AA ≤ approach under consideration, and Patients with similar risk profile

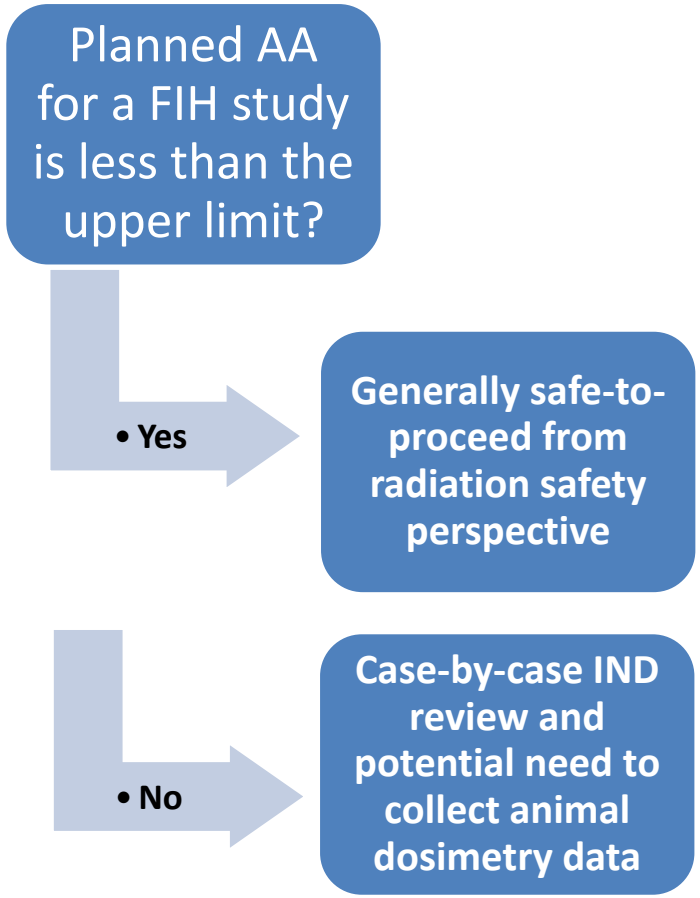
Case-by-Case IND Review

Generally safe-to-proceed from radiation safety perspective

↓

Collect Phase 1 Clinical Dosimetry Data

Nonclinical Dosimetry Studies for New PET Drug Development: A Few Examples



- **Example** (AA ≤ upper limit): **AA = 185 MBq (5 mCi)** for a new ^{18}F drug and no animal dosimetry data are available
- **Example** (AA > upper limit): **AA = 370 MBq (10 mCi)** for a new ^{18}F drug and no animal dosimetry data are available

Nonclinical Dosimetry Studies for New PET Drug Development: A Few Examples

Collect clinical dosimetry data

Recommendations:

- **Example for a new F-18 drug**: Start with an AA ≤ 299 MBq (8 mCi), OR collect animal dosimetry
- Collect Phase 1 clinical dosimetry data
- Escalation and de-escalation rules conditional on imaging and clinical dosimetry results (see example)

EXAMPLE (new F-18 drug):

1. Begin with whole-body imaging in a single human subject using an AA of about **74 MBq (2 mCi).**
2. If this 1st scan confirms that the radioactivity is widely distributed in the body, higher activities may be injected → AA of about **185 MBq (5 mCi)** for imaging to determine whether the radioligand is worth pursuing.
3. If the radioligand looks promising, perform dosimetry studies in humans.

Summary and Discussion Issues

- Large collection of radiation dosimetry data (322 PET drugs)
- Dosimetry data for PET drugs of other PET radionuclides (other than ^{11}C and ^{18}F)
- Analysis of the recommended AA values (**mean AA from drug labels**) of FDA-approved PET drugs and published clinical dosimetry data
- Approach under consideration involving AA values for new PET drugs containing ^{18}F, ^{11}C, ^{68}Ga, ^{64}Cu, ^{82}Rb, and ^{13}N

Issue 1

Discuss sufficiency of reviewed dosimetry data

Issue 2

Discuss reasonableness of approach under consideration

Thank you!

