Translation

Regulatory framework for approval of PET drug in Korea: A survey report*

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

1) Molecular Imaging Center, National Institute of Radiological Sciences

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

Translator : Chieko Kurihara

Molecular Imaging Center, National Institute of Radiological Sciences

Abstract

Objectives : To identify regulatory framework for approval of PET drugs in Korea

Method : interview and literature survey

Results : In Korea Good Manufacturing Practice (GMP) regulations specific to radiopharmaceuticals, including PET (Positron Emission Tomography) drugs, under the Pharmaceutical Affairs Act was issued in August 2014, to be enforced on July 1, 2015, and its guidance was issued in December 2014. The new facilities to be established after July 1 of 2015 have to be compatible with this new regulation and already established facilities have two years grace period until June 30 of 2017. During this period, the regulatory authority will inspect all of the production sites which hold or submit approvals of radiopharmaceuticals.

As of September 2015 in Korea, there are 7 commercial companies and 15 hospitals and institutes which have approvals of PET drugs mainly FDG, and these companies and/or hospitals can supply PET drugs outside institutions.

In this article we introduce the Korean regulations of development and approval of radiopharmaceuticals.

Conclusion : The Korean regulatory authorization policy for radiopharmaceuticals are to some extent similar to the policy which the U.S. regulators set as the new regulations of PET drug. It is expected that the situations of production sites in Korea are to be improved through actual discussions among regulators and PET community through the process of actual inspection.

Key words

drug development, new drug application (NDA), good manufacturing practice (GMP), radiopharmaceuticals, PET (Positron Emission Tomography) drug

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1. Introduction

Recently drug development target has been shifted from blockbusters of large-scale production by a big pharmaceutical company toward innovative agents of small size production for rare disease by academic medical research institutions. In such a situation, we need appropriate regulations for in-house drug manufacturing. PET (Positron Emission Tomography) drugs are one kind of drugs for which concerned communities in the world have been discussing about the issues of quality assurance of in-house manufacturing and related regulations for drug approval.

Since 1990s to 2000s, the related communities in the United States (U.S.), Europe and Japan have discussed about drug development strategies, regulations and regulatory authorization schemes of radiopharmaceuticals, especially PET drugs, as well as usage and regulations of microdose clinical trials [1~7]. These drugs and methodologies are used for investigating the pathophysiology of human or pharmacological mechanism of a drug, by means of administrating a drug of a very small, low dose.

In such a situation, related communities in Korea also have been discussing about the manufacturing standards for radiopharmaceuticals. They finally issued regulations for manufacturing and quality assurance of radiopharmaceuticals under the Pharmaceutical Affairs Act (PAA) on August 21 of 2014 [8], then issued its guidance in December of that year [9].

This article reports the Korean regulatory framework concerning approval of PET drugs, based mainly on an interview survey including visiting institutes in Korea.

2. New drug authorization to and supply from medical institutions

In Korea an institution which supplies and/or sells radiopharmaceuticals to other hospitals or clinics is required to submit a New Drug Application (hereinafter, "NDA" as well as the cases of New Drug Approval) to obtain manufacturing and marketing approval from the Ministry of Food and Drug Safety: MFDS (previously Korea Food and Drug Administration: KFDA) according to the Pharmaceutical Affairs Act; and also it needs to obtain a radioisotope production license from NSSC (Nuclear Safety and Security Commission) after review of the submitted document by KINS (Korea Institute Nuclear Safety) according to the Nuclear Safety Act. There is no discrepancy between commercial companies and medical or research institutions. By means of this authorization and license, medical or research institutions which obtained approval can supply and/or sell their approved products to other hospitals or clinics. As of September 2015, we have information about NDAs of PET drugs of 7 commercial companies and 15 hospitals (6 companies and 13 hospitals have NDAs of FDG).

The NDA-holders, companies and/or hospitals, can supply outside institutions with PET drugs in the form of a "single dose", to be used for each patient or "multi dose", which has sufficient radioactivity to be used for many patients. The MFDS has recently approved this "multi dose" as well, if a manufacturer submits the relevant documentation required. This multi dose supply is better and more efficient as it can be flexibly used to administer an optimal dose for each patient at the hospital. Although there is no such system of licensing for radio-pharmacy, this type of supply is possible in Korea.

