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Review

Bringing New PET Drugs to Clinical Practice – A Regulatory Perspective

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Abstract

The regulatory framework for radioactive drugs, in particular those used in positron emission tomography (PET) scans, has been gradually established since the release of the Food and Drug Administration Modernization Act in 1997. Various guidances specially tailored to accommodate special properties of PET drugs have been issued by the Food and Drug Administration (FDA) in order to ensure this valuable technology (i.e., PET molecular imaging) will continue to be available to patients and yet the safety and efficacy of PET drugs are well regulated so that public health will be protected. This article presents several key elements of this regulatory framework for PET drugs. New regulatory avenues proposed by the FDA to facilitate the research and development process to bring more new PET drugs to clinical practice, as well as to foster the opportunity of using "orphan" PET drugs in clinical practice are also discussed in this paper.

Key words: PET drugs, FDA, regulations, RDRC, IND, NDA, exploratory IND, expanded access IND.

Introduction

A presentation titled "2012 FDA Update" [1] made by Dr. Dwaine Rieves, Director of Division of Medical Imaging Products, U.S. Food and Drug Administration (FDA) puts focus on what FDA has been doing and plans to do next on imaging drugs as follows: (1) approvals and labeling actions on several imaging drugs occurred in 2011/2012, (2) the publication of a draft guidance on standards for clinical trial imaging endpoints (final guidance will be released soon), (3) nomination of 12 new members for Medical Imaging Drugs Advisory Committee (MIDAC) – please refer to the official web link to MIDAC [2] for the roster of membership of this committee, and (4) various regulatory activities on positron emission tomography (PET) drugs.

With the continued interest and momentum in developing new molecular imaging agents (especially PET drugs) both from clinical demands (specialized therapies and personalized medicine) and regulatory requirements (quality of drug and new drug approval), there will be an increasing need to develop more molecular imaging agents with increased specificity and sensitivity, but also escalating enforcement actions from the FDA.

Drug discovery and development can be challenging, lengthy, and expensive. It has been estimated that a therapeutic drug costs approximately $850 million to develop over 12.9 years on an average, whereas a diagnostic imaging agent takes approximately 8-10 years to develop at a cost of between $100 million and $200 million [3-6]. The new drug approval is another costly and time-consuming process; however, it is imperative to have a seal of FDA approval on the new drug to be qualified for a possible reimbursement from either the U.S. Centers for Medicare & Medicaid Services (CMS) or third-party insurance payers. This

is a key element for maintaining a sustainable clinical practice.

The main objective of this article is to present various regulatory "do's and don'ts" (some may be well-known, some are relatively new) in using new PET drugs for clinical practice, research, or investigation. PET drugs were selected as the examples for this regulatory perspective paper since PET is an ever-growing lead modality in the molecular imaging and there has been a stream of regulatory rules and guidances implemented by the FDA since the announcement of the Food and Drug Administration Modernization and Accountability Act (FDAMA) signed by the President Clinton in 1997 [7].

FDA Definitions

To have a better understanding of any regulatory document, it is important to know the official definitions associated with relevant requirements so that compliance with the established rules and regulations can be adequately achieved. Since FDA has the final authority to approve the use of any PET drug in clinical practice and research & development (R&D) settings, one must understand the definitional differences among three "use" phrases (i.e., "clinical use", "investigational use", and "research use") which commonly appear in FDA documents. Unfortunately these three phrases are being used quite interchangeably, in particular in the academia field. For PET drugs (and all other radioactive drugs), FDA defines "clinical use", "investigational use", and "research use" as follows:

Clinical use refers to administration of the PET drug to patients as a component of their clinical care with no intent to study the safety or effectiveness of the drug in any systematic way. Clinical use of any PET drug is allowed if that drug has an approved new drug application (NDA) or abbreviated NDA (ANDA) status. If the PET drug has not been approved by the FDA, the permissible situation is to use this PET drug under the expanded access IND route (this will be discussed in details later). In any case, the phrase *clinical use* has a different meaning vs. *investigational use* and *research use* in the eyes of the FDA.

