

# Assessment of PET Drug Adverse Events in the U.S. since the Implementation of 21 CFR part 212

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## Research Article

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# Abstract

**Background:** Multiple new PET radiopharmaceuticals (RPhs) have recently been approved by the U.S. Food and Drug Administration (FDA). Despite the generally accepted safety profile of PET RPhs supported by millions of doses administered per year, the microdoses used in most injections, and the low incidence of adverse events (AEs), there appear to be elevated concerns from regulatory authorities regarding the safety of PET RPhs in recent years. There have been prior reports on the prevalence of AEs from RPhs, but most of them are outdated and do not reflect the current state-of-the-art and best practices. To address the gap, this retrospective study assesses risks associated with PET RPhs by reviewing AEs reported to the FDA Adverse Events Reporting System (FAERS) since the implementation of the PET good manufacturing practice (GMP) regulations in 21 CFR 212 in 2012.

Data for AEs reported for approved PET RPhs were collected from the FAERS database. Data were collected during December 2025 for AEs reported between 2012 and 2024. FDA approved PET RPhs were searched using all known names for each drug. For each RPh, the following tables were downloaded from the database: a) case count by received year; b) cases by reaction; and c) listing of cases. Tables downloaded for each radiopharmaceutical were combined, and duplicated entries removed. AE reports were then categorized based on the manufacturing regulatory oversight and, for the purposes of this report, we focused on AEs reported for 10 PET RPhs manufactured under 21 CFR 212.

**Results:** Almost 24 million adverse event reports for all drug products were transmitted to FDA between 2012 and 2024. Of these, 932 (or 0.0039%) were AEs submitted to FAERS for FDA-approved PET RPhs manufactured in the US. Of these AEs, 451 were reported for PET RPhs manufactured under 21 CFR 212. This represents approximately 7.0 AEs per  $10^5$  RPh injections performed in 2024 for all PET RPhs or  $4.3/10^5$  for PET RPhs manufactured under the PET GMP regulations. At least one adverse reaction to the RPh was reported in 237 of the 451 cases recorded, and two-thirds of these (157, 66.2%) were characterized as non-serious.

**Conclusions:** The FAERS data confirm that PET RPhs can be generally recognized as safe and effective. The extremely low numbers of AEs for PET RPhs manufactured according to 21 CFR 212 and the lack of correlation between manufacturing issues and safety AEs overall support a low risk profile for this class of drugs. Moreover, these data do not appear to justify significant changes to the existing regulations, or more stringent regulation of PET drug manufacture beyond those currently in place.

## Introduction

Radiopharmaceuticals (RPhs) are drugs that carry a radioactive isotope and are widely used in the diagnosis as well as, increasingly, the treatment of diseases (1, 2). Diagnostic radiopharmaceuticals have been used for years in nuclear medicine and enable visualization of molecular processes such as biomarker concentration, metabolism, blood flow, and oxygen consumption (3, 4). For example, since the 1970s, clinical studies using RPhs tagged with a positron-emitting radionuclide have found use in

Positron Emission Tomography (PET) imaging, where they are used to diagnose disease and monitor patient response to therapy. PET is also increasingly used in drug development, where it can be used to measure receptor occupancy of investigational drugs, as well as to confirm target engagement and identify sites of off-target binding that could potentially cause unwanted side effects (5). More recently, PET RPhs are also utilized in theranostics, where they are paired with a corresponding radiotherapeutic (6–8). Reflecting these applications, PET RPhs have gained increased attention in the past decade, and multiple new PET drugs, 18 since 2010, have been approved by the U.S. Food and Drug Administration (FDA) (9).

An important aspect of assessing the ongoing safety and efficacy of any investigational or approved drug, including PET RPhs, is routine surveillance of adverse events (AEs). According to the FDA, AEs are defined as *“any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related,”* (10) and AEs can include Adverse Drug Reactions (ADRs), drug misuse, drug withdrawal, over- or under-dose of the drug, or any failure of expected pharmacological action. An ADR is *“any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event”* (10). Unlike AEs, where the relationship with the drug is not proven, ADRs are directly linked to the pharmaceutical.