As for the manufacturing standard, until the development of a new radiopharmaceuticals GMP (Good Manufacturing Practice), there used to be no GMP regulations applied to radiopharmaceuticals as the regulations for general drug had not been applied to radiopharmaceuticals, even if the radiopharmaceuticals were supplied from outside. Therefore, when the regulatory authority inspected the site responding to the NDA submission, there used to be no quality standard to refer to, previously. The only thing available was the manufacturing standard in Korean Pharmacopeia, which is for general drugs, and not legally-binding for radiopharmaceuticals. Considering such a situation, the PET community in Korea discussed about the manufacturing regulations for radiopharmaceuticals, which led to the enforcement of new GMP regulations specific to radiopharmaceuticals.

3. Manufacturing standard of radiopharmaceuticals in Korea

3.1 Enforcement of radiopharmaceuticals GMP and its contents

In Korea, manufacturing and quality control standard of radiopharmaceuticals was issued as an appendix of the regulations of drug safety, on August 21, 2014, to be enforced on July 1, 2015 [8]. This regulation is a short one of 2 pages, but its guidance is of 157 pages, which was issued in December 2014 [9]. Because manufacturing of radiopharmaceuticals should be undertaken in accordance with the principles of GMP for ordinary drug products, active pharmaceutical ingredients (APIs), and sterile medicinal products, the appendix for radiopharmaceutical GMP includes only specific articles for radiopharmaceuticals. For clinical trials of radiopharmaceuticals, investigational medicinal products (IMPs) GMP should be carried out. For in-house use only, in-house compounding approval is necessary, but there is no GMP regulations.

This enforcement date, July 1, 2015, is for newly established facilities. For the already established facilities, the enforcement date is prolonged until July 1, 2017. During these 2 years of grace period, MFDS will inspect all the facilities and grant GMP certification to the facilities which are compatible with the regulations. If there are some problems, they may issue a warning letter. As for this grace period, the Korean Society of Nuclear Medicine (KSNM) argued that it should be over 5 years. However, the regulators argued that 3 years including the year when the regulation was issued should be enough for their preparation.

The contents of these regulations are compatible with PIC/S [10] (European GMP origin) and apply not only to PET drugs but also SPECT (Single Photon Emission Computed Tomography) drugs and any other radiopharmaceuticals. However, a large part of the market of radiopharmaceuticals consist of PET drugs, therefore, the regulations focus mainly on PET drugs. The scope of the regulations cover manufacturing not only by companies but also hospitals or medical or research institutions. We summarize in Table 1 the comparison of the regulations of each regulatory framework in U.S., Korea and Japan.

The MFDS reviewed many of foreign regulations for radiopharmaceuticals in the world, but they have not visited these countries for survey of regulations. Based on this review, and to make different interpretation possible for flexibility, they included in the guidance the explanation of international standard or foreign regulations: WHO (World Health Organization); United States (U.S.); Canada; and Australia. Especially regulations of U.S. and Canada are very much in detail. They surveyed Japanese regulations but did not include them in this guidance.

Table 1　Comparison of GMP regulations for PET drugs of U. S. Korea and Japan

	U. S.[3～7]	Korea	Japan
General marketing with supply to outside	PET drug GMP*1	Drug product (DP)-GMP; API-GMP; Sterile-GMP; and Rhx-GMP	GMP for ordinary drug*6
In-house manufacturing/ compounding for clinical use	PET drug GMP*1	No specific GMP regulations*5	(reimbursement) Regulatory authorized synthesizer and JSNM guideline*7
			(without reimbursement) No specific regulation
Clinical trial	USP 823*2 (IND framework)*3	GMP specific to clinical trial (IMP-GMP) and Rhx-GMP	Clinical Trial GMP (aiming at NDA of ordinary drug)*8, 9
Clinical research	USP 823*2 (RDRC framework)*4		No specific regulation (Under governmental ethical guidelines)*10

Rhx=radiopharmaceuticals　JSNM: Japanese Society of Nuclear Medicine

*1: GMP specific to PET drug, finalized at the end of 2009 and enforced in June 2012 (Enforcement was planned at the end of 2011 but prolonged due to public arguments.). The code of federal regulations under the Food, Drug and Cosmetic Act.