Investigational use refers to the administration of PET drugs to subjects under an IND or an IND exemption (to be discussed in the "IND exemption" section of this paper) to determine its safety and/or efficacy. The typical goal of an IND study is to establish the safety and/or effectiveness of a new use of the drug and to support an application for approval of a new indication for use.

Research use refers to administration of PET drugs to human research subjects typically under a Radioactive Drug Research Committee (RDRC) application for basic science research. The objective of an RDRC study is to obtain basic information regarding the metabolism, physiology, pathophysiology or biochemistry of the PET drug. Such administration is neither intended for immediate therapeutic or diagnostic purposes, nor to determine the safety and effectiveness of the drug.

Clinical Use

NDA and ANDA

FDA was supposed to enforce the requirement that all producers of PET drugs submit applications (NDA or ANDA) by December 12, 2011 [8]. However, this deadline was extended to June 12, 2012 possibly due to concern some PET centers were unable to meet the deadline [9]. Currently, for PET drug producers that submitted the required application(s), FDA will not object if clinical use of the PET drug(s) continues during the application review period, provided that the facility complies with all other FDA requirements, including current good manufacturing practices (CGMP) [10]. Nevertheless, all PET drug producers must be operating under an approved NDA or ANDA, or effective IND, after December 12, 2015 [10].

The origin of these regulations for PET drugs was from Section 121 "Positron Emission Tomography" of the FDAMA [11]. Section 121(c)(1)(A) of the FDAMA directs the FDA to establish appropriate approval procedures (i.e., PET drug applications - NDA and ANDA) and CGMP requirements specifically for PET drugs [9]. This particular regulation also stipulates that all PET drug manufacturers and compounders would be required to submit applications for approval within 24 months of the establishment of such procedures and requirements [11]. Since the publication of the final rule on CGMP for PET drugs was on December 10, 2009 [8], this triggered the requirement that all producers of PET drugs submit applications by December 12, 2011.

It is worthy to note that U.S. Senate and Congress issued their own reports to provide background information, as well as their reasons for the establishment of these statutes [12,13] (including Section 121 specifically established for PET drugs) [14,15]. Please refer to the quotes below (with emphases added) copied from the Senate Report No. 43, 105th Congress, 1st Session – this report clearly depicts why it was so essential and necessary to revamp the U.S. regulatory framework for PET drugs [14]:

> …PET radiopharmaceuticals have been used in patients in the United States for over 30 years. Recent research and advances in imaging technology have enhanced the clinical importance of PET.… At present, there are 70 PET centers in

the United States, almost all of which are part of academic medical centers. PET technology and its applications were developed in large part with almost $2 billion in federal research funds. Yet, while PET is widely used in Europe, its benefits have not been widely available to American patients, **mainly because of lack of reimbursement and inappropriate and costly regulations promulgated by FDA.**

Under current FDA regulations, PET centers which compound PET radiopharmaceuticals on an individual dose basis would be required to meet FDA's CGMP and to file NDA's and ANDA's for each type of PET tracer and for each indication for which the tracer might be used. **This is the same type of regulation which the FDA applies to large pharmaceutical manufacturers.**

Academic medical centers are facing unprecedented cost pressures. Without regulatory relief and expanded reimbursement, particularly from the Medicare program, many PET centers are likely to close, and the benefits of PET will be unavailable to the taxpayers who funded their development.

Due to the clear and strong mandate as stated in this Senate Report [12], the PET CGMP regulations issued by the FDA [8] were sufficiently flexible to accommodate not-for-profit, academically oriented institutions as well as larger commercial producers. FDA also took into consideration of the unique nature of PET drugs and PET drug production during the development process of the final PET CGMP rule [8]. Thus, the final CGMP requirements for PET drugs differed in many significant ways from the CGMP requirements for non-PET drugs [8].

2011/2012 FDA Approvals of PET & SPECT Drugs

In 2011 and 2012, FDA approved the following PET and SPECT drugs:

- Ioflupane I 123 Injection (DaTscan) – a new molecular entity (NME) for SPECT imaging to aid in the differentiation between essential tremor from tremor due to Parkinsonian syndromes (PS) [16].
- Technetium Tc 99m sulfur colloid – an NDA supplement to add indication for an already-marketed drug. The new indication is for the localization of lymph nodes draining a primary tumor in patients with breast cancer [17].
- Rubidium Rb 82 chloride injection – an NDA supplement to address risk for unintended ^{82}Sr and ^{85}Sr radiation exposure and the methods to minimize this risk [18].
- Florbetapir F 18 Injection (Amyvid) – an NME for PET imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive decline [19].