AEs associated with PET RPhs are extremely rare, mainly due to the low pharmacologic and radioactive doses administered to patients (11–14). Most PET RPhs, for example, are administered as sub-pharmacologic and toxicologic microdoses [defined by the FDA as  $< 100 \mu\text{g}$ , but in practice often  $< 10 \mu\text{g}$  and frequently 100x or even 1000x below no-observed-adverse-effect levels (NOAELs)] (15). Despite the low incidence of AEs, there appear to be elevated concerns from the FDA regarding the safety of these drugs in recent years (16, 17). For example, there has been a steady push by agency officials during review of PET RPh submissions to reduce the mass dose further, below the established microdosing guidelines. Aseptic processes and microbial control during the manufacturing of PET RPhs have also received increased focus during FDA inspections and have been a main topic of discussion at recent workshops organized by the FDA and the PET drug manufacturing community (16, 17). During these workshops, FDA officials have referred to PET RPhs as “high risk” and have noted that the PET good manufacturing practice (GMP) regulations (21 CFR part 212) and related guidance documents are currently under revision, but the revisions have not appeared in the Federal Register or otherwise been made public to date.

Given these concerns, this analysis was undertaken to better understand the safety profile of PET RPhs both in our capacity as U.S.-based PET drug manufacturers and leaders at the Coalition of PET Drug Manufacturers, as an independent evaluation of the FDA concerns, and to identify any unforeseen issues from the patient perspective. There have been several prior reports in the literature that aim to assess the prevalence of AEs associated with radiopharmaceuticals (11–14, 18–21). Reviews have been published summarizing data from case studies in the literature (22) or from public databases such as the British Nuclear Medicine Society online database (23), the national pharmacovigilance database of France (24), or data gathered by professional societies (18, 25). Most recent published reports focus on

therapeutic RPhs (21) or present a narrative review of literature reported AEs for both diagnostic and therapeutic RPhs (20). The number of reports specifically focused on PET RPhs in the U.S. is very small and outdated (11, 12). Thus, the purpose of this work was to provide an updated assessment of PET RPhs that includes the many new agents currently in use, most of which were not FDA-approved when these earlier reviews were compiled.

The FDA Adverse Events Reporting System (FAERS) was established in 1969 and underwent a major revision in 1997 to increase reporting capabilities. The FAERS is an open-access database that collects AEs and other pharmaceutical errors reported by patients, healthcare providers, and drug manufacturers (26). Although the number of reports in the FAERS database may underestimate the true frequency of AEs, the data represent a real-world collection of incidents related to the safety of drugs, and the FAERS has been widely used in pharmacovigilance studies (27–30). Recently, the FDA launched a new unified platform for analyzing adverse event reports named FDA Adverse Event Monitoring System (AEMS). This new system aims to combine databases used for different classes of drugs and allow easier access to data.

Our retrospective study aims to assess the risk associated with PET RPhs by reviewing adverse event reports in the FAERS since the implementation of 21 CFR part 212 in 2012 (31), and to identify an association between this risk and the increased regulatory concerns regarding the safety of PET RPhs.

## Methods

Data for AEs reported to the FDA for approved PET RPhs were collected using FAERS. Data can be reported to the FAERS from the U.S. or other countries, and it is updated quarterly. For our analysis, data were collected during December 2025 for global AEs reported between 2012 and 2024. FDA-approved PET RPhs were searched using all known names for each drug, both generic and brand names. For each radiopharmaceutical, the following tables were downloaded from the database: a) case count by received year; b) cases by reaction; and c) listing of cases. The latter provide, amongst other data, information on the type of adverse event, the date of the event, the date reported to the FDA, the date of the last update the FDA received for this event, and basic patient information such as sex, age, and weight. Furthermore, information regarding the country where the event occurred, the manufacturer, and the reporter type can also be extracted from these tables.

Tables downloaded for each radiopharmaceutical were combined, and duplicate entries were removed. AE reports were then categorized based on manufacturing compliance oversight. Radiopharmaceuticals labeled with either Ga-68 or Cu-64 are commonly prepared using FDA-approved kits manufactured according to traditional GMP regulations (21 CFR part 211) and prepared for use under the practice of pharmacy or medicine. Similarly, Rb-82 generators are manufactured under 21 CFR part 211 and typically used under the practice of medicine. All other PET RPhs (see Table 1) are manufactured according to the PET GMP regulations (21 CFR part 212) in academic or commercial manufacturing facilities. For the purposes of this report, we focused only on the 11 PET RPhs listed in Table 1.

AEs for PET RPhs manufactured under part 212 were first separated into those reported in the U.S. or other countries, or those in which the country of the event was not specified. Following a conservative approach, if the country of manufacturing could not be identified, we hypothesized that those events occurred in the U.S. Subsequently, the reported AEs were segregated according to the following categories: (1) safety related, (2) efficacy related, (3) drug administration errors, (4) manufacturing errors, and (5) “other” which includes AEs not qualifying for the four previous categories. If a report included AEs for two of these categories, they were counted only once in our analysis. Finally, the AEs were separated based on the suspected active ingredient for the adverse reaction reported and further separated into three categories: a) the adverse reaction was attributed to the PET RPh, b) the adverse reaction was attributed to a different drug, or c) the suspected drug was not specified, or more than one drug was suspected.

