Translation

The trend of U.S. regulations concerning PET examination*

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Abstract

United States (U.S.) Food and Drug Administration (FDA) issued the report on the Clitical Path Initiative in 2004 in which they mentioned imaging technology as one of the tools for assessment of biomarkers of drug efficacy, which should facilitate clinical development. Additionally the FDA issued several guidances to facilitate development of imaging diagnostic drugs and regulations for PET (Positron Emission Tomography) drug specific Good Manufacturing Practice (PET drug GMP). Actually in the U.S., medical/research institutions and companies have been developing various PET drugs aiming at regulatory approval and public health reimbursement coverage. This article reports such situations in the U.S., considering related situations in Japan.

Key words
PET (Positron Emission Tomography), RDRC (Radioactive Drug Research Committee), IND (Investigational New Drug application), GMP (Good Manufacturing Practice), FDA (Food and Drug Administration)

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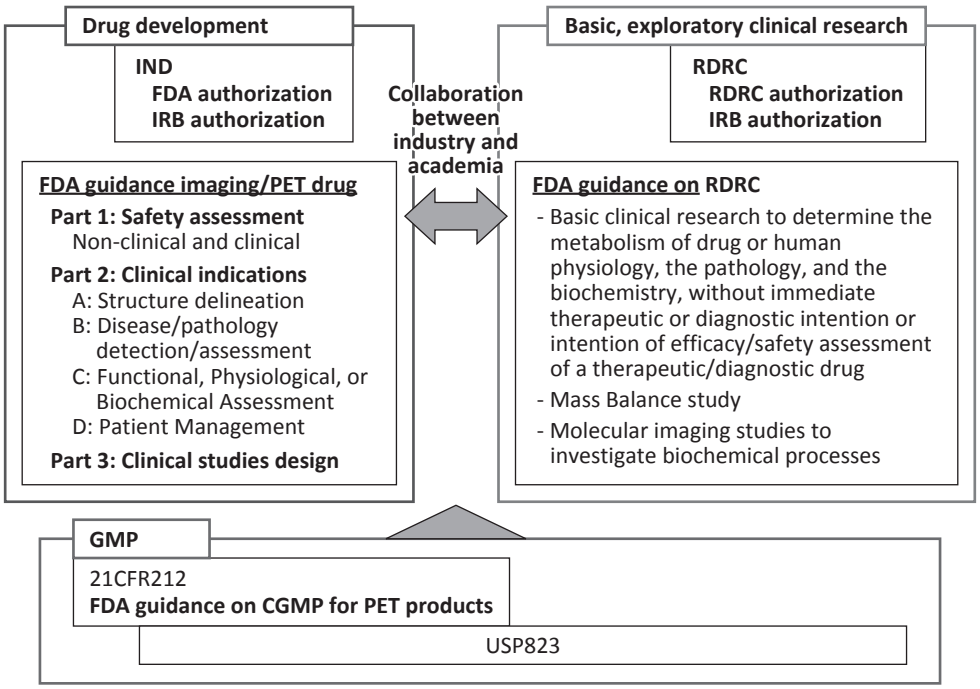
1. Regulatory framework of PET drugs

In the U.S. (United States) there are two tracks of clinical research or clinical trials using radiopharmaceuticals including PET (Positron Emission Tomography) imaging agents (Fig. 1)[1]: (1) RDRC (Radioactive Drug Research Committee) program (Fig. 1, right) for basic research using radioactive drugs in humans without an IND (Investigational New Drug application) when the drug is administered under the defined conditions where the drug is safe and effective; (2) IND framework (Fig. 1, left) where application documents have to be submitted to the FDA (Food and Drug Administration) for conduct of clinical trials of therapeutic or diagnostic drug. This IND requirement is a general rule not specific to radiopharmaceuticals. PET drugs may be submitted for IND aiming at diagnostic drug development or may be used as a measurement tool of a biomarker of the effect of therapeutic drug.

● **RDRC program** (Fig. 1, right)

The RDRC program was established by the Code of Federal Regulations (CFR) in 1975. In 2010 the FDA issued a guidance[2] to explain this program. If you use radioactive drugs which are defined "safe and effective" in this CFR, and you do not have any intention of therapeutic/diagnostic drug development or intention of clinical therapeutic/diagnostic assessment, but just have an intention of "basic" research involving human to explore pathophysiology of human or mechanism of actions of the agent, you can conduct such studies without submitting an IND to FDA. Instead, you have to submit your protocol to an FDA-approved RDRC. You also have to submit to an IRB (Institutional Review Board), which

Fig. 1　Constructions of guidance documents by FDA concerning medical imaging drug development and radioactive drug clinical research



is the same process as for ordinary clinical research. The definition of "safe" in this regulation means that the administered agent does not have any clinically detectable effect and the radiation dose does not exceed the following limit, which has to be confirmed by the RDRCs:

- In whole body; active blood-forming organs; lens of the eye; and gonads: 3 rem (30 mSv) for single dose; 5 rem (50 mSv) for a cumulative annual dose
- In other organs: 5 rem (50 mSv) for single dose; 15 rem (150 mSv) for a cumulative annual dose

According to the presentation by the FDA personnel of this program in 2010 [3], 76 RCRCs submitted their reports to the FDA as they are working in 2010 and 628 research protocols were conducted in 2009 within this RDRC program.