Dr. Lucie Yang from the FDA presented a talk titled "New Drug Approvals FDA: Year in Review" at the 2012 Annual Meeting of the Society of Nuclear Medicine [20]. In her presentation, she provided "Take Home Points" for three of the above-listed drugs (excluding rubidium Rb 82 injection) which are great lessons to be learned for R&D and IND/NDA planning strategies [20]. Please refer to the quotes as listed below for Dr. Yang's words of advice [20]:

Ioflupane I 123 Injection

- Clinical Diagnosis can be the Reference Standard in a Phase 3 trial for an imaging agent used to distinguish PS from non-PS.
- Early in development, consider the possibility that the imaging agent could be a controlled substance (even if remote).

Technetium Tc 99m Sulfur Colloid Injection

- An NDA can comprise of a systematic review of published literature, in this case, with meta-analysis of select studies.

Florbetapir F 18 Injection

- A clinically-applicable reading method and reader training program may be essential in certain situations.
- The "ability to provide useful clinical information" can be satisfied without demonstrating clinical benefit in a trial.

USP Monographs for PET Drugs

As of July 4, 2012, the following twelve PET drugs had United States Pharmacopeia (USP) monographs:

- Ammonia N 13 injection
- Carbon monoxide C 11
- Fludeoxyglucose F 18 injection
- Fluorodopa F 18 injection
- Flumazenil C 11 injection
- Mespiperone C 11 injection
- Methionine C 11 injection
- Raclopride C 11 injection
- Rubidium chloride Rb 82 injection
- Sodium acetate C 11 injection
- Sodium fluoride F 18 injection
- Water O 15 injection

However, not all of these USP-listed PET drugs have been approved by FDA. Only ammonia N 13 injection, fludeoxyglucose F 18 injection, rubidium chloride Rb 82 injection, and sodium fluoride F 18 injection are FDA-approved PET drugs which are

currently included in the USP. FDA approved florbetapir F 18 injection for PET imaging on April 6, 2012 [19], and on September 12, 2012, FDA approved choline C 11 injection – a PET imaging agent used to help detect recurrent prostate cancer [21]. The current version of USP does not include monographs for these two new PET drugs.

USP monograph development typically occurs after the FDA has accepted a NDA for a drug product. The inclusion of USP monographs for the other eight PET drugs that have not been approved by FDA is a notable exception; however, this situation is not unusual in the European Pharmacopeia which has published monographs for not-yet-approved PET drugs. In any event, one needs to understand that a USP monograph for a PET drug is not equivalent to an approval status granted by the FDA for that drug. Thus, any clinical use of an unapproved drug without permission from FDA will be facing an enforcement action against such usage from the FDA.

Expanded Access IND

Background

Expended access (EA) refers to a range of investigational new drug (IND) mechanisms intended to provide access to investigational drugs for continuing clinical use of these IND drugs, while balancing the need to safeguard the individual patient and ensure the continued integrity of the scientific process that brings safe and effective drugs to the market. FDA has allowed certain types of access to investigational therapies since the 1970's, such as emergency IND and treatment IND for patients with certain serious or immediately life-threatening diseases or conditions – particularly cancers, human immunodeficiency virus (HIV) disease and HIV-related conditions. However, the existing regulations did not adequately describe the full range of programs available and the criteria or requirements.

As such, U.S. Congress included in the 1997 FDAMA which requires the amendment of the U.S. Federal Food, Drug, and Cosmetic Act to have specific provisions concerning EA to investigational drugs for treatment use [22]. In December 2006, FDA proposed a draft rule to further address these concerns [23] and a final rule on EA to investigational drugs for treatment use was issued in August 2009 [24].

Types

There are three categories of EA INDs – (1) individual patient (including emergency or non-emergency use), (2) intermediate-size patient population (10-20 patients – may request FDA to authorize use in additional patients), and (3) widespread use under a treatment IND or treatment protocol [24].