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- Joseph Rajendran, MD
- Jonathan Cohen, PhD
- Alex Hofling, MD
- Calvin Han, MD

Nonclinical Perspective on Biodistribution and Dosimetry Studies

August 1, 2023

Meeting of the Medical Imaging Drugs Advisory Committee on New PET Drug Pre-IND and Phase 1 Dosimetry Data

Jonathan E. Cohen, PhD

Supervisory Pharmacologist

Division of Pharm/Tox, Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (DPT-RDPURM)

Division of Imaging and Radiation Medicine (DIRM)

Center for Drug Evaluation and Research (CDER), FDA

Focus

Pharmacology/Toxicology assessment on the utility of nonclinical (animal) biodistribution and dosimetry studies to support diagnostic radiopharmaceutical or PET drug IND submissions.

- Assessment is based on current Federal Regulations and FDA Guidance documents applicable to PET drugs and principles to reduce, refine, and replace animals (3Rs) in research.
  - What nonclinical and clinical data can be relied upon to support development of PET drugs?
  - How to optimize nonclinical studies to ensure efficiency of clinical development program without jeopardizing safety for first-in-human (FIH) studies?
  - Can PET drug safety be predicted by radionuclide properties?

Regulatory Context for PET Drugs

- Current regulations allow for risk benefit assessment in nonclinical study requirements
- FDA guidance documents (e.g., ICH M3R2, exploratory IND, Microdose) describe recommended studies to support safety of FIH INDs for diagnostic radiopharmaceuticals or PET drugs
- Consideration of applicable regulatory requirements
  - 21 CFR § 312.23(a)(10)(ii) *Radioactive drugs* ***"…***sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose…" (**IND**)
  - 21 CFR § 315.6(d) and § 601.35(d) Evaluation of safety for drugs and biologics "Radiation safety assessment." (**NDA and BLA**)

ICH M3(R2) and Microdose Guidance

- A microdose is defined as less than 1/100th of a dose that elicits a pharmacologic effect, "sub-pharmacologic"
- A dose which is ≤ 100 µg for small molecules or ≤ 30 nmol for protein products or biologics
- In vivo and in vitro pharmacologic characterization in pharmacodynamically relevant model
- Pharmacokinetic (PK) parameters and PET dosimetry estimates
- Studies should provide evidence that addition of radionuclide does not significantly alter pharmacology

Current Regulatory Standards for Radiopharmaceuticals

Diagnostic	Therapeutic
• Biodistribution (and dosimetry) studies recommended to inform on target organ uptake	• Biodistribution studies needed to inform human dose selection of radiotherapeutic (consider clinical condition)
• Safety pharmacology studies are not needed	• Safety pharmacology endpoints included in biodistribution, dosimetry or toxicity studies

- Primary pharmacology studies, e.g., in vitro and in vivo characterization; evidence that radiolabeling does not alter pharmacodynamic properties
- PK information in test species (exposure, $t_{1/2}$) and other information relevant to potential drug-drug interactions
- Toxicity study requirements based on mass dose (cold) and frequency of dosing

Significance of Biodistribution Studies

- Demonstrate target organ uptake (e.g., central nervous system)
- Used in disease models to support mechanism of action (MoA) of PET drug
- Provide information on PET drug stability, metabolism, and route of elimination
- Provide information to support clinical PET imaging (e.g., imaging time post dose, signal to background)
- Extent of studies dependent on marketing intent and patient numbers (e.g., exposure)

Animal Dosimetry Studies for PET Drugs

- Primary pharmacology and proof-of-concept data **support** safety and clinical efficacy of FIH clinical studies
- Value of pharmacodynamic and biodistribution studies characterizing new radioligands (e.g., organ and tumor specific uptake)
- Accumulated experience for PET agents, e.g., C-11 and F-18
- Differences in the estimates between animal and human radiation absorbed dose
- Consider other data sources in absence of animal dosimetry studies