## Results

Collectively, more than 23.9 million adverse event reports for all drug products were submitted to the FAERS between 2012 and 2024. A total of 1,090 reports were submitted for all FDA-approved PET RPhs. Of those, 7 cases were duplicates, bringing the total number of reports to 1,083, representing 0.0045% of AEs reported to the FDA between 2012 and 2024. Examination of the country where the event occurred revealed that 888 (82.0%) occurred in the U.S., 134 (12.4%) in other countries, and that the remaining 61 cases (5.6%) were not specified. Closer examination of the case data revealed that for 17 of the reports with unspecified country, the manufacturer’s control number belonged to a facility outside the US. This leaves only 44 cases (4.1%) where the country was not specified. Following a conservative approach, for the remainder of the analysis, we assumed all these cases occurred in the US, bringing the total of cases for further analysis to 932.

Of these 932 cases, 451 (48.4%) were associated with PET RPhs manufactured under 21 CFR part 212, and 348 (37.3%) were related to kits manufactured according to 21 CFR part 211 and prepared and used under the practice of pharmacy or medicine. The remaining 133 reports (14.3%) were submitted for Rb-82 generators manufactured under 21 CFR part 211 and used under the practice of medicine (Table 1).

Table 1  
Number of reported AEs in the US per PET FDA approved RPh

| Drug                                                               | Trade Name              | Number of AEs |
|--------------------------------------------------------------------|-------------------------|---------------|
| <b>Manufactured under 21 CFR 212</b>                               |                         |               |
| Ammonia N-13                                                       | N/A                     | 2             |
| Choline C-11                                                       | N/A                     | 0             |
| Florbetaben F-18                                                   | Neuraceq                | 3             |
| Florbetapir F-18                                                   | Amyvid                  | 61            |
| Fluciclovine F-18                                                  | Axumin                  | 68            |
| Fludeoxyglucose F-18                                               | N/A                     | 84            |
| Fluorodopa F-18                                                    | N/A                     | 0             |
| Fluoroestradiol F-18                                               | Cerianna                | 7             |
| Flutemetamol F-18                                                  | Vizamyl                 | 98            |
| Flortaucipir F-18                                                  | Tauvid                  | 0             |
| Flotufolastat F-18                                                 | Posluma                 | 12            |
| Piflufolastat F-18                                                 | Pylarify                | 114           |
| Sodium Fluoride F-18                                               | N/A                     | 2             |
| <b>Kits manufactured under 21 CFR 211</b>                          |                         |               |
| DOTATATE Ga-68                                                     | Netspot                 | 181           |
| DOTATATE Cu-64                                                     | Detectnet               | 7             |
| DOTATOC Ga-68                                                      | N/A                     | 0             |
| Gozetotide Ga-68                                                   | Illuccix, Locametz      | 160           |
| <b>Generators manufactured under 21 CFR 211</b>                    |                         |               |
| Rubidium Chloride Rb-82                                            | CardioGen-82, Ruby-Fill | 133           |
| <b>Total for all PET RPh</b>                                       |                         | <b>932</b>    |
| <b>Total for PET RPh manufactured according to 21 CFR part 212</b> |                         | <b>451</b>    |

**Figure 1**

Number of reported AEs per year in the US associated with PET radiopharmaceuticals manufactured in facilities under 21 CFR 212 (blue), prepared using kits in nuclear pharmacies or nuclear medicine

departments under the practice of pharmacy or medicine (red), or Rb-82 generators manufactured under 21 CFR 211 (green) and used under the practice of medicine.

The next assessment was to classify the 451 reported cases of PET RPhs manufactured under 21 CFR 212 based on the type of event reported. Events were categorized into safety, efficacy, drug administration errors, and manufacturing errors. More specifically, we categorized as safety-related adverse events any cases reporting at least one ADR, while as efficacy we categorized AEs reporting scan or expected result abnormalities. There were reports of AEs that could not be assigned to any of the above categories and were included in a separate category as “other”. AEs categorized as “other” included cases for which an investigation, either false negative or false positive, was reported with no other details given on the nature of the investigation, or cases that listed what seemed as incidental findings. The results are detailed in Table 2. We found that the largest number of reports (237) were related to safety, with at least one ADR. Of these reports, 157 were characterized as non-serious, while the remaining one-third (80) were considered serious.