Simplified IND Submission

With the content of an EA IND submission, the amount of application information required depends on the size of the population to be treated (see more discussion on the types of EA below), and a range of clinical data and information might be relied on, including data from clinical trials (e.g., IND or RDRC), clinical pharmacology data (pharmacodynamic and pharmacokinetic findings), clinical experience (e.g., case series), and other evidence from scientific literature [24].

Recoverable Costs for Drug

The purpose of permitting cost recovery for EA use is to facilitate access to investigational drugs for treatment use in situations in which a sponsor might not be able to provide such drug absent charging, or to facilitate broader access than would be possible absent charging [24]. This cost recovery is only for drug-related expenses, and not for technical- or professional-component payment [24].

A sponsor of an individual patient EA IND can only recover its direct costs, whereas sponsors of intermediate-size patient population or treatment EA IND programs can charge patients with direct costs, as well as indirect administrative costs (e.g., costs associated with monitoring the IND or protocol and complying with IND reporting requirements) [24].

Written request to charge (including a statement that an independent certified public accountant has reviewed and approved the cost calculations) must be submitted to the FDA for approval. The charging can continue only for one year from the time of FDA authorization, unless FDA specifies a short period [24]. A sponsor can request that FDA reauthorize charging for additional periods [24].

EA INDs for PET Drugs

FDA recognized that after June 12, 2012 there would still be clinical situations in which certain PET drugs would continue to be needed, and NDA or ANDA submissions might not be feasible for these PET drugs [10]. Unique difficulties associated with commercial development of these PET drugs are such as rare disease or condition, very short half-life radioisotopes, and lacking of intellectual property protection, etc. [10] Therefore, in February 2012, FDA released a draft guidance titled "Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs" which includes a significant portion to specifically deal with various EA requirements for clinical use of certain PET drugs [10].

Although the 2009 final rule on EA to investigational drugs is for treatment use [24], in the aforementioned draft guidance for IND on PET drugs [10],

treatment refers to clinical use of diagnostic purposes. This is due to the fact the in the context of PET drugs, FDA defines these drugs are "*diagnostic radiopharmaceuticals that, following injection into humans, produce signals for medical images through the emission of a positron. The dual photons that emerge from the positron emission are detected by PET scanning devices to form images that map the location of the radiopharmaceutical within the body.*" [10]

The other unique aspects of how FDA views certain PET drugs may or may not be qualified for EA are described below [10]:

General Criteria

There are four general criteria that must be met in order to permit EA to an investigational PET drug:

- Patient(s) with serious or immediately life-threatening disease/condition
- No comparable/satisfactory alternative "therapy"
- Potential benefit justifies the potential risk of the clinical use
- Provision of drug will not interfere with drug development for market approval

Patient(s) with Serious or Immediately Life-Threatening Disease/condition

A disease or condition may be considered serious if it is likely that the disease would progress to a serious condition if left untreated. Since a PET drug is able to help detect a serious or life-threatening disease even if the condition is not actively manifest, FDA considers this unique usefulness of PET drugs fits in this first general criterion.

No Comparable/Satisfactory Alternative "Therapy"

FDA recognizes a PET drug's unique capability (e.g., assess metabolic activity or identify specific receptors) to provide unique medical information that cannot be obtained with other imaging modalities (e.g., MRI [magnetic resonance imaging] or CT [computed tomography]).

Potential Benefit Justifies the Potential Risk of the Clinical Use

FDA anticipates the potential risks of diagnostic use will not prove unreasonable in most patient populations due the lacking of pharmacologic activity and generally low radiation absorbed dose with PET drugs [10].

Provision of Drug Will Not Interfere with Drug Development for Market Approval

FDA expects expanded access INDs will only apply in situations where submitting and supporting an NDA or ANDA is not feasible [10]. Thus, there should not be interference with NDA or ANDA process.

Exclusions

EA is generally not the appropriate mechanism to make a PET drug available to patients if there is an approved NDA for the same formulation, and the NDA holder does not have marketing exclusivity, even if the drug cannot be made commercially available outside the NDA holder's institution [10].

