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GUIDELINE ARTICLE Open Access

# Use of 55 PET radiotracers under approval of a Radioactive Drug Research Committee (RDRC)

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This article is dedicated to Capt. Richard Fejka, MS, RPh, BCNP, USPHS (Ret.) on the occasion of his retirement after 39 years of government service and 17 years overseeing the RDRC Program at the U.S. Food and Drug Administration.
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## Abstract

**Background:** In the US, EU and elsewhere, basic clinical research studies with positron emission tomography (PET) radiotracers that are generally recognized as safe and effective (GRASE) can often be conducted under institutional approval. For example, in the United States, such research is conducted under the oversight of a Radioactive Drug Research Committee (RDRC) as long as certain requirements are met. Firstly, the research must be for basic science and cannot be *intended* for immediate therapeutic or diagnostic purposes, or to determine the safety and effectiveness of the PET radiotracer. Secondly, the PET radiotracer must be generally recognized as safe and effective. Specifically, the mass dose to be administered must not cause any clinically detectable pharmacological effect in humans, and the radiation dose to be administered must be the smallest dose practical to perform the study and not exceed regulatory dose limits within a 1-year period. In our experience, the main barrier to using a PET radiotracer under RDRC approval is accessing the required information about mass and radioactive dosing.

**Results:** The University of Michigan (UM) has a long history of using PET radiotracers in clinical research studies. Herein we provide dosing information for 55 radiotracers that will enable other PET Centers to use them under the approval of their own RDRC committees.

**Conclusions:** The data provided herein will streamline future RDRC approval, and facilitate further basic science investigation of 55 PET radiotracers that target functionally relevant biomarkers in high impact disease states.

**Keywords:** PET imaging, Regulatory oversight, Dosimetry, RDRC, IND, Radiopharmaceuticals, Quality assurance

## Background

Human use of positron emission tomography (PET) radiotracers in a given country (or member states in the case of the European Union) is required to be conducted under appropriate governmental oversight (Schwarz and Decristoforo 2019; Schwarz et al. 2019). In this paper, we focus upon clinical use of PET radiotracers in the United States, which is regulated by the Food and Drug Administration (FDA) (VanBrocklin 2008; Harapanhalli 2010; Schwarz et al. 2014). However, we expect the regulatory concepts described herein to also hold true in other locations, particularly in light of recent efforts to harmonize PET regulations around the world (Schwarz et al. 2019).

In the US, clinical use of PET radiotracers is conducted under the umbrella of an FDA-approved New Drug Application (NDA) or, in the case of generic PET radiotracers, an Abbreviated New Drug Application (ANDA). Human research is also conducted under governance of the FDA, via three major pathways: i) the Investigational New Drug application (IND), ii) an exploratory IND (eIND), or iii) under the oversight of a Radioactive Drug Research Committee (RDRC) (Suleiman et al. 2006; FDA Guidance for Industry and Researchers: The Radioactive Drug Research Committee: Human Research without an Investigational New Drug Application 2010; Carpenter Jr et al. 2009; Mosessian et al. 2014). The necessary path to approval is dictated by parameters outlined below, as well as the stated purpose of the research in question (Fig. 1).

While the IND and eIND represent the most common pathways to FDA approval for first-in-man studies, some of the requirements (e.g., costly toxicology in two species for an IND) represent significant hurdles to overcome in the application process. One notable solution, as described by Mosessian et al., is to divide labor and preparation for different components of the application between different cores and facilities at a given institution (Mosessian et al. 2014). In contrast, conducting human PET research under RDRC oversight represents a relatively efficient and cost effective path to FDA approval. The concept of the RDRC was introduced in 1975, and committees are charged by the FDA with the responsibility of overseeing PET research at the institutional level.