Table 2  
Adverse Events Categorized by Type and Radiopharmaceutical

| Drug                 | Safety     | Efficacy   | Administration | Manufacturing | Other     |
|----------------------|------------|------------|----------------|---------------|-----------|
| Ammonia N-13         | 2          | 0          | 0              | 0             | 0         |
| Florbetaben F-18     | 3          | 0          | 0              | 0             | 0         |
| Florbetapir F-18     | 38         | 3          | 6              | 1             | 13        |
| Flotufolastat F-18   | 2          | 9          | 0              | 0             | 1         |
| Fluciclovine F-18    | 10         | 35         | 11             | 0             | 12        |
| Fludeoxyglucose F-18 | 65         | 6          | 2              | 10            | 1         |
| Fluoroestradiol F-18 | 1          | 2          | 0              | 0             | 4         |
| Flutemetamol F-18    | 92         | 5          | 1              | 0             | 0         |
| Piflufolastat F-18   | 23         | 58         | 5              | 25            | 3         |
| Sodium Fluoride F-18 | 1          | 1          | 0              | 0             | 0         |
| <b>Total</b>         | <b>237</b> | <b>119</b> | <b>25</b>      | <b>36</b>     | <b>34</b> |

As shown in Table 2, 119 cases submitted to the FAERS were related to the efficacy of the drug. All 119 cases were characterized as non-serious, and the most common problem reported was an abnormal scan (80 cases). In addition, 25 cases were related to administration errors, including the wrong product, the wrong patient, or extravasations. Additionally, 34 cases listed the AE as a false negative or a false positive investigation or reported incidental findings. No further information was provided for the nature of the event leading to the investigation or whether the additional findings were due to the performance of the drug, and thus these AEs were included in the “other” category. All these cases were characterized

as non-serious. The remaining events (36) reported were manufacturing errors, with only 3 of those reporting sterility issues.

Following categorization, the suspected Product Active Ingredient (PAI) responsible for the AE was reviewed and separated into two categories: a) the PET drug was the suspected PAI, and b) the PET drug and at least one more suspected PAI was reported. Examination of the 451 reports for RPhs manufactured under 21 CFR 212 in the US revealed that in 57 cases (12.6%), at least one more PAI was suspected of causing the AE. More specifically, of the 237 cases reporting an ADR, 42 reported at a PAI other than the RPh, bringing the number of AEs reporting a safety concern attributed only to the PET RPhs in the US to 195.

Lastly, we wanted to estimate the number of AEs reported in the US per 10,000 administrations and compare these numbers to those previously reported in the literature. According to recent reports (32), the number of PET scans performed each year in the US has doubled over the past 12 years, with almost three million estimated scans performed in 2024. Furthermore, the number of approved RPhs increased from 4 in 2012 to 18 in 2024. Despite the marked increase in PET scans performed each year, the number of reported AEs remains extremely low and is estimated to be less than 7.0 AEs per  $10^5$  administrations in 2024 (Table 3) for all PET drugs, and 4.3 AEs per  $10^5$  scans for PET drugs manufactured under 21 CFR 212.

Table 3  
Number of Adverse Events Cases and Estimated PET Scans per Year in the US for PET RPhs

| Year         | Number of Approved RPhs | Estimated Number of PET doses administered (x10 <sup>3</sup> ) | Number of AEs (all PET) | Number of AEs (under 21 CFR 212) | AEs/10 <sup>5</sup> scans<br>(all PET/under 212) |
|--------------|-------------------------|----------------------------------------------------------------|-------------------------|----------------------------------|--------------------------------------------------|
| 2024         | 18                      | 3,087 <sup>a</sup>                                             | 216                     | 132                              | 7.0/4.3                                          |
| 2023         | 17                      | 2,751 <sup>a</sup>                                             | 203                     | 101                              | 7.4/3.7                                          |
| 2022         | 17                      | 2,496                                                          | 142                     | 82                               | 5.7/3.2                                          |
| 2021         | 16                      | 2,493                                                          | 28                      | 11                               | 1.1/0.4                                          |
| 2020         | 12                      | 2,220                                                          | 47                      | 11                               | 2.1/0.5                                          |
| 2019         | 10                      | 2,201                                                          | 57                      | 17                               | 2.6/0.8                                          |
| 2018         | 10                      | 2,086                                                          | 114                     | 16                               | 5.5/0.8                                          |
| 2017         | 10                      | 1,945                                                          | 22                      | 15                               | 1.1/0.8                                          |
| 2016         | 8                       | 1,981                                                          | 22                      | 16                               | 1.1/0.8                                          |
| 2015         | 8                       | 1,719                                                          | 41                      | 20                               | 2.4/1.2                                          |
| 2014         | 7                       | 1,617                                                          | 12                      | 4                                | 0.7/0.2                                          |
| 2013         | 6                       | 1,594                                                          | 22                      | 22                               | 1.4/1.4                                          |
| 2012         | 4                       | 1,723                                                          | 6                       | 4                                | 0.3/0.2                                          |
| <b>Total</b> |                         | <b>27,903</b>                                                  | <b>932</b>              | <b>451</b>                       | <b>3.3/1.6</b>                                   |

<sup>a</sup> Numbers were not reported for 2023 and 2024, but instead are estimated based upon reported rate increase.