EA is also not appropriate for fludeoxyglucose 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection since these are approved PET drugs [10]. As such, when an NDA or ANDA is feasible, EA is not appropriate for that PET drug.

Types

To be able to provide access under a treatment IND or treatment protocol, a sponsor must be actively pursuing marketing approval of the drug, and clinical trials adequate to support the marketing application must have been completed or must be ongoing [10]. Therefore, FDA anticipates that there will be a limited utility of this pathway to make investigational PET drugs available to patients [10]. FDA generally prefers use of an intermediate-size EA IND due to the reason that it permits FDA to prospectively authorize multiple uses of the PET drugs [10].

IND Submission

With the availability of USP monographs on eight PET drugs that have not been approved by the FDA, the sponsors of EA INDs can reference, without the need for validation, any of these monographs to provide quality standards and/or quality control procedures for an associated PET drug listed in USP when applicable.

Because PET drugs are usually administered at microdose levels, an EA IND submission for these drugs will generally call for limited pharmacology and toxicology information. These data could be obtained from the sponsor's own work, the scientific literature, or by right of reference to proprietary data (e.g., drug master file [DMF]).

Once an expanded access IND or treatment protocol is submitted, FDA does not intend to object to the *continued* clinical use during the 30-day IND review period because FDA understands that the prior clinical use will have been supported by compliance with USP standards, which continue as standards for INDs [10].

Research and Investigation

RDRC

To expedite investigations of new radioactive

drugs, FDA regulations at 21 CFR 361.1 [25] describe conditions under which radioactive drugs (including PET drugs) can be used for certain research without an IND. These conditions are to ensure that radioactive drugs used under the RDRC mechanism are generally recognized as safe and effective for the proposed uses. This regulation also stipulates the formation requirements for a RDRC which functions like a mini-FDA to review and approve each research protocol (21 CFR 361.1(b)(1) and (c)(4)) [25].

As stated previously, RDRC approval to conduct research is based upon a determination that the research is, in fact, basic science research, and not research that is intended for immediate therapeutic, diagnostic, or similar purposes, or to determine the safety and effectiveness of the radioactive drug or biological product for such purposes (i.e., the research cannot constitute a clinical trial for the product).

In addition to above-mentioned limitations for an RDRC study, 21 CFR 361.1 lists three additional requirements for human subject research that may be conducted under an RDRC [25]:

- The dose to be administered must be known not to cause any clinically detectable pharmacological effect in humans (21 CFR 361.1(b)(2)).
- The total amount of radiation to be administered as part of the study must be the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study, and must be within specified limits (21 CFR 361.1(b)(3)).
- Only 30 subjects over the age of 18 are normally permitted in the research protocol. If the number exceeds 30 or if the age of any subject is less than 18, then a special summary report with justification must be submitted to the FDA for approval.

Only RDRCs approved by the FDA are authorized to review and approve the proposed basic research studies. If the basic science research study is approved by an RDRC, the research can be conducted without the submission of an IND.

RDRC is not for a first-in-human study. This type of study is considered as a clinical trial where a medical procedure, previously developed and assessed through *in vitro* or animal testing, or through mathematical modelling is tested on human subjects for the first time. An exploratory IND (eIND) is designed for this purpose, and we will discuss more details about this approach later and compare the differences between RDRC and eIND studies.

IND

Exploratory IND (eIND)

The path that a medical product takes from development to mass-production and availability to the public – "Critical Path" as referred by the FDA [26] – has become increasingly challenging, inefficient, and costly. In a move to speed up the development of new medicines, the FDA announced in January 2006 the creation of the eIND, the so-called Phase 0 clinical trials (the term "eIND" rather than "Phase 0" will be used throughout this article as it is not only used by the FDA, but mainly the eIND should be viewed as an early Phase 1 approach to identify suitable drug candidate(s) in a guidance titled "*Exploratory IND Studies*" [27]. This FDA guidance was developed in response to an important report entitled "*Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*" [28] which was released in March 2004 that urged the FDA to overhaul the national clinical trials system.

eIND studies are intended to provide clinical information for a new drug candidate at a much earlier phase of drug R&D process. Microdosing is a primary tool in eIND to allow the collection of human pharmacokinetic and pharmacodynamic data earlier in this R&D process. Since the microdosing approach is designed not to induce any pharmacological effects, these studies are safe to the participating human subjects. Microdosing studies also can be initiated with fewer preclinical safety studies, as well as require lesser resources and time for selecting promising drug candidates for further evaluation.