*2: Manufacturing standard specific to PET drugs in the United States Pharmacopeia. The volume of the regulation is very small and with a simple description, without detailed obligations of documentation.

*3: Framework of clinical trial required IND (Investigational New Drug application) to FDA (Food and Drug Administration) for starting a clinical trial.

*4: RDRC means Radioactive Research Review Committee. Exemption of IND to FDA in a certain range of radiopharmaceuticals of very small, limited dose, which does not seem to have pharmacological effects, as well as limited radioactive dose to be safe for human, without intention of clinical development or diagnosis, but with intention of basic clinical research to find human pathophysiology or mechanism of action of drug. This category of clinical research is reviewed by FDA-approved RDRC and ordinary IRB (Institutional Review Board), but not by FDA.

*5: As for GMP no specific regulation, but for clinical use, compounding approval is required.

*6: GMP for ordinary drug is applied for radiopharmaceuticals including PET drugs.

*7: Guidelines of JSNM (Japanese Society of Nuclear Medicine)[11] are voluntary, academia-initiated guidelines, and in some cases of authorization of synthesizer of PET drugs as a medical device it was conditioned to follow this academic society's guidelines.

*8: Clinical trial specific GMP and some comments related to PET drugs manufacturing are included in Q&A. This GMP is a Notification defined in the guidance (Notification) for GCP (Good Clinical Practice) Ordinance under the PAL, which is for clinical trials aiming at NDA.

*9: There is another track in Japan of clinical trials aiming at reimbursement under the Health Insurance Act ("Advanced Medical Care" scheme). There are some cases in which it was recommended to follow JSNM guidelines in this framework but they were not legally binding.

*10: In Japan if you conduct clinical research of unapproved drug without intention of NDA or reimbursement, you can conduct without GMP-like regulations. The JSNM guidelines were originally issued to be applied for this framework of clinical research.

3.2　Background story until the issue of Radiopharmaceuticals-GMP

They experienced twists and turns in the process of developing Radiopharmaceuticals-GMP. First, the government tried to develop regulations in which the process only involved 1 nuclear medicine specialist for the governmental committee, but the draft was not welcomed by the KSNM as the draft seems not to respond to the actual situations. Then in 2012 the government funded KSNM to develop the draft of regulations. KSNM tried it referring to EANM (European Association of Nuclear Medicine) guidelines for cGRPP (Guidelines of current Good Radiopharmacy Practice in the preparation of radiopharmaceuticals)[12] and U.S. PET drugs GMP guidance[13]. However, their draft was not accepted by the government. .

At the time of 2013 there was no GMP specific to radiopharmaceutical and GMP for general drugs is not applied for manufacturing radiopharmaceuti-

cals, even if they are supplied outside. It was also possible to get reimbursement of public health insurance if the PET drug is already an approved one, as public health insurance is not related to GMP. Then at this moment government planned that all of the drugs should be covered by PIC/S. So they requested KSNM to have meetings and they went into the process of negotiation. At the time of 2013, there was a possibility that PIC/S GMP may be applied strictly to both delivered drugs and in-house manufactured drugs. Therefore, KSNM protested against it.

Later on in 2014, the government set a collaboration body with 10 or more specialists, representatives of KSNM, nuclear medicine physician, radiochemist, pharmacist, hospitals, and companies. Through the discussion, they came to issue the regulations in the summer of 2014. After that, the 10 member collaboration body formed a committee of the next stage, then they developed a guidance to explain about the regulations. This means that the guidance was developed within 4 months, from the summer to the end of 2014.

During the process, they held an open seminar to discuss about the draft. There were many objections to applying GMP for in-house manufacturing. There was also an educational seminar with the lecturers from companies of general drugs (Big companies like Uninhan, Green Cross, etc.). They do not know well about radiopharmaceutical GMP, but they are experts of general GMP. This is because there are not enough human resources who have knowledge about both GMP and manufacturing radiopharmaceuticals.