Weight of Evidence (WoE) approach to provide estimates of radiation absorbed dose for FIH studies

PET Drugs and Radiation Administered Dose

- Radionuclide $t_{1/2}$ and biological $t_{1/2}$

C-11	20.38 min		
F-18	109.7 min	**Small molecules, peptides**	**< 24 hours**
Ga-68	68 min		
Cu-64	12.7 hr		
Zr-89	78.41 hr	**Antibodies**	**days**
I-124	4.18 d		

- Range of administered activities for short-lived radioisotopes (e.g., C-11, F-18, Ga-68) and the effective dose (mSv/MBq)
- Justification for organ and effective dose levels
- Administered activity should be “as low as reasonably achievable” (ALARA)

Weight of Evidence (WoE) approach to provide estimates of radiation absorbed dose for FIH studies

Summary

- Animal biodistribution studies of value for their contribution to understanding PET drug MoA, PK/ADME properties
- Ongoing evaluation on the need for animal dosimetry studies to support FIH PET drugs
- WoE approach applied on case-by-case basis and consider totality of evidence
- Consider a streamlined approach for FIH studies of PET drugs

Guidance Documents:

M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: https://www.fda.gov/media/71542/download

Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations: https://www.fda.gov/media/107641/download

FDA Redbook: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/redbook-2000-ivb1-general-guidelines-designing-and-conducting-toxicity-studies

Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry: https://www.fda.gov/media/129547/download

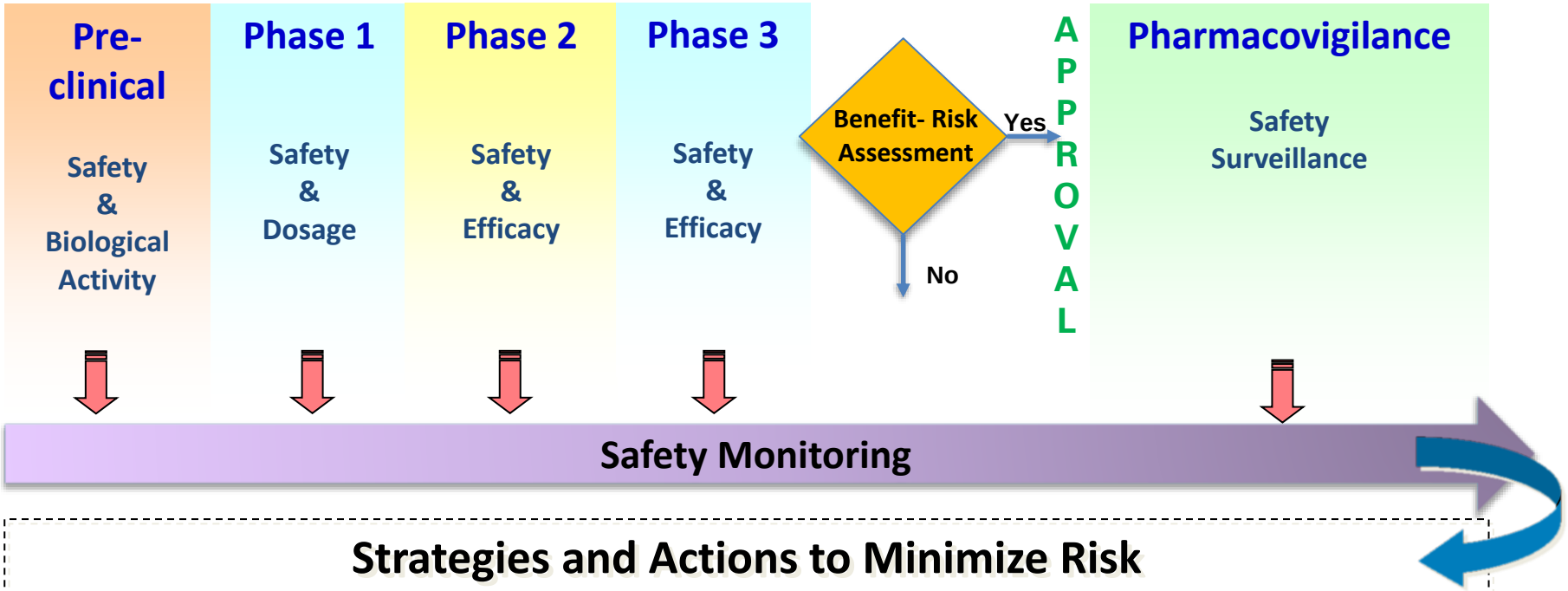
Pharmacovigilance in CDER
August 1, 2023, Meeting of the
Medical Imaging Drugs Advisory Committee on
New PET Drug Pre-IND and Phase 1 Dosimetry Data