However, there are three potential weakness areas associated with the microdosing technique. First, the database for microdose studies is still very small. This is partly due to the length of time required to get new approaches adopted, the lack of validation programs, scientific inertia, and a failure to recognize the potential benefits of microdose studies. Nevertheless, the adoption of microdosing approach is accelerating due to the fact that the regulatory climate in Europe and the U.S. has changed and small to medium size biotech companies are conducting microdose studies earlier than big pharmaceutical companies. Second, PET assay has the disadvantages of short tracer half-lives. For both PET and accelerator mass spectrometer (an ultrasensitive analytical tool that is capable to measure drug and metabolite concentrations in the low 10^{-12}–10^{-15} g range), test drug substance must be radiolabeled at metabolically stable site and both assays have limited specificity (assays may contain metabolites). Third, a "microdose" may not predict the actual behavior of clinical doses as it cannot get a sense of dose proportionality with microdoses, or for oral drugs, a good sense on bioavailability since microdoses may not saturate absorption mechanisms thereby leading to a false conclusion of high bioavailability.

Even though eIND involves very limited human exposure, nonclinical safety studies (i.e., animal testing) must be carried out in order to support the initiation of the limited human studies in eIND stage. However, the preclinical testing requirements for eIND studies can be less extensive or different than is required for traditional IND studies. This is because the eIND approach involves administering sub-pharmacologic doses of a candidate drug compound or compounds.

The microdose study will become an accepted approach in drug development and that eventually all first-in-human studies will commence with an eIND clinical trial. Is it ethical to expose human subjects unnecessarily to a pharmacological dose of potential drug that has poor PK/PD (pharmacokinetic/pharmacodynamic) properties, whose development is terminated as a result, when the same information could have been obtained in a microdose study? Has there not been an unnecessary use of animals, including dogs and primates, on the terminated compound? Microdose approach used in the eIND trial will make a contribution to smarter drug development by enabling early human data to be obtained. Drug selection as a result will become more human based and therefore more predictive.

In fact, a good example of utilizing the eIND approach in selecting the lead promising drug candidate is the recently approved PET drug, florbetapir F 18 injection, developed by the Avid Radiopharmaceuticals, Inc. Their positive experience in eIND pathway is nicely presented in their published paper titled "The use of the exploratory IND in the evaluation and development of 18F-PET radiopharmaceuticals for amyloid imaging in the brain: a review of one company's experience" [29]. It is interesting to note from this paper that the compound (i.e., ^{18}F-AV-45) which is the code name of florbetapir F 18 injection during R&D and IND processes was not anticipated to be the best candidate of the series tested [29]. It was found to be a promising candidate during the human eIND studies [29].

Differences between RDRC and eIND

There are some similarities between RDRC and eIND, namely both processes do not pose safety concerns to the studied human subjects, and both pathways have no therapeutic or diagnostic intent although eIND is more designed to assess feasibility for further drug development. Other than these likenesses, several differences are noted between the two regulatory mechanisms:

- RDRC is specifically for radioactive drugs whereas eIND could apply to all drugs (including non-radioactive drugs).
- An eIND study is considered as a true first-in-human study (as a part of IND trial – an early phase 1 study) whereas an RDRC study is not.
- Extended single-dose toxicity studies in a single mammalian species (both sexes) are required for each eIND submission whereas there is no such requirement for an RDRC protocol.
- An RDRC protocol typically involves 30 or more subjects and there is no limitation in completion time. In eIND studies, the number of subjects and duration of dosing are expected to be limited. Screening studies (or microdosing studies) are typically conducted in less than 30 human subjects and during of dosing is about 7 days.
- The FDA directly approves and monitors the eIND, whereas the approval and minoring responsibilities are delegated to the local RDRC by the FDA.
- In RDRC, if studied subjects of age less than 18 are included and/or the number of subjects exceeds 30, a special summary report has to be submitted to the FDA. No such restrictions exist in eINDs.
- The RDRC limits the radiation exposure to human subjects, whereas there is no such limit in eIND. Nevertheless, the strict limitation on mass quantity for the test substance used in a microdose approach [23], radiation risk to human subjects is very limited. It is far less than the potential human exposure for a traditional Phase 1 study as one of the objectives of this particular phase is to seek the establishment of a maximally tolerated dose.