3.3 Characteristics of quality assurance of radiopharmaceuticals

We received some comments from radiochemists describing the characteristics of the quality assurance system of radiopharmaceuticals:

- They apply PIC/S but with a flexible approach according to ICH-Q guidelines concerning a risk-based approach [14]. If you can assure the credibility of the outcome, various kinds of procedures may be acceptable.
- The endotoxin test is performed according to Korean Pharmacopeia, which is specific to radiopharmaceuticals and is a simple one. After the validation of the test method, you can perform a simple test with positive and negative controls, before the release.
- You can also use PTS (portable transport system) for the endotoxin test, which uses a small cartridge. It takes 1/3 hour using 20 micrograms of drug (actually, we drop 25 microliters each into 4-well spots from a diluted solution (LAL water + product). This method is not fully accepted by the regulatory authority so it has a research status. According to the experience of a manufacturer, there was no problem at the time of some NDA approvals from MFDS. (This PTS is not regarded to be in accordance with Japanese Pharmacopeia.)
- Basically the endotoxin test has to be performed before the release; however, there is a possibility that parametric release may be acceptable, if it is according to the PIC/S.
- There is a possibility that the sterility test after the release, sometimes using the material after the decay, may be acceptable if it is according the PIC/S.
- Using gamma spectrometry, you test radionuclide purity.

4. Required data for the conduct of clinical trial until NDA

4.1 Overall clinical trial regulations

Next we will summarize required information for starting clinical trials and for submitting NDA, as

well as several rules of exemptions.

Unlike the Japanese regulatory situation where only clinical trials aiming at NDA are regulated by GCP (Good Clinical Practice) Ordinance under the Pharmaceutical Affairs Law (PAL), in Korea to conduct clinical trials of a non-approved drug or for a non-approved indication, including radiopharmaceuticals, whether it is for a research purpose or aiming at NDA, it is required to get regulatory authorization of starting clinical trial, under the Korean pharmaceutical affairs Act (PAL), and the trial should be according to the GCP regulations. This regulatory framework is the same as in other countries except Japan. If you inject an unauthorized product in a human, it should be a clinical trial, and should be compatible with GCP.

Therefore, you have to submit Investigational New Drug application (IND) to the regulatory authority, along with the quality assurance of the manufacturing of the investigational product, as well as nonclinical safety data to support the conduct of a clinical trial.

4.2 Required nonclinical and clinical data for the conduct of clinical trial until NDA

As for the required nonclinical and clinical data for the conduct of clinical trial until NDA, there are the following regulatory documents. We summarized a comparison among U.S., Korea and Japan in Table 2.

● Korean version of ICH-M3

As for the nonclinical studies for general drugs, ICH-M3[19] is implemented in Korea, and there is a Korean version of ICH-M3[20]. This guideline defines non-clinical safety data required at the each stage from the first-in-human until the marketing authorization. This guideline excludes radiopharmaceuticals from its scope.

● Guidelines for data required for IND

There is a Korean guideline for starting a clinical trial, which means Investigational New Drug application (IND)[21]. This is not limited to nonclinical safety study but includes GMP and clinical issues. This guideline also includes guidance for an

Table 2 Comparison among U. S., Korea and Japan of nonclinical and clinical data required for IND and NDA: Global/general and Local/Specific

	U. S.	Korea	Japan
Global standard/General drugs			
Nonclinical safety data for each stage of clinical trial, including IND	ICH-M3	ICH-M3	ICH-M3
Nonclinical and clinical data required for NDA	CTD	(radiopharmaceuticals do not need CTD preparation)	CTD
Local standard/Specific drugs			
Requirements for starting clinical trial (Starting part of M3)	Ex-IND＊1	IND (microdose was drafted but not published)	Microdose＊3
Specific products related to PET drugs (Specific exemption/considerations for CTD)	Medical imaging agent＊2	(No specific guidelines but exemptions for Rhx in CTD)	Diagnostic Rhx＊4

Rhx=radiopharmaceuticals

＊1: Guidance for nonclinical study for exploratory-IND[15].

＊2: Guidance for nonclinical and clinical safety assessment of medical imaging agents[16].

＊3: Guidance specific for microdose clinical trials of therapeutic drugs which covers all aspects of clinical, nonclinital and manufacturing issues[17].