Samantha Cotter, PharmD, BCPS, FISMP Safety Evaluator
Division of Pharmacovigilance (DPV) II
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER), FDA

Clinician Reporting to FDA is Important

- When a clinician administers a PET drug and becomes aware of an adverse event or medication error that may be related to the drug, it is important for them to communicate this to FDA
- Key points from this presentation
  - Review how to report adverse events to FDA
  - Discuss how the agency uses adverse event report information to monitor the safety of marketed products
  - Discuss FDA Adverse Event Reporting System (FAERS) reporting trends for PET drugs
  - Provide examples of PET drug safety labeling changes and communications

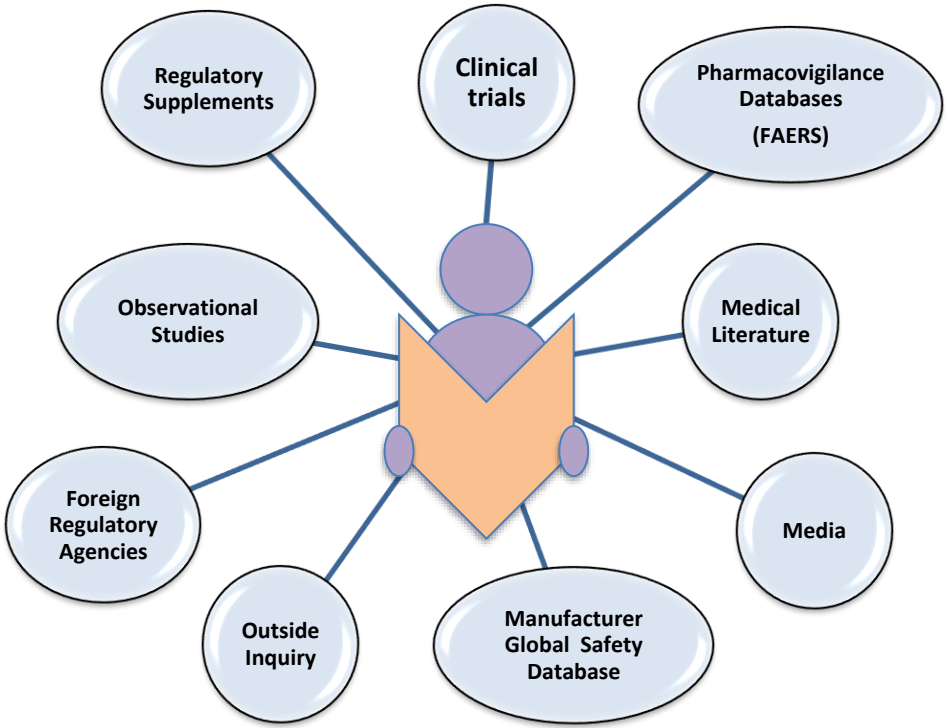
Lifecycle Approach to Safety Assessment



The Void That Pharmacovigilance Fills

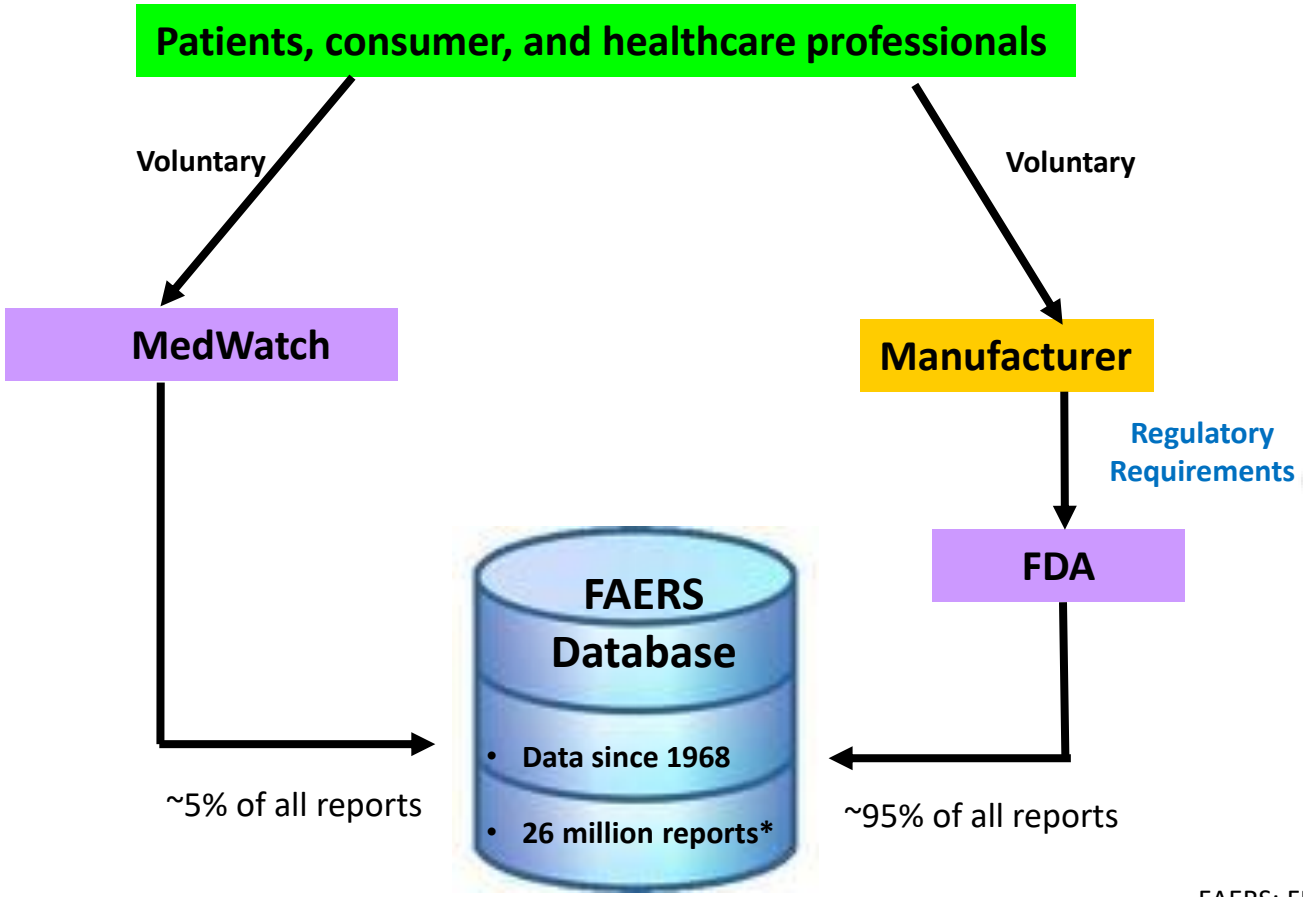
Limitations of Clinical Trials

- While completion of phase 1-3 trials are the standard for generating evidence to evaluate efficacy and safety, not all potential safety outcomes will be known at the time of approval
- Because trials are limited in size, duration, use of a comparator, and may not always reflect real world use of the drug, it is not uncommon for safety events to emerge after a drug is approved
- FDA relies on a robust postmarketing surveillance program to detect and evaluate new safety signals, and these signals come from a variety of sources