IND Exemptions

In considering whether a study or trial of a PET drug is exempt from an IND, one needs to ensure all of the criteria for an exemption in 21 CFR 312.2(b) [30] are met:

- The drug product is lawfully marketed in the United States.
- There is no intent to report the investigation to FDA as a well-controlled study in support of a new indication for use and no intent to use it to support any other significant change in the labeling of the drug.
- If the drug is lawfully marketed as a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) asso-

ciated with the use of the drug product.

- The investigation is conducted in compliance with the requirements for review by an Institutional Review Board (IRB) and with the requirements for informed consent.
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the sponsor or investigator does not intend to promote or commercialize the drug product) [28].

Therefore, an IND exemption is permissible for each of the six FDA-approved PET drugs (i.e., ammonia N 13 injection, fludeoxyglucose F 18 injection, rubidium chloride Rb 82 injection, sodium fluoride F 18 injection, florbetapir F 18 injection, and choline C 11 injection) as long as the other criteria as stated above are met. However, when considering the possible exemption of an investigation from the IND submission requirement based on the fact that the drug is approved, investigators should be aware that FDA approval of a PET drug or submission of an NDA or ANDA for a PET drug allows manufacturing of the drug only at the approved manufacturing facility. Thus, although fludeoxyglucose F 18 injection is an FDA-approved PET drug, an IND would be required for investigational use of this PET drug if it is obtained from a PET drug producer who has not submitted an NDA or ANDA for fludeoxyglucose F 18 injection.

FDA allows any producer who makes PET drug(s) that is/are not yet approved by the FDA to continue the clinical uses of any of these PET drugs if this producer submitted an NDA or ANDA for each of these PET drugs by June 12, 2012 [10]. During the review period of submitted NDA or ANDA, FDA does not intend to object to use of any of these PET drugs in a clinical trial without an IND. Although this special permission of IND exemption is not subjected to the final NDA or ANDA approval, the IND exemption will be revoked if significant manufacturing deficiencies are found during the NDA/ANDA review, or during inspection of the facility the PET drug is sourced from. After December 12, 2015, investigational use of a PET drug must be covered by an IND unless it is exempt from all of the IND requirements [10].

Conclusions and Perspectives

The increased regulatory requirements from the FDA, in particular towards the production and usage of PET drugs are challenging and may be burdensome to the PET community. However, it is important to recognize that clinical PET flourished after the release of 1997 FDAMA [8] due to the improvement in expanded reimbursement, particularly from the CMS. Needless to say, the regulatory relief that FDA has granted under the new requirements for PET CGMP, EA IND, and NDA/ANDA submission, etc. is quite helpful to us for easier compliance. They also greatly enhance our R&D and clinical practice in PET.

Hopefully this article will help to provide a better understanding of the regulatory framework in place for PET drugs, and allow the PET community to make the best use of these new rules for enhancing the clinical utility of various PET drugs and/or the discovery and development of exciting new PET drugs!

Abbreviations

ANDA: abbreviated new drug application; CGMP: current good manufacturing practice; CMS: Center for Medicare & Medicaid Services; CT: computed tomography; DMF: drug master file; EA: expanded access; eIND: exploratory investigational new drug; FDA: Food and Drug Administration; FDAMA: Food and Drug Modernization Act; HIV: human immunodeficiency virus; IND: investigational new drug; IRB: Institutional Review Board; NDA: new drug application; MIDAC: Medical Imaging Drugs Advisory Committee; MRI: magnetic resonance imaging; NME: new molecular entity; PD: pharmacodynamic; PET: positron emission tomography; PK: pharmacokinetic; RDRC: radioactive drug research committee; R&D: research and development; USP: United States Pharmacopeia.

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Conflict of Interests

The author has declared that no conflict of interest exists.

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