＊4: Notification for standards of clinical evaluation for NDA of diagnostic radiopharmaceuticals, which includes the issues of evaluation of non-clinical study[18].

Exploratory-IND. The construction of this guideline seems to be similar to Japanese guidance for microdose clinical trial [17]. In Korea, they once developed the draft guidance of microdose clinical trial, but they did not issue it as the number of microdose clinical trials conducted is very small.

As for the nonclinical studies for PET drugs, a single dose toxicity study may be sufficient for starting a clinical trial because a PET drug requires only a very small dose and only one injection. Safety pharmacological data may be omitted during the early phase of clinical development but safety pharmacology and ADME may be required (not mandatory) for marketing approval.

● Guidelines for nonclinical and clinical data required for NDA

There is also a Korean version [22] of guideline for the Common Technical Document (CTD) [23] which defines the non-clinical and clinical data required for NDA. This guideline defines the required data for each stage of clinical development, according to the classification of the drug: chemistry origin drug (category Ⅰ); generic drug (category Ⅱ); radiopharmaceuticals (category Ⅲ) (Biologics are not included this guideline.) According to this classification, some of the nonclinical or clinical data are defined as Mandatory (◎); not mandatory (×); optional (△). The required/optional data is shown in the Table 3.

● Possibility of the use of foreign approved data

The Korean pharmacopeia recently listed radiopharmaceuticals including FDG. In Korean pharmaceutical law, when the drugs are already listed in the pharmacopeia of the defined industrial countries (U.S., European Union, Japan, United Kingdom, Germany, France) it is regarded as a "generic" drug, therefore full spec information for NDA is not required. As far as the evidence of efficacy and safety, generally clinical trials in Korea are not required in this case. If there are some SCI (Science Citation Index) papers, phase 3 clinical trials may be omitted, but this is not defined in a regulatory document.

ICH-E5 [24] is adopted by Korea in 2002 and since then domestic clinical data (bridging study) may be required in some cases. Therefore, even if the drug is listed in the above mentioned pharmacopeia, there are some cases where domestic clinical data is required. In most cases of PET drugs, domestic clinical data may not be required if they are listed in the above mentioned foreign pharmacopeia, and

Table 3 Items of required data for NDAs of Rhxs in Korean guidelines for CTD

1,2: chemistry or development history
3: stability
4: Toxicologycal data
  a. single dose toxicity: mandatory
  b. repeated dose toxicity, genotoxicity, reproduction/developmental toxicity, carcinogenicity and other toxicity: non mandatory
5: pharmacological data
  a. effectiveness data: optional
  b. general pharmacological data or pharmacological safety data: optional
  c. ADME: mandatory
  d. drug interaction: mandatory
6: clinical trial
7,8: other country data

the procedures are not changed.

● 2 CMC/STM required for NDA of PET drugs

As for the CMC (chemistry, manufacturing and control), in Korea there is a standard called STM (standard and test method). STM is in the same category as CMC and required for NDA but not such a high level as CMC. It specifies the way of preparation, production, quality control and management of the drug. CMC is an international standard but STM is a Korean standard. This is the standard for all categories of drugs, not only for PET drugs.

5. Public health insurance coverage

As for the public health insurance coverage, an NDA-holder submits for coverage of the drug, and a hospital submits for coverage of a procedure (nuclear medicine procedure, PET scan, etc). If a hospital is an NDA-holder, this hospital may submit both of them. For example, Asan Medical Center has an NDA of FP-CIT and submitted for these drugs for insurance coverage but has not yet submitted for coverage for procedures as it is under preparation.

Officially, according to the regulations, each hospital should submit for procedures, and the Ministry of Health & Welfare will decide among coverage; partial coverage; or deny. There may be the cases of coverage of several percent; limitation of the times of procedures; or limitation to a specific protocol. Officially, each hospital should perform these submissions, but actually, if one hospital does the submission, another hospital can wait during the review time without submission. After the review by the Ministry of Health& Welfare, which generally requires 6 months, they announce the result as an official notification. After this procedure, all hospitals can perform this medical procedure being reimbursed, without any additional submission. If there is no public insurance coverage or only partial coverage, patients will pay for it.