U.S. Food and Drug Administration. Guidance for Industry – E2E Pharmacovigilance Planning, April 2005. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073107.pdf

Postmarketing Adverse Events & FAERS Submission



Under 21 CFR 314.80 individual case safety reports must be submitted to FDA for:

- **Expedited reports**: Both **serious*** and **unexpected**† adverse events from all sources (domestic and foreign)
- **Non-expedited reports**: Domestic spontaneous adverse events that are:

-Serious and expected‡
-Non-serious and unexpected
-Non-serious and expected
-Quarterly for the first 3 years then annually

***Serious adverse events are those that result in any of these outcomes:** Death, Life-threatening adverse experience, Inpatient hospitalization – new or prolonged, Persistent/significant disability or incapacity, Congenital birth defect, Other serious

†**Unexpected**: not listed in product's current labeling

‡ **Expected**: listed in product's current labeling

* N=25,998,916 ICSRs from 1/1/1968 to 12/31/2022

FAERS: FDA Adverse Event Reporting System
CFR: Code of Federal Regulations

How to Directly Report Adverse Events to FDA

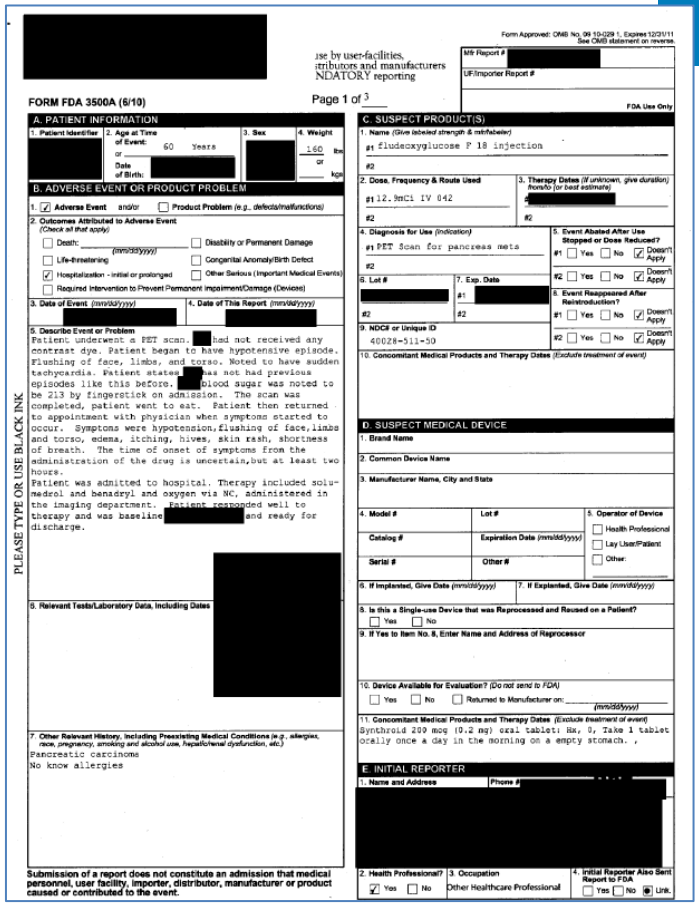
Food and Drug Administration
MEDWATCH

- How to Report:
  - Online (www.fda.gov/medwatch)
  - Download the form
    - Mail
    - Fax 1–800–332–0178
- For questions about the form:
  - 1–800–332–1088

U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available at: https://www.fda.gov/Safety/MedWatch/default.htm

How Does FDA Use FAERS Reports?