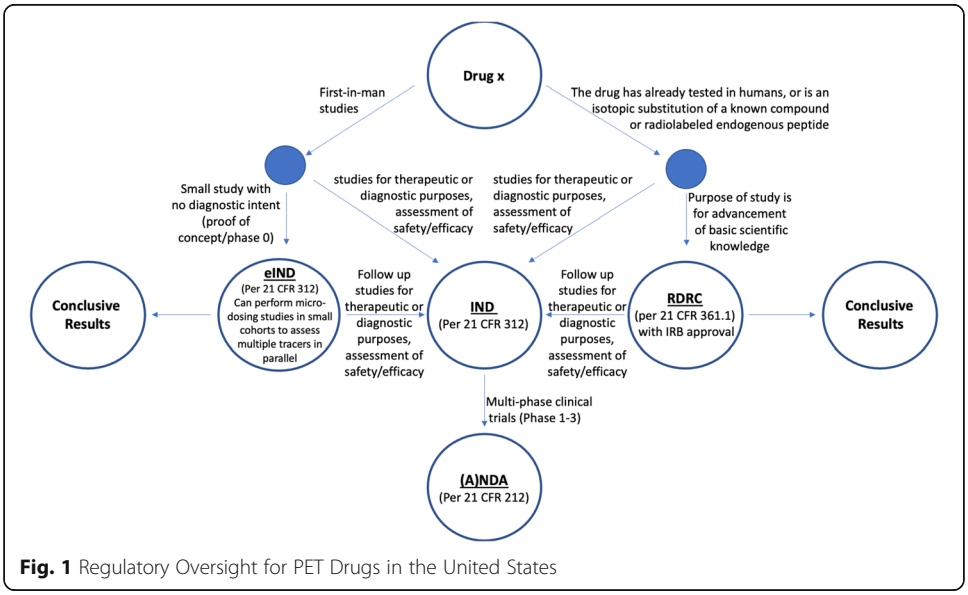


**Fig. 1** Regulatory Oversight for PET Drugs in the United States

RDRC committees are comprised of at least 5 members and are required to include people with the following expertise:

- Physicians specializing in nuclear medicine;
- Nuclear pharmacists and/or radiochemists that are trained and qualified to formulate radioactive drugs;
- Persons having training in radiation safety and radiation dosimetry;
- Individuals specializing in disciplines pertinent to nuclear medicine (radiology, internal medicine, hematology, endocrinology, radiation therapy, clinical pharmacology, etc.).

In order for a given PET imaging study to be conducted under RDRC approval, the proposed research must meet the following criteria (as described comprehensively in 21 CFR 361.1):

- Stated purpose of the research must fall under the category of basic science, including but not limited to studies of: metabolism, kinetics, biodistribution, pathophysiology, biochemistry, transporter processes, and receptor binding/occupancy.
- The research cannot be *intended* for immediate therapeutic or diagnostic purposes, or to determine the safety and effectiveness of the PET radiotracer, but can have therapeutic/diagnostic *implications*. If at any point research initiated under RDRC approval shifts to directly address these subjects, IND approval must be obtained prior to further studies.
- The protocol must involve less than 30 patients, of age 18 or older (exceptions possible pending special approval), and women of child bearing potential must provide a written statement that they are not pregnant (without exception).
- The PET radiotracer is generally recognized as safe and effective (GRASE). Specifically:
  - The mass dose to be administered must not cause any clinically detectable pharmacological effect in humans. It is important to note that this generally precludes first-in-human testing of a PET radiotracer from being done under RDRC approval. Notably, RDRC approval can be used for study of radiolabeled endogenous molecules, as well as isotopic substitutions on clinically characterized compounds (i.e; substituting $^{18}F$ for $^{19}F$ on a small molecule ligand that has previously been approved and studied by the FDA, often via IND)
  - The radiation dose to be administered must be the smallest dose practical to perform a given study. Specifically, the radiation dose to an adult research subject from a single study, or cumulatively from a number of studies, conducted within 1 year may not exceed established regulatory dose limits:
    (a) Whole Body / Active Blood-Forming Organs / Lens of Eye / Gonads: Single Dose (Effective Dose) = 3 rem (0.03 Sv), Annual & Total Effective Dose Commitment = 5 rem (0.05 Sv);
    (b) Other Organs: Single Dose = 5 rem (0.05 Sv); Annual and Total Dose Commitment = 15 rem (0.15 Sv).

  The radiation dose to a subject consists of the sum total of all sources of radiation associated with the research protocol, including the PET radiotracer(s),

associated x-ray procedures (including CT scans, PET transmission scans etc.) and any follow-up studies.
◦ For research subject under 18 years of age at his or her last birthday, the RDRC regulations require that the radiation limits do not exceed 10% of the radiation dose values given above.

- Other key criteria as described in 21 CFR 361.1 include providing evidence of: Qualified investigators, high quality of drug, research protocol, appropriate licensure to handle radioactive material, and review/approval for work with human subjects (via the Institutional Review Board (IRB)).

