Translation

New regulations of PET drugs in the U.S. and the trends in FDA approvals

— PET Drug American Dream World History: The 1st Report —*1

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Abstract

In the U.S. (United States), new regulations for PET (Positron Emission Tomography) drugs went into effect in June 2012, which enforced GMP (Good Manufacturing Practice) regulations specific to PET drugs (PET drug GMP) common between industries and medical/research institutions. Several medical/research institutions have obtained FDA (Food and Drug Administration) approvals for PET drugs under this new regulatory system.

In this first report of the series, we introduce the latest status of the PET community and regulatory environment in the U.S.

Key words

PET (Positron Emission Tomography), GMP (Good Manufacturing Practice), FDA (Food and Drug Administration), IND (Investigational New Drug application), NDA (New Drug Application)

Rinsho Hyoka (*Clinical Evaluation*). 2015 ; 43 : W47-W54. [Epub ahead of the issue publication]

*1 This article is an English translation of the article originally written in Japanese and published in *Rad Fan*. 2013; 11(8): 108-11, under the permission of the publisher, Medical Eye. The information included is not completely identical with the original one and has not been updated since the time of original publication except for some of the important information subsequently added.

1. Introduction

We have found that PET (Positron Emission Tomography) communities in the U.S. (United States) and Japan have been in a similar situation. Both of them have been intensively discussing and making efforts about the PET drug-specific regulations; developing similar PET drug products; as well as aiming for a similar goal to expand use of various PET drugs for better public health. So what is the difference? The "American Dream World" does not necessarily mean that the PET community in the U.S. is far superior in the levels of science and technology of this field or of diagnostic practices using PET. It implies that it is praiseworthy that the ways in which the U.S. PET community has implemented a well-designed regulatory system, has succeeded in consensus formation and collaboration among industry, academia, and regulators, within the clarified timelines of developing the new regulatory framework and of implementing their policies.

We previously discussed the trends concerning PET drug regulations in the U.S. in the November 2011 issue of *Rad Fan* [1]. Later on, we surveyed the actual situation in the U.S., having interviewed all concerned parties that appeared in the previous *Rad Fan* article and summarized it in our task force report [2]. So we now introduce these situations in this series of articles with the title of "PET Drug American Dream World History."

2. Historical background of the regulations of PET drugs in the U.S.

The U.S. PET drug community and regulators had discussed during the 1980s about whether the PET drug is a product of "compounding" by a pharmacy or of the "manufacturing" process. The FDA (Food and Drug Administration) Modernization Act of 1997 (a bill to amend the overall regulations concerning FDA, which includes PET drugs) required that PET drugs be prepared according to the standards and monographs in the **USP (United States Pharmacopeia)** *2 until the FDA would establish appropriate approval processes and **GMP (Good Manufacturing Practice)** regulations specific to PET drugs [3] *3.

Then the monographs of 12 well-known PET drugs were listed in the USP, which the FDA can make use of. The FDA was obligated to develop frameworks for GMP regulations specific to PET drugs and other related systems. Then, as long as these drugs were manufactured in accordance with these monographs, until the new regulations went into effect, it had been possible to use them in clinical practice, and companies were allowed to commercially market these PET drugs even though they were unapproved.

Members of the PET community in the U.S. often mention the following key words:

- **"PET is special"** (different from other drugs in terms of the half-life, stability, etc.)
- **"Patients are the same"** (since every patient's right to get the best medicine is the equal,

*2 The terms shown in **bold letters and underlined** are explained in Box (glossary).

*3 This article (Reference 3) was published by the members of the Committee on Pharmacopeia, Society of Nuclear Medicine and Molecular Imaging at the time when the new regulatory framework was implemented, in which they argued that these monographs should be deleted from the list in USP. (Responding to this argument, on December 1, 2014, USP omitted unapproved 8 PET drugs from their list of monographs in the USP.)

when they undergo the examination using diagnostic drugs produced at a small facility or supplied by a big manufacturing company, the safety and reliability should be assured at the same level.)

According to such principles, GMP regulations specific to PET drugs (PET drug GMP) that do not differentiate companies from medical/research institutions were proposed, and finalized on December 10, 2009. Although the deadline for enactment of the regulations was initially December 12, 2011, people involved in this issue expressed the opinion that they would not be able to meet the target date, therefore the date of enactment was postponed until June 12, 2012.