6. Approval status of each PET drug

As mentioned in the beginning, there are 7 companies and 15 hospitals which obtained an NDA of PET drugs, mainly FDG. We summarize in Table 4 the regulatory approval and public health insurance coverage of each PET drug.

There are both types of company's production sites: a company has independent sites; or has its production facility in a hospital and produces PET drugs and supply them to this hospital and outside hospitals. Also, there are the following examples of collaboration between hospitals and companies.

Asan Medical Center (AMC) obtained NDAs of FLT, FP-CIT, FDG and deliver them to outside hospitals. They obtained an NDA of FP-CIT and licensed it to a company for consignment production. This company and AMC cover over the entire area of Korea.

Sometimes in a university, companies and university students share a cyclotron, and a company supplies FDG to outside hospitals and the students perform nonclinical experimentation using other synthesizers.

As one example of the companies having a delivery service of PET drugs, duchembio started their business 7 years ago and they recently established their 5th production site on the sub basement B5F of Severance Cancer Hospital in 2014. They produce 100 doses a day, among which 20 to 30 doses are delivered outside of this site. Their production sites in Korea and the PET drugs they supply are shown in Table 5.

As for the 3 beta-amyloid PET drugs: florbetapir (AV45, Amyvid™), flutemetamol (F-18 version

Table 4 Regulatory approval and public health insurance coverage of each PET drug

FDG (Cancer imaging)
- FDG has been approved in the conventional regulatory framework and has obtained public insurance coverage for most types of of cancer, but there are some indications excluded from coverage or limitation of the number of scans. There are 6 companies and 13 hospitals which have an NDA of FDG.
- Care Camp, HDX, duchembio (the three major companies) have their production facilities in hospitals and produce FDG and sell it to outside hospitals. For example, Severance Hospital provides their facility to the company duchembio and duchembio owns and operates a cyclotron, and supplies FDG to Severance Hospital and other hospitals.
- Asan Medical Center; Samsung Medical Center; Seoul National University Hospital; Korea Cancer Center Hospital; National Cancer Center , etc. own their own cyclotrons and have been manufacturing FDG. These companies and hospitals supply FDG to other hospitals.

F-18 FP-CIT (dopamine transporter imaging)
- Asan Medical Center (AMC) got the first approval of FP-CIT and licensed it to a company "duchembio" for consignment production. AMC covers the area of Seoul, and supplies 20 to 30 imaging sites. duchembio has their production sites in Daejeon, Daegu and from these sites they can supply all the imaging sites except Seoul. Then supply to the entire area in Korea is covered by AMC and duchembio. There are no such regulations in Korea in which the NDA-holder has to cover the whole country.
- Because this PET drug is not listed in the regulatory-defined foreign pharmacopeia, substantial data of safety and efficacy was required for the NDA, at the time of AMC's application. Nonclinical and clinical data from phase 1 to 3 and CMC (chemistry, manufacturing, and control) were required. The review took nearly 8 months or 1 year before its approval. This is also the same in the case of FLT, as described in the following.
- Public health insurance is 20% (parkinsonism: bradykinesia, tremor, instability) , for medical procedure (PET scan). There is no coverage for the drug, so AMC decides they should apply for drug coverage.

F-18-FLT (lung cancer imaging)
- Only AMC got approval of FLT, for lung cancer only. There is some superiority to FDG but it is not so widely used. Nuclear medicine physicians seem to think it will take a long time to obtain evidence of effectiveness. Other hospitals do not need FLT because they can use FDG for cell proliferation imaging. AMC does not supply FLT to other hospitals but uses it only in their hospital. This is because of the hospital's policy to assure safety and efficacy for their patients.
- There is no public health insurance coverage.

F-18-NaF (Sodium Fluoride) (bone imaging)
- Five companies and university hospitals (Care Camp, HDX, duchembio, Seoul National University, Siemens PETNET) obtained approval. In the U.S. the indication is PET imaging of bone to define areas of altered osteogenic activity, and it is listed in USP, therefore an ANDA application is possible in Korea.
- Public health insurance coverage for hospital procedure was defined in September 1 in 2014, as 20% coverage. Then Care Camp applied for drug coverage on the same date, but it was denied within 2014 as the evidence was insufficient.