## Discussion

In the past 25 years there has been a drastic increase in the number of PET scans performed in the U.S., and the current estimate is more than 3,000,000 scans per year (32). One of the factors contributing to this increase has been the approval of new PET RPhs by the FDA for imaging of Alzheimer's disease such as Florbetaben F-18, Florbetapir F-18, Flutemetamol F-18 and Flortaucipir F-18, as well as for imaging of specific types of cancer such as Fluoroestradiol F-18 for breast cancer, and Choline C-11, Fluciclovine F-18, Flotufolastat F-18 and Piflufolastat F-18 for prostate cancer. Gozetotide Ga-68 for prostate cancer and DOTATATE Ga-68 for neuroendocrine tumors have also shown a growth in utilization because of theranostics and their use in tandem with the corresponding Pluvicto and Lutathera

radiotherapies, respectively. Despite the increased number of PET scans, adverse events related to PET RPhs remain rare mainly due to the very small amount of mass administered, low radiation dose, and the low frequency of administration compared to non-radioactive drugs. Although reporting of AEs relies on healthcare providers, manufacturers, and patients, and can be under-reported, studies in the literature for AEs in the U.S. and other countries estimate a frequency of  $1.63/10^6$  (14), or  $1.2\text{--}3.4/10^5$  (11–12, 18–19) for all diagnostic radiopharmaceuticals, both PET and non-PET.

Fludeoxyglucose F-18 has been used since the 1970s and first garnered FDA approval in 1994. Based on experience gained during this approval, the FDA Modernization Act of 1997 (FDAMA) required the FDA to create specific GMP regulations for PET RPhs. These GMPs were officially implemented in 2012 as 21 CFR part 212, and designed to ensure the safety and efficacy of PET RPhs while accommodating their unique characteristics such as the short half-life, the emission of high-energy gamma radiation, and need for distributed manufacturing in commercial facilities and academic medical centers. Since the initial approval of all PET manufacturing facilities in 2015, the FDA has slowly increased compliance expectations and demands through inspections (16, 17). Consequently, several workshops and meetings have been organized between the FDA and PET manufacturing stakeholders to discuss the evolution of compliance standards and concerns from PET manufacturers regarding inspection and review inconsistencies (33). During these workshops, the FDA often described PET RPhs as “high risk” products but has not elucidated the basis for this risk assessment (16, 17), and multiple times FDA officials have referred to the FAERS, stating that there is an increase in reported AEs for RPhs. Further, the Agency stated that 21 CFR part 212 will be revised to presumably address concerns regarding the safety of PET RPhs (16, 17). As of this report, the revisions to the PET GMP regulations have not appeared in the Federal Register or otherwise made public.

The FAERS Public Dashboard is an open-access database that collects ADR, performance concerns or pharmaceutical manufacturing errors reported by patients, providers and/or drug manufacturers (26). There are several limitations related to this dashboard, including: a) underreporting of events since this is voluntary, or duplicate reports since the same event can be individually reported by the physician, the patient, or the facility; b) categorization of the AEs is left to the party reporting the AE, and c) lack of verification of the information reported to the FDA. Even though there are inevitably gaps in the reporting of such incidents, mainly due to a lack of familiarity with this reporting system, it provides a representative view of incidents related to the safety of drugs (including radiopharmaceuticals) and has been widely used in pharmacovigilance studies (21, 27–30).

With this study, we aimed to shed light on the frequency of AEs reported to the U.S. FDA for PET RPhs, to identify any correlation between the frequency of AEs and the safety profile of these drugs, as well as the perceived need to update the GMP regulations. For the purposes of this study we focused on AEs reported, since 2012 when the new 21 CFR part 212 was implemented, for FDA-approved PET RPhs (listed in Table 1) manufactured in cyclotron facilities. PET RPhs labeled with either Ga-68 or Cu-64 were not included in the most comprehensive analysis since they are usually prepared from FDA-approved kits under the practice of medicine or pharmacy. Rb-82 was also not included because it is produced from a

generator manufactured under 21 CFR part 211 and administered directly to patients without further processing, in accordance with the practice of medicine.