Three sets of guidance that explained the steps from development of PET drugs through clinical studies to acquisition of FDA approval were also published in 2004 [4~6]. Furthermore, exploratory clinical research employing a certain limited usage of radioactive drugs not intended for development of diagnostic drugs nor clinical diagnosis can be carried out within the framework of the **RDRC (Radioactive Drug Research Committee)** without submitting an **IND (Investigational New Drug application)** to the FDA. The guidance explaining this framework was finalized in 2010 [7]. Please refer to our previous article [1] for these details.

3. Updates of the regulations of PET drugs in the U.S.

Since the enactment of the new system, if companies and medical/research institutions are to use PET drugs in general practice, they all have to submit an **NDA (New Drug Application)** or **ANDA (Abbreviated New Drug Application)**, and pass GMP inspections by the FDA to obtain approval. The FDA will sequentially implement inspections according to the applications and plans to complete inspections and determine whether or not to approve. For the NDAs submitted by the time of enactment of new regulations on June 12, 2012, the FDA's determination would be made by December 12, 2015. The U.S. approved medical/research institutions can prescribe the drugs not only in their institutions, but also supply and sell them to other medical institutions*4. If institutions do not submit an NDA/ANDA, they must use the drugs as part of a clinical trial or research within the framework of an IND or RDRC.

Outside these frameworks, "clinical" use of unapproved PET for routine practice is prohibited. When they have to use an unapproved drug for clinical practice for necessity, they have to submit an **Expanded Access IND**. Manufacturing regulations to be applied for NDA/ANDA status are found in **21 CFR (Code of Federal Regulations) 212 (PET drug GMP)** ; and manufacturing standards applied for clinical trials or research of an IND or RDRC status are found in **USP823** (more flexible manufacturing standard specific to PET drugs).

The enactment of the new system was scheduled during the **SNM (Society of Nuclear Medicine)** Annual Meeting. The society's name was changed to **SNMMI (Society of Nuclear Medicine and Molecular Imaging)** during the meeting period. A total of at least 16 presentations by FDA personnel (at least 3 sessions provided by the FDA and 2 sessions not provided by the FDA but containing presentations by FDA personnel) were performed,

*4 In Japan, there are two tracks to develop new PET drug from research status to general practice: medical institutions buy PET drugs supplied from companies who obtained approval for the PET drugs; or purchase a PET drug synthesizer apparatus approved as a medical device, and manufacture and use drugs only in their institution or hospital, but not permitted to supply outside.

Table 1　Comparison of authorized status of PET drugs in Japan and in the U.S., at the time of May 2013: Approval as "established techniques" (See page W52 footnote 5) in Japan and Listing USP in the U.S.; regulatory approval status in Japan and in the U.S.

Names of Drugs (Authorized as "established techniques") USP: USP listed Needs: *1	Usage ("established techniques") / Regulatory approved indications (Device/Drugs): *2	Years of authorizations as "established techniques"	Approved by Ministry of Health, Labour and Welfare (Year/Month): *3	Approved by FDA (Year/Month): *4 ( ) indicates NDA discontinuation Underlines indicate "under the new system"
[^{11}C] Carbon monoxide gas (^{11}C) USP	Blood amount, blood pool	85		
[^{13}N] Nitrogen gas ($^{13}N_2$)	Lung ventilatory performance	85		
[^{15}O] Oxygen indicator gas ($^{15}O_2$)	Oxygen metabolism, lung functions / local tissue oxygen metabolism, local lung functions	85	(Covered by insurance since 1996) Medical device (synthesizer system) SHI: 91/9 CYPRIS-G, 00/01 Supplementary application JFE: 97/3 (DAINIPPON) [^{15}O] Gas synthesis system, 05/4 Transferred from DAINIPPON, 10/2 Supplementary application (manufacturer: DAINIPPON) MIL: 12/11(manufacturer: UG) ^{15}O-labeled gas synthesis and supply device	
[^{15}O] Carbon dioxide indicator gas ($C^{15}O_2$)	Blood flow, lung functions / local tissue blood flow, local lung functions	85		
[^{15}O] Carbon monoxide indicator gas ($C^{15}O$)	Blood amount, blood pool / local tissue blood amount, blood pool	85		
[^{13}N] Ammonia injection ($^{13}NH_3$) USP	Blood flow / diagnosis of ischemic cardiac disease	85	(Covered by insurance since 2012) Medical device SHI: 10/3 N100 JFE: 12/3 (manufacturer: Kyorin) Lab-CUBE NH_3	NDA, 07/8, Feinstein Institute ANDA, 12/12, Houston Cyclotron
[^{15}O] Water injection ($H_2{}^{15}O$) USP	Blood flow, blood flow imaging	85		
2-deoxy-2-[^{18}F] fluoro-D-glucose injection *2 USP Needs *1	Glucose metabolism / assessment of abnormal glucose metabolism in diagnosing malignant tumors; evaluation of myocardial glucose metabolism; confirmation of abnormal regions for glucose metabolism focusing on epileptic fit	85	(Covered by insurance since 2002) Medical device GE: 01/12 FDG MicroLab → discontinued, 03/7 (JFE) TRACERlab MX FDG, 05/5 Supplementary application → 05/9 Transferred from JFE, 11/12 FASTlab JFE: 02/12 (DAINIPPON) [^{18}F] FDG injection synthesis system, 05/4 Transferred from DAINIPPON (manufacturer: DAINIPPON) SHI: 02/3 F100, 05/6 F200, 10/7 F300 CMI: 07/6 Explorer (FDG4) SCETI: 07/6 FDG automated synthesizer, 11/6 IBA-1 Drugs NMP: 05/7 FDG scan injection Advanced (manufacturer) / NMP (marketer): 05/07 FDG scan-MP injection	(NDA, 94/8, Downstate Clinical PET Center) NDA, 04/8, Weill Medical College NDA, 05/8, Feinstein Institute ANDA, 11/2, PETNET Solutions
L-[^{11}C] Methionine injection USP Needs *1	Amino acid uptake rate	88		
[^{11}C] Acetate injection USP	Myocardial aerobic metabolism	94		
N-[^{11}C] methyl-spiperone injection USP	Dopamine D2 receptor	94		
[^{11}C] Choline injection	Malignant tumors	01		NDA, 12/9, Mayo Clinic
[^{18}F] Sodium fluoride injection ($Na^{18}F$) USP Needs *1	Bone diseases	09		(NDA, 72/2, GE Healthcare) (NDA, 11/1, NIH-NCI) ANDA, 12/12, Houston Cyclotron