If all of these criteria are met, then the research can proceed following RDRC and IRB approval. Research conducted in RDRC studies is considered basic science. Specifically, basic science research is intended to advance scientific knowledge, but not to evaluate safety or efficacy of a PET radiotracer or to make clinical decisions. Failure to meet this, or any of the other RDRC criteria outlined above, necessitates that the research be conducted under an IND or eIND application that has been approved by the U.S. Food and Drug Administration (FDA), as outlined in 21 CFR 312 (Mosessian et al. 2014).

To ensure compliance with the pertinent regulations, FDA vests RDRC committees with oversight responsibility for basic science research conducted at the committee's institution. The committee reviews and approves research protocols to ensure compliance with RDRC regulations, and submits annual reports to FDA that list committee members and summarize all studies conducted under the committee's approval in the preceding year. The RDRC committee must also submit a special summary (Form FDA 2915) for any approved study involving > 30 research subjects (Suleiman et al. 2006).

Conducting human PET imaging under RDRC approval represents a straightforward and economical pathway to clinical use, particularly since there is no requirement for resource intensive pharmacology-toxicology studies. In our experience, the main barrier to using a PET radiotracer for basic science under RDRC approval is actually accessing the required information about pharmacological dose/mass and radioactive dose. For a given radiotracer this information can either come from the peer-reviewed scientific literature or other valid data, often in the form of a signed letter from an institution already working with the radiotracer in question. In an effort to remove barriers to those wishing to conduct clinical PET research under RDRC, herein we provide pharmacological dose and radioactive dosimetry details for 55 such PET radiotracers that will enable other PET Centers to use them under the approval of their own RDRC committees, eliminating the need to obtain a specific signed letter on a case-by-case basis. The article is made available Open Access in an attempt to further improve accessibility for our imaging colleagues, and we encourage other PET Centers with large clinical radiotracer portfolios to publish sister articles in the near future.

## Methods

### Radiosyntheses

PET radiotracers were commercially available, or synthesized according to the literature radiosyntheses referenced in Table 1 or novel radiosyntheses described in the Supporting Information. Production and quality control of all radiotracers was conducted

**Table 1** Radiotracers used clinically at the University of Michigan

| Radiotracer | Abbreviation | Application | Radiosynthesis | Dosimetry | Historical Imaging |
|---|---|---|---|---|---|
| **[$^{11}$C]Radiotracers** | | | | | |
| [$^{11}$C]Acetate | [$^{11}$C]ACE | Metabolism | Runkle et al. 2011 | Seltzer et al. 2004 | Duvernoy et al. 2016 |
| [$^{11}$C]Aminocyclohexane carboxylic acid | [$^{11}$C]ACHC | Amino acid transport | Koeppe et al. 1990a | Washburn et al. 1982[a] | Koeppe et al. 1990a |
| 1-[$^{11}$C]Methyl-4- piperidinyl n-butyrate | [$^{11}$C]BMP | Butyrlcholinesterase | Snyder et al. 2001 | Virta et al. 2008 | Kuhl et al. 2006 |
| [$^{11}$C]Butanol | [$^{11}$C]BUT | Blood flow | See Supporting Information | See Supporting Information | [b]; Quarles et al. 1993 |
| [$^{11}$C]Carfentanil | [$^{11}$C]CFN | Mu opioid receptors | Blecha et al. 2017 | Newberg et al. 2009 | Zubieta et al. 2000 |
| [$^{11}$C]Choline | [$^{11}$C]CHO | Choline biochemistry | Shao et al. 2014 | Tolvanen et al. 2010 | Piert et al. 2009 |
| [$^{11}$C]DASB | [$^{11}$C]DASB | Serotonin transporter | Shao et al. 2014 | Lu et al. 2004 | Albin et al. 2008 |
| [$^{11}$C]Dihydrotetrabenazine | [$^{11}$C]DTBZ | Vesicular monoamine transporter 2 (VMAT2) | Shao et al. 2014 | Murthy et al. 2008 | Koeppe et al. 1995 |
| [$^{11}$C]Epinephrine | [$^{11}$C]EPI | Norepinephrine Transporter (NET) | Chakraborty et al. 1993 | Wrobel et al. 1997 | Münch et al. 2000 |
| [$^{11}$C]Flumazenil | [$^{11}$C]FMZ | $GABA_A$ Receptors | Shao et al. 2011a | Laymon et al. 2012 | Koeppe et al. 1991 |
| [$^{11}$C]*meta*-Hydroxyephedrine | [$^{11}$C]HED | NET, Sympathetic nervous system | Shao et al. 2014 | Wrobel et al. 1997 and Supporting Information | Duvernoy et al. 2016 |
| [$^{11}$C]LY2795050 | [$^{11}$C]LY2795050 | Kappa opioid receptors | Yang et al. 2018 | See Supporting Information | [b]; Naganawa et al. 2015 |
| [$^{11}$C]Methionine | [$^{11}$C]MET | Amino acid | Shao et al. 2014 | Deloar et al. 1998 | Miller et al. 2019 |
| [$^{11}$C]Methoxytetrabenazine | [$^{11}$C]MTBZ | VMAT2 | DaSilva et al. 1993a | Wrobel et al. 1997 | Vander Borght et al. 1995 |
| [$^{11}$C]Methylphenidate | [$^{11}$C]MPH | Dopamine transporter | Moran et al. 2010 | See Supporting Information | Albin et al. 2009 |
| [$^{11}$C]N-Methylpiperidinyl benzilate | [$^{11}$C]NMBP | mAChR | Mulholland et al. 1995 | Mulholland et al. 1995 | Zubieta et al. 2001 |
| [$^{11}$C]OMAR/[$^{11}$C]JHU 75528 | [$^{11}$C]OMAR | Cannabinoid 2 receptors | Shao et al. 2015 | Wong et al. 2010 | Wong et al. 2010 |
| [$^{11}$C]Palmitate | [$^{11}$C]PALM | Fatty acid metabolism | Runkle et al. 2011 | Christensen et al. 2017 | [b]; de Jong et al. 2009 |
| [$^{11}$C]PBR28 | [$^{11}$C]PBR28 | Translocator protein 18 kDa (TSPO) | Shao et al. 2014 | Brown et al. 2007 | [b] Kreisl et al. 2016 |
| [$^{11}$C]Pittsburgh Compound B | [$^{11}$C]PiB | Amyloid plaques | Shao et al. 2014 | O'Keefe et al. 2009 | Burke et al. 2011 |
| [$^{11}$C]((*E*)-N-(3-iodoprop-2-enyl)-2β-(4′-tolyl) nortropane) | [$^{11}$C]PE2I | Dopamine transporter | Dollé et al. 2000; Halldin et al. 2003 | Ribeiro et al. 2007 | [b:] Halldin et al. 2003 |