- Pharmacovigilance staff review the report or literature reporting a new safety concern with a drug
- We will consult the prescribing information of the drug to determine if the event reported is already known or new information
- If a new signal is identified, we will work with DIRM to open a newly identified safety signal (NISS) and ask the company to assess the issue too.
  - NISS is posted to a public FDA website
- If we determine that a new safety concern should be labeled or communicated to the public, then we work to make that happen



FORM FDA 3500A (6/10)

Page 1 of 3

A. PATIENT INFORMATION

B. ADVERSE EVENT OR PRODUCT PROBLEM

C. SUSPECT PRODUCT(S)

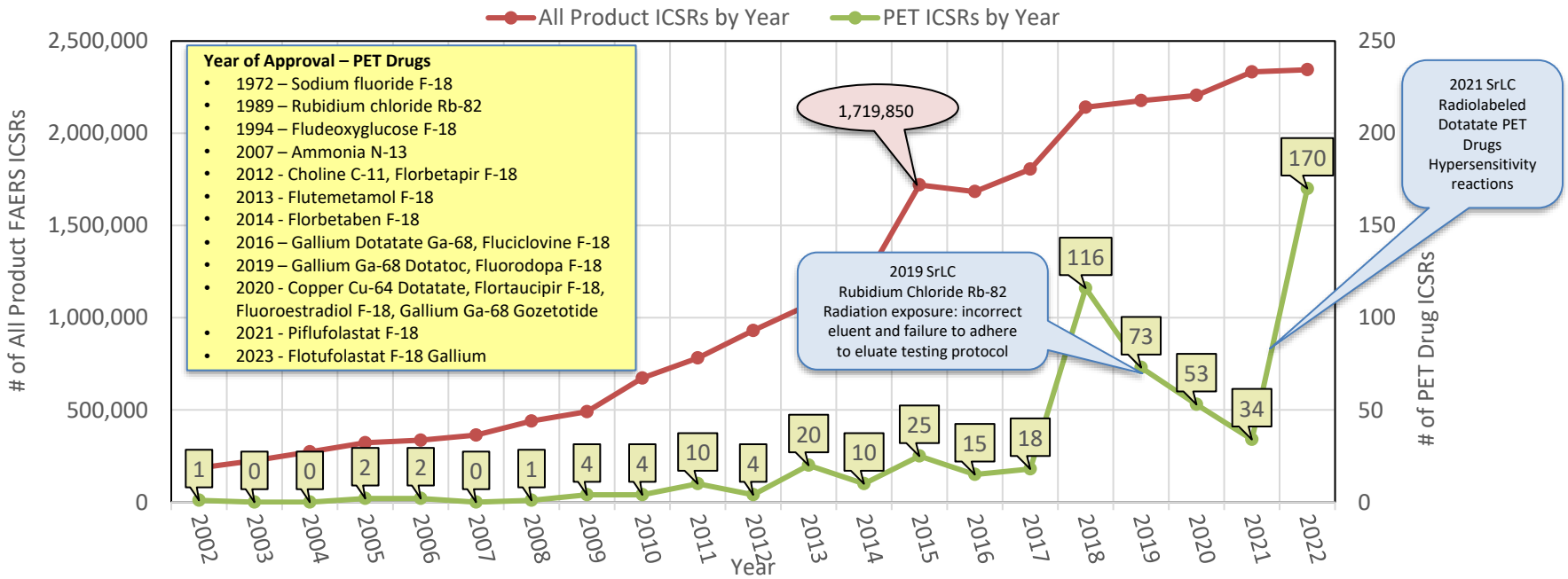
D. SUSPECT MEDICAL DEVICE

E. INITIAL REPORTER

PLEASE TYPE OR USE BLACK INK

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

Number of Adverse Event Reports in FAERS for All Products Compared to PET Drugs (N=562) by Year 1/1/2002 – 12/31/2022



