Translation

PET drug clinical trials and networking strategy for development

— PET Drug American Dream World History: The 2nd Report —*1

Chieko Kurihara [1)] **Tomio Inoue** [2)]

1) Molecular, Imaging Center, National Institute of Radiological Sciences

2) Department of Radiology, Graduate School of Medicine, Yokohama City University

Abstract

In the U.S. (United States), there are various activities to develop diagnostic PET drugs toward the use in medical practice being covered by healthcare insurance and also to make use of PET drugs for assessment of biomarkers for therapeutic drug development. In this second report of 3-part series, we introduce some of the strategic initiatives to promote multi-center clinical research and clinical trial network being facilitated by collaboration among academia, industry, and regulators.

Key words

NCI (National Cancer Institute), SNMMI-CTN (Society of Nuclear Medicine and Molecular Imaging-Clinical Trial Network), DMF (Drug Master File), LOA (Letter of Authorization), Shared-IND

Rinsho Hyoka (*Clinical Evaluation*). 2015 ; 43 : W55-W61. [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(9): 118-21, 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. Strategy with NaF by National Cancer Institute (NCI)[1)]

In our first report[2)] of this series, we reviewed the status of PET (Positron Emission Tomography) drugs in the United States (U.S.). Various industrial and medical centers have begun to receive authorizations of **NDAs (New Drug Applications)**[*2] or **ANDA (Abbreviated NDAs)** to market and use PET drugs in routine clinical practice from the FDA (Food and Drug Administration) in compliance with the newly established PET drug regulations, including PET drug GMP (Good Manufacturing Practice regulations specific to PET drugs).

Soon after the FDA issued the new regulations of PET drug GMP, the U.S. National Cancer Institute (NCI) received approval of their NDA of NaF ([^{18}F] – Sodium Fluoride) on January 26, 2011. The NCI notified the FDA to discontinue this NDA, on May 3, 2012. The reason was as follows: NCI is a governmental agency so they are not required to pay user fees for the FDA's review of NDA or any other user fees to keep the NDA active. Once an NDA of a drug is approved, any other companies or medical institutes can submit ANDA for the drug, if the sponsor holding the NDA waives an exclusivity period, and NCI did do that. Furthermore, in the case of PET drugs (different from other general therapeutic drugs), a new regulation starting from January 2012 makes ANDA free of charge for commercial companies and academic institutes ("PET is special")[2)]. It was NCI's strategy from the beginning to gain approval of an NDA of NaF to facilitate others to submit ANDAs. Dr. Jacobs, during our interview, said, "Free is good!" and explained that it would help make these small volume drugs more readily available for patients.

According to the FDA's review report, the shortage of molybdenum-99 didn't make approval condition to be mitigated, but it supported NaF categorization for "priority review", to shorten the review time. NaF was one of the drugs established in the FDA's guidance regarding required information for NDA/ANDA using historical data (505(b)(2), "literature NDA")[3)]. Toxicological data was not reviewed, but one **DMF (Drug Master File)** owned by PETNET Solutions was approved as a manufacturer of this approved NDA for NaF. Since this time, many institutions and commercial firms have filed ANDAs based on the the NCI NDA.

2. NCI's strategy of "Shared INDs"[1)]

NCI was previously authorized INDs of various PET drugs and has conducted clinical trials and owns information of the toxicology and pharmacology of these drugs. They also have another strategy named "Shared INDs". They have a mission of the national institute to promote the development of PET drugs and under the NCI group named the "Cancer Imaging Program," they submitted INDs of various PET drugs and have conducted clinical trials. Once the FDA approved the INDs of these drugs, other institutes can submit INDs of these drugs saving duplicated procedures, if the NCI provides a **LOA (Letter of Authorization)** to other institutes. Other institutes that received a LOA from the NCI can refer to toxicology and pharmacology data of NCI and the FDA can have access to the NCI's previous IND information for their reviews of newly submitted INDs.

Another merit is to save the lives of animals and save the cost of toxicology and pharmacology stud-

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

ies. Also it is possible to shorten the time of the FDA's review and they can focus on the review of the clinical trial protocol.