**Table 1** Radiotracers used clinically at the University of Michigan *(Continued)*

| Radiotracer | Abbreviation | Application | Radiosynthesis | Dosimetry | Historical Imaging |
|---|---|---|---|---|---|
| [$^{11}$C]Phenylephrine | [$^{11}$C]PHEN | NET | Del Rosario et al. 1996 | Wrobel et al. 1997 | Raffel et al. 1996 |
| (*R*)-[N-Methyl-$^{11}$ C]PK11195 | [$^{11}$C]PK11195 | TSPO | Alves et al., 2013 | Hirvonen et al. 2010 | Junck et al. 1989 |
| [$^{11}$C]PMP | [$^{11}$C]PMP | Acetylcholinesterase | Shao et al. 2014 | See Supporting Information | Kuhl et al. 1999 |
| [$^{11}$C]Raclopride | [$^{11}$C]RAC | Dopamine $D_2$ receptors | Shao et al. 2014 | Ribeiro et al. 2005 | Scott et al. 2006 |
| [$^{11}$C]Ro-54,864 | [$^{11}$C]Ro-54,864 | TSPO | Watkins et al. 1988 | see Supporting Information[a] | Junck et al. 1989 |
| [$^{11}$C]Sarcosine | [$^{11}$C]SARC | Sarcosine biochemistry | Piert et al. 2017 | Piert et al. 2017 | Piert et al. 2017 |
| [$^{11}$C]Scopolamine | [$^{11}$C]SCOP | mAChR | Mulholland et al. 1988 | Frey et al. 1992 | Frey et al. 1992 |
| [$^{11}$C]Tetrabenazine | [$^{11}$C]TBZ | VMAT2 | DaSilva et al. 1993b | DaSilva et al. 1994 | Kilbourn et al. 1993 |
| [$^{11}$C]Tropanylbenzilate | [$^{11}$C]TRB | mAChR | Mulholland et al. 1992 | Mulholland et al. 1992 | Koeppe et al. 1994 |
| [$^{11}$C]WAY-100365 | [$^{11}$C]WAY | 5-$HT_{1A}$ Receptor | Krasikova et al. 2009 | Parsey et al. 2005 | Mickey et al. 2008 |
| **[$^{18}$F]Radiotracers** | | | | | |
| [$^{18}$F]Flortaucipir | [$^{18}$F]AV1451; [$^{18}$F]T807; Tauvid | Tau | [c]; Mossine et al. 2017 | Choi et al. 2016 | Drake et al. 2019; Kramer et al. 2020 |
| 3-(1,4-Diazabicyclo[3.2.2] nonan-4-yl)-6-[$^{18}$F]fluoro-dibenzo[b,d]thiophene 5,5-dioxide | [$^{18}$F]JHU82132, [$^{18}$F]ASEM | α7 nicotinic acetylcholine receptor (nAChR) | Gao et al. 2013 and Supporting Information | Wong et al. 2014 and Supporting Information | [b]; Wong et al. 2014 |
| Fluciclovine (anti-1-Amino-3-$^{18}$F-fluorocyclobutane-1-carboxylic acid) | [$^{18}$F]FACBC; Auxumin | Amino acid transport | [c]; Sörensen et al. 2013 | Nye et al. 2007; McParland et al. 2010 | [b]; Songmen et al. 2019 |
| [$^{18}$F]Fluoroazomycin arabinoside | [$^{18}$F]FAZA | Tumor hypoxia | Shao et al. 2011b | Savi et al. 2017 | Beck et al., 2007 |
| 2-[$^{18}$F]Fluoro-2-deoxy-D-glucose | [$^{18}$F]FDG | Glucose metabolism | Richards and Scott 2012; Sowa et al. 2018 | Srinivasan et al. 2020 | Koeppe et al. 2005 |
| [$^{18}$F]6-Fluoro-L-DOPA | [$^{18}$F]FDOPA | Dopamine | See Supporting Information, Mossine et al. 2019, 2020 | Kaushik et al. 2013; Mejia et al. 1991 | Minn et al. 2009 |
| [$^{18}$F]-Fluoroethoxy- benzovesamicol | [$^{18}$F]FEOBV | Vesicular acetylcholine transporter | Shao et al. 2011b | Petrou et al. 2014 | Petrou et al. 2014 |