Between January 2012 and 2024, more than 23.9 million AEs were transmitted to the FAERS database. These included cases for pharmaceuticals manufactured in the U.S. or abroad, reported by physicians, consumers, or manufacturers. Of these, we found 1,090 cases reported for FDA-approved PET RPhs. Seven (7) cases were duplicates resulting in a final count of 1,083 cases, representing 0.0045% of all reported cases to the FAERS. No AEs were reported for Choline C-11 or Fluorodopa F-18. There was 1 report for Flortaucipir F-18, but it was removed from further analysis since the AE occurred in Great Britain.

As mentioned previously, AEs can be reported to the FAERS regardless of whether the event occurred in the U.S. or a different country. Our first focus was to identify the incidents reported for PET RPhs manufactured in the U.S. Examination of the reported cases revealed that 888 AE cases were reported for PET RPhs manufactured in the U.S., while 134 cases were for PET RPhs manufactured in a different country. Although for 61 cases the country for the event was not specified, the drug manufacturer's control number indicated that 17 reports involved drugs manufactured outside the U.S. Following a conservative approach, we decided to include the cases where the country of the event was not specified in our analysis. Combining these parameters, we concluded that 932 AEs were reported for events occurred in the US representing 86% of the cases.

Approximately half of the 932 cases (451) were reported for 10 PET RPhs manufactured under 21 CFR part 212 (Table 1), representing 48.4% of all reports for PET RPhs or 0.0019% of the reports for all drug products that were submitted to the FAERS between 2012 and 2024. The other half (481) were reported for 3 PET drugs prepared under practice of pharmacy and for Rb-82 generators manufactured according to 21 CFR part 211 and used under the practice of medicine.

The 451 AE cases reported for RPhs manufactured under 21 CFR part 212 were categorized based on the type of reported event according to the following categories: safety, efficacy, drug administration errors, and manufacturing errors. Reports that could not be assigned to any of these categories were characterized as "other" and were included in a separate group. As shown in Table 2, 237 cases were reported as safety related with at least one ADR. One third (80) of these cases were characterized as serious. The most common reported ADRs were flushing (50), nausea (31), dyspnoea (25), hyperhidrosis (25), dizziness (23) and back pain (20). There were also 4 cases where exposure to radiation was reported. One case filed for Florbetapir F-18 reported suspected transmission of an infectious agent via the product and was characterized as serious.

Notably, 15 cases reported death as the adverse event or the outcome of the event. One case of death was reported for Ammonia N-13 without providing other information regarding any observed ADR. The AE case included a long list of concomitant medication the patient was receiving at the time of the event. Two cases of death were reported for Fluciclovine F-18 with one of them being reported for a 44-year-old female, this indicates that the drug was probably used off label or the wrong drug was included

in the report, since Fluciclovine F-18 is FDA approved for prostate cancer imaging. The remaining 12 cases were reported for Fludeoxyglucose F-18. For six of these cases more than one drug was the suspected PAI, while for three other cases Keytruda is listed as the suspected product name (pembrolizumab, a PD-1 inhibitor used in cancer immunotherapy). For another case, although no further information is provided for the cause of the death or the suspected PAI besides the RPh, the reported ADR was a contrast agent reaction.

Most of the cases (80) categorized as efficacy related were reported by healthcare providers. The most common reported events were “scan abnormal” (79) followed by “drug ineffective” (46). Both events were reported for 31 of the cases. For 20 other cases, the AE reported was “therapeutic response unexpected”. No further information was provided in the database regarding these events, and it is not clear what constitutes an abnormal scan or what it means for a diagnostic radiopharmaceutical to have an unexpected or less than expected therapeutic response. We speculate that these events were due to poor scan quality or unexpected diagnostic data.

We found 25 cases that reported an error during the administration of the drug with all of those characterized as non-serious. AEs in this category include extravasations (6), administration of the wrong product (4) or the wrong patient (4) or the wrong dose (9).

Further, 36 reports were related to manufacturing errors. These events included: dispensing errors (17), product preparation errors (10), and wrong label on the product (8). For 3 of these a sterility issue was also reported. For all these cases, no adverse drug reaction was reported, and all events were characterized as non-serious. Although accurately characterized as manufacturing errors, some of these events represent handling errors and are not related to product attributes such as purity, quality, and strength.

Finally, 34 cases could not match any of the above categories and were included in a different group. Of those, 19 reported either a false positive (5) or a false negative (14) investigation. Incidents that may require an investigation can include but are not limited to an abnormal scan, administration of the wrong radiopharmaceutical or dose, or a manufacturing or sterility problem. No further information was provided about the nature of the investigation for the majority of these reports (16), and only for 3 of these cases an abnormality of the scan or the effectiveness of the drug was also reported. Additionally in this category we included 13 cases for Florbetapir F-18 that reported amyloid related imaging abnormalities such as microhemorrhages and hemosiderin deposits. Lastly, there were 2 cases reporting “no adverse event” with no further information on why they were reported and included in FAERS.