The NCI lists the PET drugs which can be utilized in this "Shared INDs" strategy as shown in the Table 1. These drugs are not necessarily manufactured in the NCI. The NCI has manufacturing facilities for human use but in the case of multicenter trials, it is preferable to use commercial manufacturing sites that are more quality-assured for large-scale production. Therefore, manufacturers who are the holders of the DMF issues a LOA to the NCI and the NCI submits INDs to the FDA along with these LOAs from manufacturers, then the FDA can have access to these DMFs of the manufactures. Fig. 1 shows supplies of FLT ([^{18}F]-fluorothymidine) in U.S. in this framework of strategy.

Table 1 NCI's "Shared INDs"

- [^{18}F]-FLT – proliferation
  LOA with 9 companies for drug development, 34 research institutes, and SNMMI. DMF of several number of manufactures. 80 clinical trials, 1/4 of these are multicenter trials and half of these are based on a LOA from NCI. 75% is in U.S. and others are in Europe, Asia. Academic institutes: Companies= 1:4.
- [^{18}F]-FMISO – hypoxia
  DMF of 1 company. 9 LOAs, 25 clinical trials (5 multi-center).
- [^{18}F]-FES – estrogen receptor
  3 LOAs, 10 clinical trials (1 multi-center)
- [^{18}F]-Sodium Fluoride – bone seeking
  10 clinical trials (3 multi-center)
- [Zr-89]-panitumumab – EGFR directed
  (There are two other imaging drugs listed, along with the above PET drugs)

As of 2013, at the time of original Japanese publication, quoted from the reference 1

Fig. 1 Commercial FLT supply sites 5/2012

Not updated from the original Japanese publication in 2013, ©National Cancer Institute, quoted from the reference 1.

3. SNMMI's CTN (Clinical Trial Network)

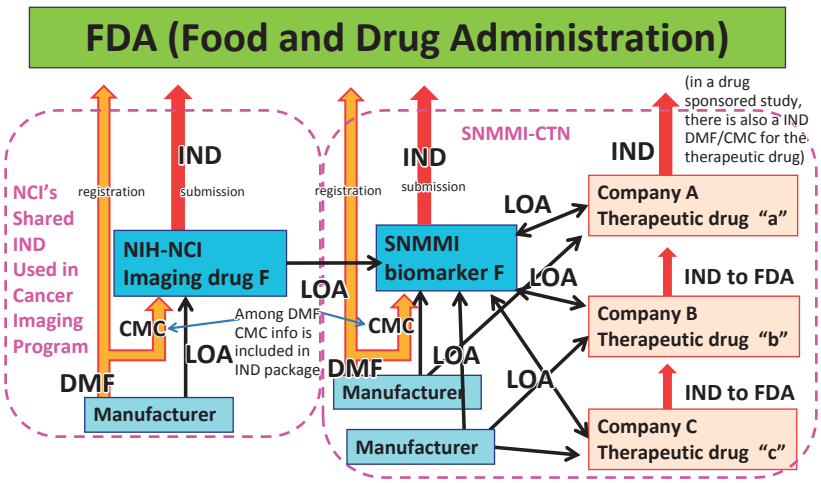
U.S. Society of Nuclear Medicine and Molecular Imaging's Clinical Trial Network promotes the initiative of manufacturing sites registration and scanner sites registration and validation for their organization of global drug development [3]. They also take "Shared IND" strategy (Fig. 2).

SNMMI submits an IND of FLT to the FDA, making use of a LOA from NCI, to conduct a clinical trial of FLT as a diagnostic drug. The SNMMI-CTN has established a collaborative clinical trial network with therapeutic and diagnostic companies and academic institutes, being funded by some of the partner companies. By using the LOA from the CTN's IND for FLT imaging in their therapeutic trials, drug companies can put their expenditure saved towards other drug development efforts, either done in-house or as part of their ongoing support to the CTN for its continued efforts in facilitating the effective use of molecular imaging biomarkers in clinical trials.

Diagnostic drug companies and academic sites manufacture and provide FLT as a biomarker for the therapeutic companies' clinical trials. These manufacturers own their DMFs and issue a LOA to the SNMMI and therapeutic drug companies. The SNMMI and therapeutic drug companies exchange LOAs of each IND and the SNMMI utilize FLT based on their IND and therapeutic drug companies utilize their therapeutic drug based on their IND. These LOAs and cross reference among SNMMI, manufacturers, therapeutic drug companies, and the FDA avoid duplication of tasks.