| [$^{18}$F]Fluorocholine | [$^{18}$F]FCH | Choline biochemistry | Rodnick et al. 2013 | DeGrado et al. 2002; Fabbri et al. 2014 | Davenport et al. 2020 |
| [$^{18}$F]Florbetapir | Amyvid; [$^{18}$F]AV45 | Amyloid plaques | c | Joshi et al. 2014 | Frey and Koeppe 2016 |

**Table 1** Radiotracers used clinically at the University of Michigan *(Continued)*

| Radiotracer | Abbreviation | Application | Radiosynthesis | Dosimetry | Historical Imaging |
|---|---|---|---|---|---|
| [$^{18}$F]-Fluoro-3′-deoxy-3′-L-fluorothymidine | [$^{18}$F]FLT | Cellular proliferation | Shao et al. 2011b | Vesselle et al. 2003; Mendes et al. 2018 | Bertagna et al. 2013 |
| [$^{18}$F]Flubatine | [$^{18}$F]FLBT | $\alpha_4\beta_2$ nAChR | Hockley et al. 2013 | Kranz et al. 2016 | Sattler et al. 2012 |
| [$^{18}$F]Flutemetamol | Vizamyl, [$^{18}$F]GE67 | Amyloid plaques | [c]; Snellman et al. 2014 | Koole et al. 2009 | Frey and Koeppe 2016 |
| [$^{18}$F]Fluoromisonidazole | [$^{18}$F]FMISO | Tumor hypoxia | [d]; Riss et al. 2012 | Graham et al. 1997 | Bruehlmeier et al. 2004 |
| [$^{18}$F]Fluoropropyl-dihydrotetrabenazine | [$^{18}$F]FP-TBZ, [$^{18}$F]AV133 | VMAT2 | Lin et al. 2010 | Lin et al. 2010 | Kilbourn and Koeppe 2019 |
| [$^{18}$F]GBR13119 /[$^{18}$F]GBR12909 | [$^{18}$F]GBR | DAT | Haka and Kilbourn 1988, 1990 | Kilbourn et al. 1989 | Koeppe et al. 1990b |
| 4-[$^{18}$F]Fluoro-*m*-hydroxyphenethylguanidine | [$^{18}$F]MHPG | NET | Raffel et al. 2018 | Raffel et al. 2018 | Raffel et al. 2018 |
| 2′-Methoxyphenyl-(N-2′-pyridinyl)-p-$^{18}$F-fluoro-benzamidoethylpiperazine | [$^{18}$F]MPPF | 5-$HT_{1A}$ Receptor | Shao et al. 2011b | See Supporting Information | [b]; Aznavour and Zimmer 2007 |
| [$^{18}$F]Sodium Fluoride | [$^{18}$F]NaF | Bone imaging | Shao et al. 2011b | Segall et al. 2010; Silveira et al. 2010 | Wong and Piert 2013 |
| [$^{18}$F]N-Methyl Lansoprazole | [$^{18}$F]NML | Tau | Kramer et al. 2020 | Kramer et al. 2020 | Kramer et al. 2020 |
| 4-[$^{18}$F]Fluoro-*p*-hydroxyphenethylguanidine | [$^{18}$F]PHPG | NET | Raffel et al. 2018 | Raffel et al. 2018 | Raffel et al. 2018 |
| **Other Radiotracers** | | | | | |
| [$^{13}$N]Ammonia | [$^{13}$N]$NH_3$ | Blood flow | Scott 2012 | Yi et al. 2015 | Beanlands et al. 1994 |
| [$^{15}$O]Water | [$^{15}$O]$H_2O$ | Blood flow | Dick and Watkins 2015 | Brihaye et al. 1995 | Minoshima et al. 1993 |
| [$^{68}$Ga]DOTATATE | NETSPOT | Somatostatin receptors | NETSPOT prescribing information 2016 | Walker et al. 2013 | [b]; Fallahi et al. 2019 |
| [$^{68}$Ga]PSMA-HBEDCC | [$^{68}$Ga]PSMA-11 | Prostate specific membrane antigen | See Supporting Information; Rodnick et al. 2020 | Afshar-Oromieh et al. 2016; Sandgren et al. 2019 | Rodnick et al. 2020 |