This framework of the RDRC program is similar to "clinical research" in Japan which does not require an IND submission to the regulatory authority conducted under the governmental guidelines. However in the U.S., FDA oversees the research within this RDRC program under the legally-defined rules and also the number of protocols and research subjects with summarized characteristics of these studies are annually reported to the FDA from the RDRCs. This point is different from the regulatory framework of Japanese clinical research.

● **IND framework** (Fig. 1, left)

If you conduct a clinical trial of PET drug for new diagnostic drug development or use a PET drug as a tool of measurement of a biomarker in a clinical trial of a therapeutic drug, you have to submit an IND to the FDA for conducting a clinical trial. You also need to get authorization of an IRB. (In case you do not have an intention of development of this PET drug for an approved biomarker, it may be applicable for an IND exemption.)

In 2004, FDA issued the report on the Critical Path [4] in which they mentioned about imaging technology as one of the tools for assessment of biomarkers of drug efficacy for facilitating clinical development. At the same time, the FDA issued a set of three guidances for the development of medical imaging drugs (including the agents of PET and SPECT imaging, etc.) for (1) safety assessments [5], (2) clinical indications [6]; and (3) design, analysis and interpretation of clinical studies [7]. The FDA also issued and finalized in 2009 the PET drug specific regulations of GMP (PET drug GMP) and issued its guidance [8].

Also in 2006, the FDA issued the Exploratory-IND guidance [9] which allowed the conducting of the first-in-human study of specific design with administration of smaller doses to human, and based on less preclinical data, compared to traditional phase 1 studies, which typically include a dose escalation design for safety assessment in human. This Exploratory-IND guidance facilitated research using PET not only for biomarker assessment of therapeutic drug trial but also for diagnostic drug development, because the required preclinical data for PET agents were clarified in this guidance.

● **Manufacturing standard (GMP and USP823)** (Fig. 1)

As for the manufacturing standard, the above mentioned PET drug GMP regulation was intended at first to cover manufacturing of the investigational drug in the IND framework; however, in response to public consultation, this regulation came to cover only manufacturing for clinical use in general practice, after the approval of each PET drug (Actually in later phases of clinical trials NDA applicants will follow PET drug GMP). In the framework of RDRC and IND, the manufacturing standard is not the above PET drug GMP but "USP (United States Pharmacopeia) 823". This USP 823 was amended to make it compatible with the PET drug GMP. Comparing with PET drug

GMP, USP 823 is a short document and its implementation is rather flexible. In the U.S., monographs and related standards in pharmacopeia are developed by a non-governmental institution named the "United States Pharmacopeial Convention" collaborating with specialists from academic institutes and companies. FDA makes use of the monographs of drugs listed in USP (Aside this exceptional cases of PET drugs in USP, monographs in USP are those of approved ones, reviewed by FDA).

● **RDRC and IND** (Fig. 1)

The framework of IND in U.S. is similar to clinical trials in Japan under the GCP (Good Clinical Practice) Ordinance covered by the Pharmaceutical Affairs Law but an interesting point is that some strategic researchers in the U.S. make use of both of these IND and RDRC frameworks for development of new PET drugs [1]. This means that they conduct clinical research for proof of concept in the RDRC framework and then conduct clinical trials for development aiming at regulatory approval within the IND framework. In Japan some researchers also adopt such strategy to make use of both frameworks of clinical trials under GCP Ordinance and clinical research under guidelines, but it has not become so common in Japanese PET community.

2. Aiming at FDA approval of PET drugs

FDA has provided various opportunities to discuss with the PET community and they provide educational lecture meetings or workshops, collaborating with the Society of Nuclear Medicine (SNM) (since June 2011 "Society of Nuclear Medicine and Molecular Imaging: SNMMI"). They encouraged medical institutions to get approvals of PET drugs by the end of 2011 when the PET drug GMP was implemented, if the institutions wanted to use a PET drug in their general clinical practice. If the institutions did not get approval, they have to use the drug in a research status within the frameworks of RDRC or IND. In this case, the medical institution should not provide a diagnostic examination as a part of clinical practice and should not ask patients for payment.