[11C] Raclopride injection USP	Dopamine D2 receptor	09		
[11C] Flumazenil injection USP	Central benzodiazepine receptor	09		
Name of Drugs (Listed in USP (USP))/ FDA approved				
Fluorodopa F 18 injection USP				
Rubidium chloride Rb 82 injection USP				NDA, 89/12, Bracco
Florbetapir F 18 injection				NDA, 12/6, Avid*5

*1: Needs: The designated medical technologies as of high needs at the "Working Group on Early Introduction of Medical Devices with High Medical Needs" of the Ministry of Health, Labour and Welfare in November 2011 in response to a request from Japanese Society of Nuclear Medicine. Based on these designations, companies are recommended to apply for approval of these medical devices, synthesizers of these PET drugs. Although the indications of FDG stated on the front have already been approved, additions of the efficacy to differentiate Alzheimer's type and to diagnose causal lesions of fever of unknown origin were requested. The requests were approved for methionine with tumors (brain tumor, etc.) as the indications, and for NaF with malignant bone tumor as the indication.

*2: Since approved indications as well as coverage by insurance may vary depending on the individual product, caution is needed in actual practice.

*3: At the times of applications noted here, no differentiations were made between the new medical device and the generic medical device as they are at present. Thus, this differentiation is not shown regarding the status of Japan. These data are as of May 2013, which have not been changed since January 2013 when we surveyed the situation in the U.S.

*4: Data as of January 2013. Those with NDA/ANDA approval are listed, and different manufacturers are not noted. See the end of this article and the next report for NIH-NCI.

*5: The only newly developed PET drug in this table, and is indicated for measurement of the beta-amyloid plaque buildup in patients suspected of Alzheimer's disease. Avid Radiopharmaceuticals, Inc. obtained approval, but was acquired by Eli Lilly subsequently. Whether or not it will be covered by insurance is to be determined in July 2013. (After the publication of Japanese original version of this report other two PET drugs for beta-amyloid, Florbetaben, Flutemetamol, were approved by FDA, but coverage is for only a 1 time scan under the program of Coverage for Evidence Development, according to the protocol approved by CMS (Center for Medicare and Medicaid Services. Details of this system are reported.) In Japan also these three PET drugs were applied for NDA and only Florbetapir was approved as of 2015 February.)