All 451 cases reported for RPhs manufactured under 21 CFR 212 were categorized based on the suspected PAI. As mentioned, for 57 cases, at least one more drug besides the RPh was suspected to cause the adverse event. More specifically, for the 237 cases reporting an ADR and categorized as safety related, 42 had at least one more suspected PAI. Most common drugs listed as suspected to have caused the adverse reactions included chemotherapy drugs (e.g., doxorubicin, etoposide), antibodies

(e.g., obinutuzumab, glofitamab), immunotherapy medications (e.g., pembrolizumab), and anti-amyloid agents (e.g., aducanumab) among others.

Combining all the different parameters used for our analysis, we found that over the past 12 years, there were 195 cases submitted to the FAERS database for PET radiopharmaceuticals manufactured in the U.S. and unspecified countries under 21 CFR part 212 that caused a safety-related adverse event for which the PET drug was the suspected product active ingredient. This represents 0.0008% of all reported AEs between 2012 and 2024, or 3.3 AEs/ $10^5$  RPh administrations.

Despite the marked increase of PET scans performed each year, which has doubled over the past 12 years to ca. 3 million annually, the number of reported AEs remains very low and is estimated to be less than 7.0 AEs per  $10^5$  scans in 2024 for all PET RPhs, and 4.3/ $10^5$  AEs for RPhs manufactured under the PET GMP regulations (Table 3). This represents “real world” data for PET radiopharmaceuticals obtained only from the FAERS database, unlike former reports that used data reported to the authors from the manufacturers (11, 12), data from reports in the literature (14), or data for both PET and non-PET RPhs (18, 19). Notably, our findings are within the same order of magnitude as those reported by Silberstein, 2.3 AEs per  $10^5$  (11) and 2.1–2.3 AEs per  $10^5$  administered doses for PET or all PET and non-PET RPhs (19), respectively, although our retrospective study design based on FAERs is completely different from these prospective studies. In our opinion, this indicates that AEs are consistent over time, reflecting the inherent safety and low risk of PET RPhs.

Based on our analysis, we cannot conclusively connect reported ADRs to PET RPh sterility or production failures. As shown in Table 2, there is no clear trend connecting the reported safety AEs to those related to manufacturing, distribution or sterility issues. The reported AEs for the radiopharmaceuticals manufactured under GMP requirements for PET drugs over the last 10–12 years (451) appear to be equal to those manufactured according to 21 CFR part 211 or prepared under the practice of pharmacy or medicine (481), and thus imply that the PET GMP regulations do not increase the risk of PET radiopharmaceuticals.

## Conclusions

Despite the increased concerns regarding the safety of PET RPhs from regulators in recent years, our analysis of the AEs reported to the FAERS public dashboard revealed that the number of AEs remains extremely low (less than 7.0 AEs per  $10^5$  RPh administrations per year) compared to the annual number of doses administered (estimated at about 3,000,000) (32). The findings confirm our assertion that PET radiopharmaceuticals can be generally recognized as a safe and effective drug class for which very low levels of adverse events are observed year to year, and which present low risk to patients. It is also evident that the manufacturing of PET RPhs under 21 CFR part 212 does not increase the frequency of AEs reported compared to part 211 or the practice of pharmacy. In addition, reports filed about sterility or production issues are not associated with any adverse events or ADRs. Taken together, it is challenging to conclusively link reported AEs to PET RPh sterility or production failures; thus, in our

opinion, these data should not be used to justify any revision of manufacturing regulations. Finally, this analysis shows the importance of adverse event data in establishing the safety profile of PET RPhs. It is our hope that this study inspires the PET community to re-establish prospective studies and data collection around AEs to corroborate the data collected in the FAERS.

## **Declarations**

## **Competing interests**

SSZ is an employee of Siemens PETNET Solutions. In addition to their primary employment, SSZ, HVB, and PJHS hold volunteer leadership positions at the Coalition of PET Drug Manufacturers, a 501(c)(6) trade association operating as a not-for-profit organization dedicated to the advancement of scientific and regulatory principles associated with the manufacturing and distribution of safe and effective drugs for diagnostic PET imaging. MD is a member and involved with various committees at the Coalition. Due to his role as an Associate Editor, PJHS was not involved in the peer-review of this article and has no access to information regarding its peer-review.

## **Ethics approval**

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

### **Consent for publication**

Not applicable.