FDA especially encouraged the institutions to get approvals of the three PET drugs, F-18 FDG, F-18-NaF, N-13 Ammonia and issued guidance to explain necessary information for getting approvals of these specific drugs [10]. Among these three, F-18 FDG and F-18 NaF were previously approved (supply of NaF had been terminated), so it is possible for an applicant to apply within the framework of an Abbreviated New Drug Application (ANDA), which is the same as a generic drug application, if the applied indication is in the range of the previously approved one. Even if the indication is different, the applicant can apply based on a retrospective review of the literature, without conducting new clinical trials. Responding to these suggestions by the FDA, the National Cancer Institute (NCI) received approval for an NDA of F-18 NaF in January 2011 and PETNET Solutions also received approval for an ANDA for FDG in February 2011. It is notable that among the literature which supported the NCI's application, two academic reports of Japanese researchers were included [11, 12].

In Japan, most of the NDA applicants are companies (including small venture companies and Contract Research Organizations), but in the U.S. medical institutions and research institutions are also NDA applicants. In 2011 August FDA issued the PET drug GMP guidance for small businesses [13]. The PET drug is characterized by its short half-life and is not suitable for large-scale production for supplying large areas. Therefore, it is useful that each manufacturing site inside hospitals can get an NDA for their clinical use so that the PET drug is not only supplied by a company.

3. Promoting development of diagnostic drugs and devices

The PET community in the U.S. has also been promoting the development of new PET diagnostic drugs, not only the above mentioned well-known PET diagnostic drugs. In October 2008, the FDA formed the "Peripheral and Central Nervous System Drugs Advisory Committee" to discuss about the conditions for approval of beta amyloid imaging to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease [14]. The regulators and three applicant companies: Avid Radiopharmaceuticals; Bayer HealthCare Pharmaceuticals; and GE Healthcare, discussed about the necessary information and design of phase three pivotal studies for approval, based on the presentation of each company's scientific results of studies up until then. It seems to be a good opportunity to make use of the above mentioned guidance for clinical development of medical imaging agents toward approval. Then according to the FDA's recommendation, the first of these three companies, Avid Radiopharmaceuticals completed a study to compare brain imaging during the life time of the research subjects and brain autopsy after their deaths and submitted these research results to the FDA for an NDA. At the end of 2010, Eli Lilly purchased Avid. Then in January 2011, the FDA held an Advisory Committee and they made a recommendation for approval on the condition that the applicant should develop an educational program for the method of reading these images to improve the validity of the image results among the physicians. Now the company is preparing such a program, collaborating with specialists in this area. (Later on they developed an educational program and obtained approval. The other two companies also obtained approvals of amyloid imaging PET drugs and these three are now at the stage of limited public insurance coverage. See the other articles [15, 16] for details.)

In addition, the FDA issued a guidance on medical imaging devices and imaging drug/biological products [17]. This guidance provides instructions necessary for an NDA submission when some part of the device or drug/biological product is already approved and the applicant is applying for a new indication for some of them. It provides a similar approach as in the case of the co-development strategy for therapeutic and diagnostic drugs focusing on pharmacogenomics. In the case of imaging diagnostics, we should promulgate the harmonized development strategy among diagnostic drugs, diagnostic devices, and therapeutic drugs.

4. Public insurance coverage and accreditation of imaging facilities

As for the public insurance coverage of imaging diagnosis in the U.S., we should first discuss about the process of expanding coverage of the new indications for FDG as the result of the patient registration system. We also have to discuss about the accreditation program of imaging facilities for ordinary imaging practice.

Coverage expansion of new indications for FDG was achieved as the result of the program named the National Oncologic PET Registry (NOPR) which was led by the Academy of Molecular Imaging and the American College of Radiology. This registration program was reviewed by the Department of Health and started in May 2006 and more than 30,000 cases were registered. This project succeeded in showing how the FDG-PET examination influenced physicians' decision-making for patient management [18]. This project was designed in response to the policy of the Centers for Medicare

& Medicaid Services (CMS), named "coverage with evidence development (CED)", which described their evidence-based reimbursement policy.

Another discussion point is the accreditation program of the imaging facility, which is a part of the Medicare improvement program. It came to be required that imaging facilities (except hospitals, which provide clinical imaging diagnostic examination using advanced imaging technologies, such as PET, SPECT, CT, MRI (but excluding X-ray, ultrasound, as they are not "advanced" technology)), that are reimbursed by the Medicare program have to get accreditation for their imaging procedures by January 2012. It was specified by the Medicare Improvements for Patients and Providers Act (MIPPA).