[Explanations for the abbreviations used in Table 1]

SHI: Sumitomo Heavy Industries, Ltd.
JFE: Nihon Kokan Kabushiki-gaisha (NKK Corporation) → (omitted) → JFE Engineering Corporation (its operation was transferred, the company name was changed, partially omitted)
DAINIPPON: DAINIPPON SEIKI Co., Ltd.
Kyorin: Kyorin Systemac Co., Ltd.
MIL: Molecular Imaging Labo Inc.
UG: UNIVERSAL GIKEN CO., LTD
GE: GE Yokokawa Medical Systems Co., Ltd. → GE Healthcare Japan Corporation (the company name was changed)
SCETI: SCETI Co., Ltd. → SCETI K.K. (the company name was changed)
CMI: CMI Inc.
NMP: Nihon Medi-Physics Co., Ltd.
Advanced: Japan Advanced Medicine and Pharmacology Research Center

In the U.S. with the new system described in this report and also in Japan with the efforts by Japanese Society of Nuclear Medicine facilitating the discussion at the Working Group of *1 above, various PET drugs other than FDG are expected to receive approval by authorities both in U.S. and in Japan, and become available in clinical practice in the near future. This table shows the start line for both Japan and the U.S. toward such a new trend of clinical practice using newly approved PET drugs.

which demonstrated their focus on promoting the new regulatory system. FDA has a Division of Medical Imaging Products (DMIP). In addition, PET Working Group (WG) specific to PET drug regulations has been formed, and 9 WG specialists accepted our visit to their office in February 2012 as a part of our task group survey to discuss general issues of PET drugs which are open to the public.

According to the presentations by the FDA at the SNMMI Mid-Winter Meeting (MWM) in January 2013, 3 out of 86 ANDAs for PET drugs were approved by December 2012. There were 2 approved NDAs, one of which was Florbetapir F 18 (Amyvid®) in the framework of **505(b)(1)** (based on data from clinical studies), and the other was Choline C 11 in

the framework of **505(b)(2)** (based on a retrospective review of the literature). There were 115 INDs for PET drugs between December 10, 2009 and January 4, 2013, and of those, at least 4 applications were made as Expanded Access INDs. (These numbers are from our quick short note and not confirmed.)

Table 1 shows the approval status of PET drugs in the U.S. [8], compared with Japanese situation (at the time of May 2013). In Japan, there had been so-called "Drugs of established technique" (PET drugs of established manufacturing technique) approved by the Expert Committee of the Japan Radioisotope Association, which was academic society initiative [9) *5, 6]. There are also regulatory-approved PET examinations using approved PET drugs or approved synthesizer apparatus, by the Ministry of Health, Labour and Welfare.

Box Basic terms to understand the framework of the new system for PET drugs in the US

FDA
United States Food and Drug Administration

USP
United States Pharmacopeia:
A non-governmental organization called the United States Pharmacopeial Convention, founded in 1820, which was earlier than the enactment of the Federal Food and Drugs Act of 1906. They have been working with the FDA and specialists in academia and companies to establish monographs listed in the USP and the related standards. As with the Japanese Pharmacopoeia (JP) and the European Pharmacopoeia (EP), USP basically lists monographs of approved drugs. However, the USP also lists as an exception the monographs (specifications for manufacturing) of 12 approved/unapproved PET drugs (Later monographs of 8 unapproved PET drugs were omitted from the USP. See the Footnote 2 and the Reference 3).

SNM
Society of Nuclear Medicine

SNMMI
Society of Nuclear Medicine and Molecular Imaging
(The name was changed from SNM in June 2012)

NCI
National Cancer Institute:
One of the institutes of the NIH (National Institutes of Health), focusing on cancer research.

NDA
New Drug Application

ANDA
Abbreviated NDA:
New Drug Application by a simplified procedure for an already approved drug, which is the same as the application for generic drugs.

505(b)(1), 505(b)(2)
A 505(b)(1) is the article number of the regulation for drug approval application, which requires full data package.
A 505(b)(2) is the article number of the regulation for drug approval application, which does not require a full data package but will accept an application with published literature for which the applicant does not own or has not obtained a right of reference (similar to "a public knowledge-based application" in Japan). These article numbers are of the Federal Food, Drug, and Cosmetic Act. The ANDA noted above is under 505(j).

*5 The compounds so-called "established techniques" are PET drugs with established manufacturing techniques approved by the Subcommittee on Medical Application of Positron Emitting Radionuclides, Medical Science and Pharmaceutical Committee, the Japan Radioisotopes Association. The approved drugs shown in Table 1 are based on Reference 9. This academic-initiated approval system was asked to be redesigned, and new standards were established in 2011 by the Japanese Society of Nuclear Medicine (See http://www.jsnm.org/guideline/molecule). Instead of the system to approve "established techniques", they are implementing activities to support and promote "regulatory approval" and clinical use of PET drugs and synthesizers.