[a]Historical dosimetry data is no longer extant. Biodistribution data are provided to enable estimation of dosimetry; [b] UM Imaging data not yet published; [c] Commercially available under an approved (A)NDA; [d] Commercially available under an IND

according to current Good Manufacturing Practice (cGMP) using the guidelines outlined in the US Pharmacopeia, (USP < 823> Positron Emission Tomography Drugs for Compounding, Investigational, and Research Uses 2020).

### Dosimetry

Radiation-absorbed-dose estimates can either be obtained from literature sources or determined using the OLINDA/EXM 1.0 software package (Stabin et al. 2005). Table 1 provides literature sources of dosimetry wherever available. For any radiotracers where literature dosimetry is unavailable, dosimetry is provided in the Supporting Information.

### Imaging

Research PET scans have been conducted since the first PET scanner was installed at the University of Michigan (UM) in the 1980s. Historical examples of imaging studies mostly conducted at our Center with the various radiotracers are provided in Table 1, including practical information on both scanning protocols and image kinetic analysis. Injected dose (MBq), mass dose limits (μg) and historical numbers of subjects scanned are provided in Table 2.

## Discussion

At the University of Michigan we have a long history of using PET radiotracers in clinical research studies (using both the RDRC and IND mechanisms). Detailed information for 55 such radiotracers is provided in Table 1, including references for radiosyntheses and dosimetry available in the peer-reviewed literature. Synthesis ([$^{11}$C]butanol, [$^{18}$F]ASEM, [$^{18}$F]FDOPA, [$^{68}$Ga]PSMA-11) and dosimetry ([$^{18}$F]ASEM, [$^{11}$C]butanol, [$^{11}$C]HED, [$^{11}$C]LY2795050, [$^{11}$C]MPH, [$^{18}$F]MPPF, [$^{11}$C]PMP, [$^{11}$C]RO-54864) information that has not previously been published is provided in the Supporting Information associated with this article. Pharmacological dose and radioactivity dosing information for the PET drugs is also provided (Table 2), along with historical numbers of administrations to subjects at the University of Michigan PET Center. Rationale for those radiotracers without mass dose limits is provided in the Supporting Information.

As noted above, a study conducted under RDRC oversight cannot exceed 30 subjects without special provisions. The PET drugs corresponding to some of the larger numbers of subjects discussed herein have been used in numerous different RDRC studies over the course of many years (and decades in some instances). In the event any given study exceeded 30 research subjects, the RDRC committee filed a special summary (Form FDA 2915). At the doses specified, no pharmacological or physiological changes were observed after intravenous administration of any of the PET drugs, and the basic science studies were conducted without exceeding any regulatory radiation dose limits. All scans have been reported to the US FDA in the annual RDRC reports required by the agency.