The CMS authorized three accreditation organizations: the American College of Radiology (ACR); the Intersocietal Accreditation Commission (IAC); and the Joint Commission (JC). Both the ACR and IAC have a history of more than 20 years of accreditation activities since the time before this MIPPA regulation started and the ACR has given accreditation to more than 20,000 facilities. This imaging facility accreditation program excludes hospitals because hospitals have to get general accreditation for all the hospital activities. The JC has been chiefly engaged in this type of accreditation, not specific to imaging. The international section of this JC is the JCI (Joint Commission International), which is well known for their accreditation activities given to the hospitals around the world which welcome medical tourists.

5. Clinical Trial Network

Apart from the above mentioned imaging accreditation for clinical practice, the Society of Nuclear Medicine (SNM), (Now the Society of Nuclear Medicine and Molecular Imaging: SNMMI) started the activity of the Clinical Trial Network (CTN). The FDA's position is that if you use PET imaging for the measurement of drug efficacy during the process of clinical development of therapeutic drugs, you need standardization of the techniques of manufacturing the PET drug and you also need scanner validation. Based on this position, the SNM-CTN (now the SNMMI-CTN) developed a registration and accreditation program of manufacturing sites and imaging sites, collaborating with industries. The SNM submitted an IND for FLT to the FDA and therapeutic drug companies using FLT to evaluate the efficacies of their cancer drug. The SNM is the IND holder of FLT and several companies are able to use this FLT under the cross reference agreement of this IND with the SNM. The SNM is the IND holder of FLT and several companies are able to use this FLT under the cross reference agreement of this IND with the SNM (Fig. 2, Table 1).

At the time of starting this program, the SNM-CTN provided accreditation free of charge, but recently it has begun to charge for scanner validation. Now the SNMMI-CTN supplies their phantom to imaging facilities and the facilities send their imaging data to the CTN, and then specialists collaborating with the CTN review it and write a report. As of 2011, more than 200 manufacturing and 200 imaging facilities had been registered. Ninety-two imaging sites passed the scanner validation and 29 had completed the process and are waiting for the accreditations. In Japan three imaging sites completed scanner validation at the beginning of 2011 (Update information is included in another report [19]).

In 2011 August FDA issued a guidance for use of imaging data for the endpoint of clinical trials [20].

Fig. 2 "Central IND" strategy by SNM (now SNMMI)

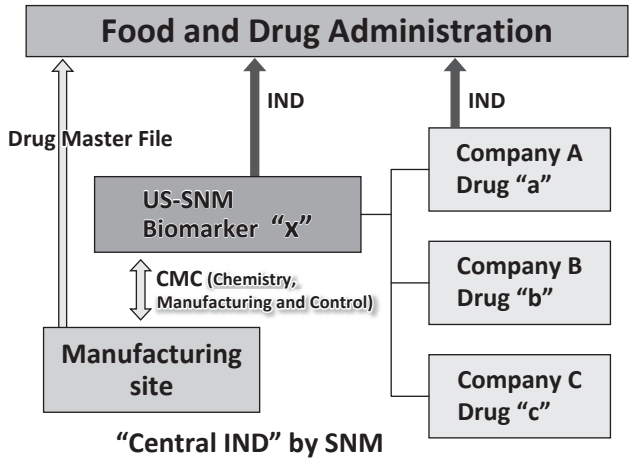


Table 1 SNM, Imaging CRO, therapeutic industry — Each role and collaboration

US-SNM	• Scanner/manufacturing validation, education, standardization • Policy, methodology, open information • Equality, credibility
Imaging CRO	• Specific technology of imaging • Detailed job responding needs of company • Accumulation of knowledge and information inside the company
Therapeutic drug company	• Their interest is therapeutic drugs, not biomarkers • Biomarker issue is committed to SNM • Annual fee to SNM + cost for each protocol

6. Conclusion

As described above, the new regulatory framework of PET examination in the U.S. had been developed by the end of 2011 and we will be able to see the outcomes of this newly developed framework from the end of 2011 through the year of 2012 (Please see the other reports to find the outcomes [15, 16, 19]).

In Japan, the Molecular Imaging Strategic Committee was established by the Japanese Society of Nuclear Medicine in 2011 and developed standardization guidelines for manufacturing, safety evaluation, and clinical development, learning from the U.S. framework. In the August of 2011, they started public consultation concerning this guideline and it will be finalized in October 2011 (This was authorized and then they started manufacturing audit and scanner validation programs). The Japanese PET community is now at the starting point of a new era to promote the use of PET

molecular imaging for diagnostic and therapeutic drug development as well as general clinical practice, and finally to contribute to the improvement of public health.

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