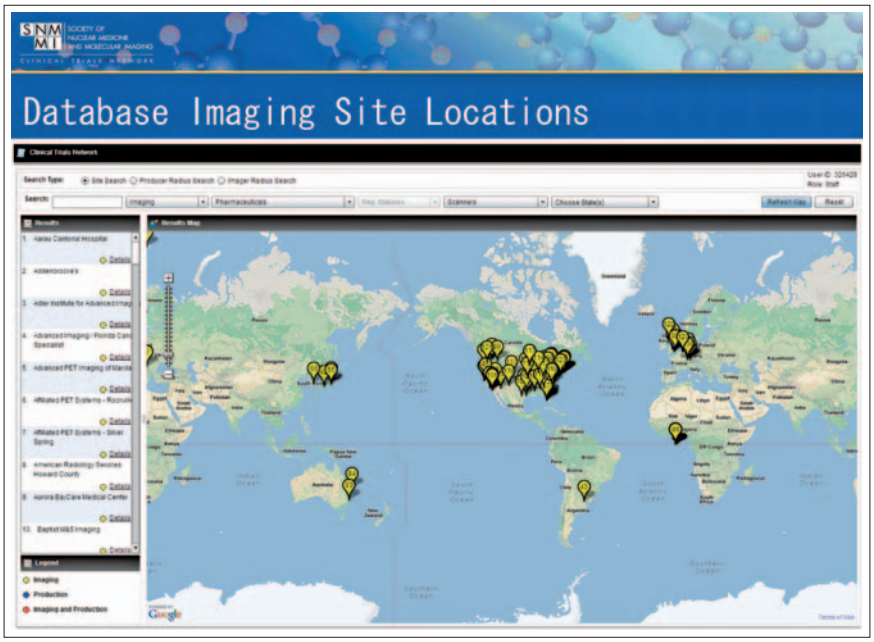
Now many of the scanners in the world have completed SNMMI-CTN's validation process (Fig. 3, provided by SNMMI) and clinical trials have been facilitated (Table 2).

Fig. 2　Shared-IND strategy of NCI and centralized-IND strategy of SNMMI



This figure doesn't show the numbers and scales of projects but only show each relationship and usage of LOA (update of ref. 3 Fig. 3).
NCI is the original holder of IND of FLT and leads more various organizations of shared INDs with other manufacturers, and IND holders. SNMMI uses IND info from NCI (tox, pharmacology) based on LOA, and submits IND of FLT to FDA. SNMMI submits in their IND packet the LOAs from FLT manufacturers allowing FDA to reference required parts of their DMF for SNMMIs IND; Manufacturers listed under the SNMMI IND must meet the same end-product specifications outlined in the IND application. Therapeutic drug company submits IND of therapeutic drug along with an LOA from SNMMI for IND of FLT (biomarker) and LOA from manufacturers for DMF of FLT.

Fig. 3　Database Imaging Site Locations



Not updated from the original Japanese publication in 2013, ©Society of Nuclear Medicine and Molecular Imaging

Table 2　Registration/validation and clinical trial in the SNMMI-CTN's initiative

- As of February 1, 2015, the CTN database has 410 sites registered in three distinct categories (the increase in numbers is based upon the information from June of 2013, at the time of previous, original Japanese publication):
  - imaging sites only: 170 sites (19 increase)
  - manufacturing only: 114 sites(commercial) (5 increase)
  - sites with both imaging and manufacturing capabilities (primarily academic): 126 sites (28 increase)
- CTN has validated 241 (27 increase) scanners at 163 (10 increase) sites using its unique oncology chest phantom. Sites with validated scanners are located in the U.S., Canada, Australia, Germany, Switzerland, Netherlands, Belgium, United Kingdom, Korea, Taiwan, Spain, and Japan (No change of the countries). The number of validated scanners broken down by country/region are: US (166); Asia (15); Australia (13); Canada (13); UK-Europe (34).
- The CTN has recently developed a new model of their chest phantom to more closely harmonize with the number and size of lesions found in the NEMA NU-2 phantom. It is expected that the new model will be available for use in multicenter clinical trials by 2Q2015. The CTN has completed scanning their unique brain phantom on PET/CT scanners currently being used in an NIH Pediatric Brain Tumor Consortium study. Analysis of the data is being performed with a report anticipated to be released by mid summer 2015. (Progress from the previous original report in 2013.)
- CTN is currently engaged with industry and investigators in projects using 7 different investigational agents and has four trials open in 24 (previously 41*) sites in U.S., Canada, and Australia. Sites in Germany and Korea have completed clinical trials with the SNMMI-CTN. Among the four studies actively recruiting patients, 1 protocol (5 sites) uses HX4, 1 protocol (10 sites) uses 18F-Choline, 1 protocol (4 sites) uses FDHT and the fourth study (7 sites) uses FLT under the SNMMI-CTN held IND for FLT. (Increase in number of PET investigational agents. Previously only FDG and FLT were used**.)