## Conclusion

While an IND (or eIND) is the dominant route to FDA approval for first-in-man studies, collection of the requisite data and preparation of the application can be a daunting

**Table 2** Dosing information

| Radiotracer | Injected Dose (MBq) | Mass dose limit | Number of subjects scanned | Clinically detectable pharmacological effects in humans |
|---|---|---|---|---|
| **[$^{11}$C]Radiotracers** | | | | |
| [$^{11}$C]ACE | 740 | None | 475 | No |
| [$^{11}$C]ACHC | 740 | ≤5000 μg/subject | 2 | No |
| [$^{11}$C]BMP | 444 | ≤4625 μg/subject | 65 | No |
| [$^{11}$C]BUT | 555 | ≤125 μg/kg | 0[a] | a |
| [$^{11}$C]CFN | 555 | ≤0.03 μg/kg | 1492 | No |
| [$^{11}$C]CHO | 592 | None | 44 | No |
| [$^{11}$C]DASB | 666 | ≤8 μg/subject | 179 | No |
| [$^{11}$C]DTBZ | 555 | ≤50 μg/subject | 1823 | No |
| [$^{11}$C]EPI | 740 | < 9 μg/subject epinephrine & ≤1 μg/subject norepinephrine precursor | 96 | No |
| [$^{11}$C]FMZ | 370 | ≤50 μg/subject | 668 | No |
| [$^{11}$C]HED | 666 | ≤50 μg/subject[b] | 643 | No |
| [$^{11}$C]LY2795050 | 555 | ≤10 μg/subject | 0[c] | c |
| [$^{11}$C]MET | 444 | None | 129 | No |
| [$^{11}$C]MTBZ | 580 | ≤10 μg/subject | 6 | No |
| [$^{11}$C]MPH | 666 | ≤25 μg/subject | 170 | No |
| [$^{11}$C]NMBP | 740–1480 | ≤127 μg/subject[d] | 59 | No |
| [$^{11}$C]OMAR | 666 | 0.14 μg/kg | 0[e] | e |
| [$^{11}$C]PALM | 740 | None | 8 | No |
| [$^{11}$C]PBR28 | 666 | ≤10 μg/subject | 34 | No |
| [$^{11}$C]PiB | 666 | ≤13 μg/subject | 592 | No |
| [$^{11}$C]PE2I | 555 | ≤6.3 μg/subject | 1 | No |
| [$^{11}$C]PHEN | 740 | ≤6800 μg/subject | 29 | No |
| [$^{11}$C]PK11195 | 888 | ≤420 μg/subject | 118 | No |
| [$^{11}$C]PMP | 555 | ≤200 μg/subject | 801 | No |
| [$^{11}$C]RAC | 555 | ≤50 μg/subject | 627 | No |
| [$^{11}$C]Ro-54,864 | 555 | ≤160 μg/subject | 6 | No |
| [$^{11}$C]SARC | 592 | None | 20 | No |
| [$^{11}$C]SCOP | 1480 | ≤50 μg/subject | 14 | No |
| [$^{11}$C]TBZ | 1018 | ≤10 μg/subject | 2 | No |
| [$^{11}$C]TRB | 1110 | ≤31 μg/subject | 26 | No |
| [$^{11}$C]WAY-100365 | 555 | ≤15 μg/subject | 51 | No |
| **[$^{18}$F]Radiotracers** | | | | |
| [$^{18}$F]AV1451 | 370 | ≤20 μg/subject | 92 | No |
| [$^{18}$F]ASEM | 370 | ≤0.67 μg/subject | 1 | No |
| Auxumin | 370 | ≤20 μg/subject | 228[f] | No |
| [$^{18}$F]FAZA | 296 | ≤3.5 μg/subject | 14 | No |
| [$^{18}$F]FDG | 185–296 | None | 6804 | No |
| [$^{18}$F]FDOPA | 148 | ≤15 μg/subject | 0[g] | g |
| [$^{18}$F]FEOBV | 296 | ≤1.23 μg/subject | 308 | No |
| [$^{18}$F]FCH | 222 | ≤100 μg/subject | 67 | No |
| Amyvid | 370 | ≤50 μg/subject | 222 | No |