C-11 acetate, C-11 methionine, N-13 ammonia
- There is drug approval of ammonia, and compounding approvals of C-11 acetate, C-11 methionine. Compounding approval is for compounding in the pharmacy of medical institutions and it should not be delivered to the outside. If the drug is listed in a defined foreign pharmacopeia, it is far easier to get compounding approval. This ease is not because of its short half-life, but because it is listed in a foreign pharmacopeia.
- Care Camp, Siemens PETNET, and Seoul National University Hospital have ANDA approval of ammonia, but no health insurance coverage.

Amyloid imaging (Florbetapir (AV45, Amyvid™), flutemetamol (F-18 version of C-11 PiB, Vizamyl™), Florbetaben (AV1, Neuraceq™))
- Ci-Co Healthcare (duchembio is the 100% share holder for Ci-Co) submitted an NDA of florbetapir in May 2014, and it was approved on December 19, 2014. duchembio has 6 production sites in Korea and they are going to produce florbetaben from three of them. Care Camp obtained approval of flutemetamol in August 2015 under agreement with GE Healthcare. There is no public insurance coverage for these drugs.

DOTA agents (^{68}Ga-dotatoc, dotatate, dotanoc)
- Dotatoc is included in EP since 2014, although it is not included in USP. In Korea, there is compounding approval of Dotatoc but no insurance coverage.
- In the U.S. the regulatory status of precursor, kit, generator for manufacturing DOTA agents is discussed but in Korea in case of compounding approval, kit approval is not required.

Table 5 6 RP (radiopharmaceuticals) Centers of duchembio in Korea

Centers	Supplied PET drugs
Eulji RP center	FDG, FP-CIT, NaF
Incheon St. Marys RP center	FDG
Gang Won RP center (run by Ci-Co)	FDG
Han Yang RP center	FDG, FP-CIT, NaF (1 or 2 new drugs are to be added in 2015)
Chilgok-Kyungpook RP center	FDG, FP-CIT, NaF
Severance RP center	FDG, NaF

of C-11 PiB, Vizamyl ™), and florbetaben (AV1, Neuraceq ™), they were approved in the U.S. and only a 1 time of scan in the "Coverage with Evidence Development (CED)" program can be reimbursed by Medicare. In Japan florbetapir was first approved and other two were also approved in June of 2015. All of these are under consideration for public insurance coverage. In Korea, florbetaben was submitted by Ci-Co Healthcare (duchembio is the 100% share holder for Ci-Co) for an NDA and was approved in December, 2014. Then Care Camp got approval of flutemetamol in August 2015 under agreement with GE Healthcare. There is no public insurance coverage for these drugs.

7. Imaging standardization and clinical trial network

Korean Society of Nuclear Medicine (KSNM) issued on December 2, 2013, the guidelines for FDG-PET/CT for standardization of ordinary clinical practice [25]. This guideline was developed referring to the each guideline of the American College of Radiology (ACR), Society for Pediatric Radiology (SPR) [26], EANM [27~30], and the Japanese Society of Nuclear Medicine [31, 32].

As for the clinical trial network, the KSNM has conducted a few retrospective studies, but they have not conducted a prospective clinical trial. Recently, KSNM is going to start to organize a clinical trial, so they conducted questionnaire survey for nuclear medicine physicians to ask which kind of topics they are interested in.

In 2014, the Clinical Trial Network was established. There are some candidate topics, such as expansion of indications of FDG and a safety study of authorized drugs.

8. Conclusion

We described in this article the situations in Korea of PET drug development and authorization and related regulations, as well as standardization and clinical development activities of PET imaging examination.

This newly developed legal framework in Korea was completed through various discussions, and actual implementation is just now starting. They established a 2-year grace period and during this term, regulatory authority will inspect the production sites. This policy is very similar to the policy when the U.S. regulators established the new regulations of the PET drug GMP. It is expected that the situations of production sites will be improved through various discussions among regulators and people at the sites.

We wish to watch the future situation of improvement of Korean PET drug production sites and future clinical development and regulatory authorizations of new PET drugs in Korea.

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Conflict of interests

There is no conflict of interest to be declared.

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