*6 As shown in Table 1, 10 out of 15 drugs approved as "established techniques" in Japan match those listed in USP, and discussions about them at the drafting stage had been published prior to the finalization of specifications of the drugs listed in USP of 1997. As for the FDA approved items, we confirmed them on the FDA web site based on Reference 8.

In the U.S., the Mayo Clinic and **NCI (National Cancer Institute)** have obtained their NDA approval as medical/research institutions. At the above-mentioned SNMMI- MWM, the Mayo Clinic and PETNET Solutions Inc. presented their experiences in accepting FDA's GMP inspections as a medical institution and as a company, respectively, and discussed that the same applicable rules might be put into effect in different manners. NCI first received NDA approval with PETNET Solutions Inc. as PET drug manufacturer, and soon afterwards notified the FDA to discontinue this NDA (That is why this was not included in the 2 applications noted above). At the time of our visit to NCI, we found that this was an excellent strategy involving the collaboration among academia, industry, and regulators, which we will introduce in detail in the next (2nd) report of this series [10].

IND
Investigational New Drug application:
An application for authorization by FDA to conduct clinical trials. Although it corresponds to "Clinical Trial Notification" in Japan, unlike in the case of Japan where only the clinical trials aiming for new drug approval are covered, in the U.S. any clinical trials of a new drug investigation or comparative clinical studies of approved drugs the results of which may be used for new indication approval or for drug promotion are required to submit IND.

Expanded Access IND
A procedure for clinical use of unapproved drugs for treatment of serious or life-threatening disease for which there is no other available drug. They submit to the FDA almost the same information as in the case of an IND but in a simplified manner. They also have to obtain IRB approval.
With regard to a PET drug, the FDA seems to allow the interpretation of the above conditions in the meaning "clinical use of unapproved diagnostic drugs for examination for serious or life-threatening disease for which there is no other available diagnostic procedure." It is a framework similar to "Compassionate Use" currently being discussed in Japan.

RDRC
Radioactive Drug Research Committee:
The Radioactive Drug Research Committee (RDRC) program began when the Food and Drug Administration published a Federal Register notice in 1975 classifying all radioactive drugs as either new drugs requiring an IND for investigational use (21 CFR 312) or as generally recognized as safe and effective when administered under the conditions specified in the RDRC regulations (21 CFR 361.1). The RDRC program under 21 CFR 361.1 permits basic research using radioactive drugs in humans without an IND when the drug is administered under the following conditions: Based on other already conducted human studies in which the radiation dose from a single study can be estimated not to exceed 3 rem (5 rem for a cumulative annual dose) in the whole body; active blood-forming organs; lens of the eye; and gonads, or 5 rem (15 rem for a cumulative annual dose) in other organs. The number of subjects is limited and the study should not be intended for drug development or clinical diagnostic purposes. The FDA will approve the Committees and requires the committees to submit an annual report to the FDA, by which the FDA can monitor the contents of the protocols of research. In 2012, there were 72 approved active committees in the U.S.

IRB
Institutional Review Board

GMP
Good Manufacturing Practice:
Regulatory standards for manufacturing drug products. In Japan, we have "Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs" under the Pharmaceutical Affairs Law.

21 CFR 212 (PET drug GMP)
Article number of the U.S. Code of Federal Regulations (CFR) on GMP specific to PET drugs for clinical use. There is a guidance that explains the regulations. They were initially intended to apply for clinical studies as well. However, after receiving public objections just before their finalization, it was decided that USP 823 would be applied for clinical trials under an IND and exploratory clinical research within the framework of RDRC.

USP 823
USP contains not only specifications of individual drug products but also general rules for drug manufacturing. USP 823 includes manufacturing standards applied for clinical trials or research of PET drugs. USP 823 was amended so as to be consistent with 21 CFR 212, but it contains much fewer requirements than 21 CFR 212, and has little binding force and few documentation requirements.

Acknowledgement

We deeply appreciate the specialists in the U.S., some of whom appear in this series of articles and those in Japan who gave us meaningful cooperation for our survey and for this manuscript. This report is based on the following task force research fund. Ministry of Health, Labor and Welfare, 2011, 2012 fiscal year: Regulatory frameworks of the United States and other countries concerning nuclear medicine diagnosis using PET drugs produced by an in-house PET drug synthesizer; and 2013, 2014 fiscal year: Regulatory science concerning clinical application of nuclear medicine diagnosis using PET drugs produced by an in-house PET drug synthesizer (including this publication of English translation of an article written in Japanese).

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(Published March 24, 2015)