**Table 2** Dosing information *(Continued)*

| Radiotracer | Injected Dose (MBq) | Mass dose limit | Number of subjects scanned | Clinically detectable pharmacological effects in humans |
|---|---|---|---|---|
| [$^{18}$F]FLT | 370 | ≤20 μg/subject | 8 | No |
| [$^{18}$F]FLBT | 296 | ≤0.02 μg/kg | 92 | No |
| Vizamyl | 370 | ≤20 μg/subject | 11 | No |
| [$^{18}$F]FMISO | 370 | ≤15 μg/subject | 8 | No |
| [$^{18}$F]FP-TBZ | 370 | ≤7.5 μg/subject | 23 | No |
| [$^{18}$F]GBR | 148 | ≤900 μg/subject | 2 | No |
| [$^{18}$F]MHPG | 241 | ≤10 μg/subject | 17 | No |
| [$^{18}$F]MPPF | 259 | ≤2 μg/subject | 34 | No |
| [$^{18}$F]NaF | 222 | None | 9 | No |
| [$^{18}$F]NML | 370 | ≤10 μg/subject | 6 | No |
| [$^{18}$F]PHPG | 241 | ≤10 μg/subject | 15 | No |
| **Other Radiotracers** | | | | |
| [$^{13}$N]$NH_3$ | 740 | None | 1472 | No |
| [$^{15}$O]Water | 555 | None | 1153 | No |
| NETSPOT | 200 | ≤40 μg/subject | 981[f] | No |
| [$^{68}$Ga]PSMA-11 | 185 | ≤10 μg/subject | 751[f] | No |

[a] [$^{11}$C]Butanol is validated for clinical production but studies have not yet commenced. We do not expect clinically detectable pharmacological effects as the mass limit (≤125 μg/kg) was selected since it is 1000 times below the NOAEL (125 mg/kg, see: Wagner 2005); [b] combined mass of HED and metaraminol precursor must be ≤50 μg/subject; [c] [$^{11}$C]LY2795050 is validated for clinical production but studies have not yet commenced at UM. We do not expect clinically detectable pharmacological effects as the mass limit (≤10 μg/subject) has been used without significant adverse events at other institutions (see: Naganawa et al. 2015); [d] See published limits (Yoshida et al. 1998); [e] [$^{11}$C]OMAR is validated for clinical production but studies have not yet commenced at UM. We do not expect clinically detectable pharmacological effects as the mass limit (≤0.14 μg/kg) has been used without significant adverse events at other institutions (see: Wong et al. 2010); [f] Includes subjects numbers scanned for clinical care and research; [g] [$^{18}$F]FDOPA is validated for clinical production but studies have not yet commenced. We do not expect clinically detectable pharmacological effects as the mass limit (≤15 μg/subject) is significantly less than administered masses historically used when employing the electrophilic synthesis of [$^{18}$F]FDOPA (13 mg/62 kg subject, see: Chevalme et al. 2007)

and resource intensive task. Proceeding under approval of a Radioactive Drug Research Committee therefore represents an attractive mechanism for clinical studies of compounds that have (a) already been studied in man and (b) are well characterized in terms of pharmacology and dosimetry. Initiation of a new study for such an established compound is contingent upon access to mass dose and dosimetry data. The data provided herein will streamline future RDRC approval, and facilitate further basic science investigation of 55 PET drugs that target functionally relevant biomarkers in high impact disease states.

## Supplementary Information

**Supplementary information** accompanies this paper at https://doi.org/10.1186/s41181-020-00110-z.

**Additional file 1.**

### Abbreviations

ANDA: Abbreviated new drug application; Bq: Becquerels; cGMP: Current good manufacturing practice; eIND: Exploratory IND; FDA: Food and Drug Administration; IND: Investigational new drug; NDA: New drug application; PET: Positron emission tomography; QC: Quality control; RDRC: Radioactive drug research committee; USP: United States Pharmacopeia

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**Authors' contributions**
IMJ and PJHS analyzed data and wrote the manuscript. SJL, ARS, JT, XS, MER, LB, MC, SP and AFB conducted radiosyntheses. VER maintains historical PET records and databases. JR is the lead PET technologist who coordinated scheduling and clinical dosing. BGH, BDH, MC and JT provided quality control and/or quality assurance for PET drug manufacture. LEB coordinated RDRC/IRB submissions. DMR calculated dosimetry. KAF, RAK, MRK and PJHS have supervision responsibility. KAF is Chief of Nuclear Medicine and the authorized user physician. The author(s) read and approved the final manuscript.

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**Availability of data and materials**
The datasets used in the current paper are available from the corresponding author on reasonable request.

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This article does not contain any original studies with human or animal subjects performed by any of the authors.

**Consent for publication**
All authors gave their consent for publication.

**Competing interests**
The authors declare no competing financial interests.

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