As of February 1, 2015, updated from the table in the original Japanese publication in 2013.
* This decrease of number is because one large FDG study closed because it met the recruitment goal.
** This is because large FDG study closed and they are working on studies using investigational PET agents, which can change at any time depending on what a sponsor may need.

4. Initiative of Japanese Society of Nuclear Medicine Scanner and manufacturing validation and networking

Learning from the U.S., the Japanese Society of Nuclear Medicine (JSNM) has been setting up a framework of PET drug development and also for making use of PET for therapeutic drug development. In June 2012 JSNM Molecular Imaging Strategic Committee and U.S. SNMMI-CTN agreed on the MOU (Memorandum of Understanding), for collaboration and information sharing each other (Photo).

The JSNM developed a standard for clinical research of PET drug molecular imaging and started an initiative of a manufacturing and scanner audit and authorization (http://www.jsnm.org/english/15-01-23). Also, based on collaboration with regulators, companies, and academic institutes, JSNM supports the activities of multi-center clinical trials and IND/NDA submissions to translate clinical research towards regulatory authorization and clinical practice with healthcare insurance coverage.

In the next issue, we report about the imaging authorization system in U.S. which is linked to insurance coverage.

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

June 12, 2012, US Society of Nuclear Medicine and Molecular Imaging Annual Meeting. In the front row, the middle is Michio Senda, the chairman of Molecular Imaging Strategic Committee, Japanese Society of Nuclear Medicine; on both of his sides are co-chairs of SNMMI-CTN, John M. Hoffman (left) and Michael M. Graham (right). In the back row, on the far right, is the president at this time of the SNMMI, Frederic H. Fahey and next is Tomio Inoue, the president of the Japanese SNM. (As of 2013, at the time of original Japanese publication)

Box Basic terms to understand PET drugs development strategy by academia, industry and regulators in the U.S.

DMF (Drug Master File)
DMF contains all the information of the drug concerning manufacturing and quality assurance, including **CMC**. A manufacturer owns its DMF and can voluntarily register it with a domestic or foreign regulatory authority.

CMC (Chemistry, Manufacturing and Controls)
Information of components, raw materials, chemical synthesis, manufacturing production, quality control and validation of the drug, which is a part of the DMF, and should be included in IND.

LOA (Letter of Authorization／Letter of Access)
A DMF holder manufacturer or another IND holder gives a Letter of Authorization (LOA) to applicants of an IND/NDA and the applicant submits the IND/NDA along with the LOA to the FDA, then the FDA can have access to DMF of the manufacturer or the IND of the other sponsor. This sharing of information among manufacturer, IND/NDA applicant and the FDA is called "cross-reference". The data does not have to be shared, but the letter authorizes the FDA to look at it when reviewing the new IND.

(The following terms are explained in the first piece of this series) [2]
NDA (New Drug Application)
ANDA (Abbreviated NDA)
IND (investigational new drug application)

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).

References

1) Jacobs PM. NCI's Initiative in INDs: Update on Investigational Radiopharmaceuticals. Jun 11. Society of Nuclear Medicine Annual Meeting: Jun 9-13, 2012.
2) Kurihara C, Inoue T. New regulations of PET drugs in the U.S. and the trends in FDA approvals－PET Drug American Dream World History: The 1st Report－. *Rad Fan*. 2013; 11(8): 108-11. Japanese. English translation is available from: http://homepage3.nifty.com/cont/43_1/w47-w54eng.pdf
3) Kurihara C. The trend of U.S. regulations concerning PET examination. *Rad Fan*. 2011; 9(11): 76-9. Japanese. English translation is available from: http://homepage3.nifty.com/cont/43_1/w37-w45eng.pdf

(Published March 24, 2015)

*　　*　　*