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## **Authors' contributions**

MD analyzed the data and wrote the manuscript. HVB, SSZ and PJHS edited the manuscript. PJHS had supervisory and project management responsibility. All authors read and approved the final manuscript.

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## Availability of data and materials

The data obtained from the FAERS database that was the basis of this study is provided in the Supplementary Information accompanying the article.

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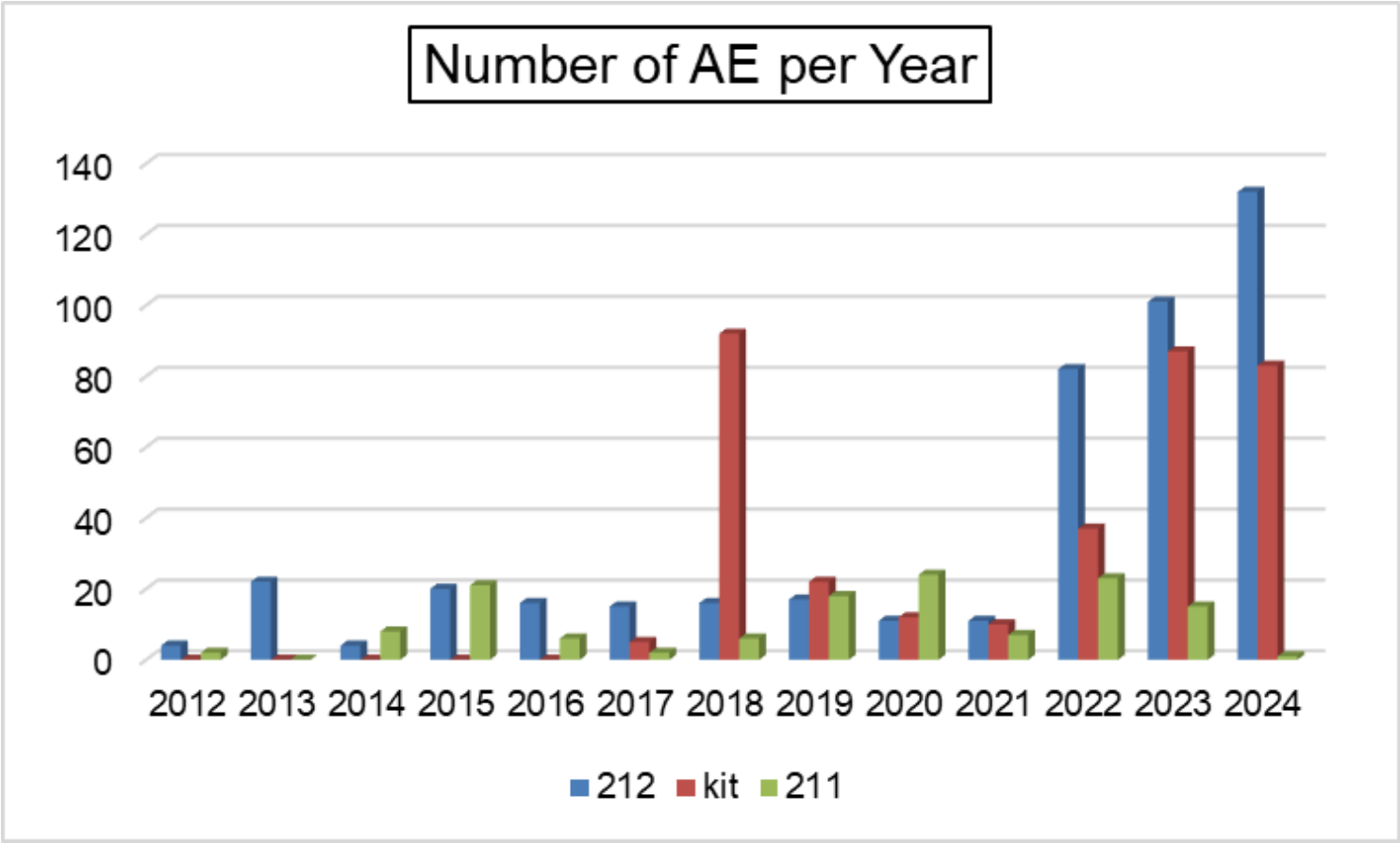
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Figures



## Figure 1

Number of reported AEs per year in the US associated with PET radiopharmaceuticals manufactured in facilities under 21 CFR 212 (blue), prepared using kits in nuclear pharmacies or nuclear medicine departments under the practice of pharmacy or medicine (red), or Rb-82 generators manufactured under 21 CFR 211 (green) and used under the practice of medicine.

## Supplementary Files

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