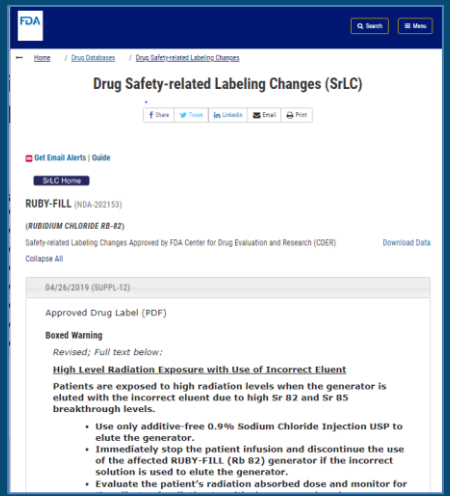
- Slide adapted from FAERS Public Dashboard displaying all report types (direct, expedited and periodic) received by the FDA for drugs and therapeutic biologic products.
- FAERS database contains 25,998,916 ICSRs from 1/1/1968 to 12/31/2022
- A case-level analysis was not performed on all reports. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports.

Acronyms: C – carbon; Cu – copper; F – fluorine; FAERS – FDA Adverse Event Reporting System; Ga – gallium; ICSR – Individual Case Safety Report; N – nitrogen; PET – Positron emission tomography; Rb – rubidium,; SrLC – safety-related labeling change

Public Communication of PET Radiopharmaceutical Drug Safety-Related Labeling Changes (SrLC)

Active Ingredient	Event	SrLC Date
Rubidium Chloride Rb-82	High level radiation exposure with incorrect eluent; quality control testing procedure	04/26/2019
Rubidium Chloride Rb-82	Patient Counseling Information - pregnancy, lactation, post study voiding	10/15/2020
Fluciclovine F-18	Patient Counseling Information – voiding	05/21/2021
Gallium Dotatate Ga-68	Radiation exposures – infants, pregnancy; drug-drug interaction of false negative image with glucocorticoid	6/22/2021
Copper Cu-64 Dotatate	Hypersensitivity reactions	12/22/2021
Gallium Dotatate Ga-68	Hypersensitivity reactions	12/22/2021

SrLC Database [1]



Provides updates to safety information in labeling for regulated NDAs and BLAs.

1. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/

FDA: Drug Safety Information to the Public

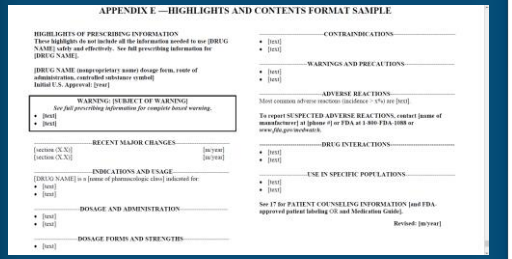
FAERS Public Dashboard [1]

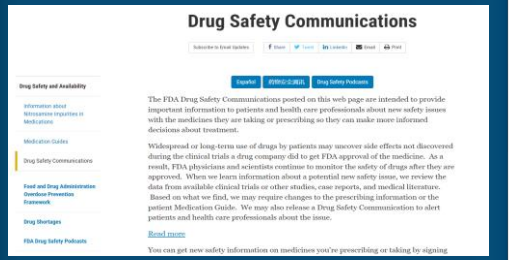
An interactive web-based tool that allows for the querying of FAERS data

Potential Signals [2]

FDA shares early safety signals or potential signals identified through FAERS

Communications [3, 4]





U.S. Prescribing information, Drug Safety Communications, and other communication tools

Resources

[1] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard
[2] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system
[3] https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications
[4] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

All accessed May 4, 2023

Overall Summary

- FDA continues to monitor all products, including PET drugs, throughout the life cycle utilizing pharmacovigilance data sources, multidisciplinary teams and a risk-based approach to surveillance
- Voluntary reporting of adverse events associated with drug products, including PET drugs, by healthcare professionals and patients, is an important activity to support the safe use of FDA-approved drug therapies.
- We encourage continued reporting of drug related AEs through MedWatch: the FDA Safety Information and Adverse Event Reporting Program (https://www.fda.gov/Safety/MedWatch/default.htm)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