2. 本田憲業．教育講演「医療の質：診断」医療情報システム標準化の意義．第 73 回日本医学放射線学会総会．2014 年 4 月 10～13 日、パシフィコ横浜.

3. 本田憲業．医療の質：診断（品質管理・ＩＴ・遠隔画像）－放射線部門システムの標準化は医療の質に寄与する－．第 445 回日本医学放射線学会関東地方会定期大会．2014 年 6 月 14 日、東京コンベンションホール.

G: 研究成果物

IHE ITI テクニカルフレームワーク第 10 版（2013）Vol. 1, 2a, 2b., 2x, 3 全巻和訳（2014 年訳語訂正）

追補 XCA-I

IHE RAD クニカルフレームワーク第 13 版（2014 年改訂） vol. 1, 2, 3, 4　全巻改訂和訳

IHE　RAD テクニカルフレームワーク追補 XCA-I_Rev1-1 和訳

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表レイアウト（参考）

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
	該当なし						

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Temple R., Kurihara C	Interview with Dr. Robert Temple on drug evaluation policy of FDA: Ethics, science of placebo-control and comparative effectiveness studies.	*Rinsho Hyoka (Clinical Evaluation)*	42(2)	539-51	2014
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Ⅳ. 研究成果の刊行物・別刷・資料

4. 米国におけるPET医薬品規制に関する動向

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１．はじめに

PET医薬品に関する米国の規制については、2012年中施行の新規制の動向を中心に現地訪問調査を重ねてきた。合理的な制度設計、目標とタイムラインを明確に、医療・研究機関、学会、企業、規制当局の協力のもと進められる体制整備[1]の様子を「PET Drug American Dream World History」のキャッチフレーズで報告してきた[2~4]。今回アップデート情報を加え基本情報をまとめる。

２．米国PET医薬品新規制の施行

米国では2012年6月からPET医薬品特有のGMP（製造及び品質管理基準、以下「PET-GMP」）が企業と医療・研究機関を区別せず適用され、「臨床試験」「臨床研究」ではなく、診療としてPET医薬品を使用する限りは、PET-GMPに従い製造し、医療・研究機関もFDA（米国食品医薬品局）の査察を受けて、承認取得しなければならない。承認取得すれば、医療・研究機関から他機関に販売できる。この枠組みは、1980年代から続いた「PET医薬品をつくることは製造なのか？薬局での調剤なのか？」という論争の決着として、1997年「FDA近代化法」（PET医薬品に限らず医薬品規制に関し全般的に見直しがされた改正法）に定めた「約束」が、2012年に履行されたことを意味する。

FDA近代化法では、PET-GMP施行までの間は、よく知られたPET医薬品12種類の製造方法を未承認でも「米国薬局方」（USP）に収載し、これに従えば企業の製造販売も可能とした。この12種類は、承認薬ではFDGが含まれるが多くは未承認で、日本アイソトープ協会が「認定」していたいわゆる「成熟薬剤」（この認定の仕組みは2012年に中止された）とよく似たリストであった。これら未承認PET薬剤はFDA近代化法の定めにより2012年6月失効し（2014年末にUSPから削除）、以降は新たにGMP査察を受けて承認を取得しないと、臨床使用や販売はできなくなった。

承認取得の方法については、主に以下の2通りがある。

① NDA（New Drug Application、新薬承認申請）

通常どおりの承認申請で、国際基準とされる承認申請用文書が求められる。New Drug Authorization/Approvalの意味でこの語が使われることもある。

② ANDA（Abbreviated NDA、簡易新薬承認申請）

既に過去に承認取得された製品についての既承認適応の範囲内であれば簡略手続き（新たな非臨床・臨床試験を必要とせず文書のみの申請）によることができる。ジェネリック医薬品の承認申請と同様。

３．「臨床試験」「臨床研究」としてのPET医薬品使用

日本の「治験と臨床研究の違い」は世界でも独特であるが、米国では一般的な「臨床試験」の枠組みとしての「IND（研究用新薬申請）」の枠組み、放射性医薬品を用いる臨床研究特有のIND除外規定として「RDRC（放射性医薬品研究委員会）」の枠組みがある。他にINDの枠組みの一部として未承認薬の治療目的の使用に関する例外としてExpanded Access-INDという制度がある。

３．１ IND（Investigational New Drug Application）

未承認医薬品のヒトへの投与や、割り付けを行う比較試験などの医薬品臨床試験は一定の例外を除き、「臨床試験」としてFDAの許可及びIRB（研究審査委員会）の承認が必要とされる。臨床試験の計画書だけではなく、科学的組成や毒性試験に関する情報、製造法などを示した「試験薬概要書」に類する情報をFDAに提出するが、研究者主導の場合には簡略な様式がFDAによって準備されている。

未承認薬を「臨床試験」ではなく「治療目的」で患者に用いる場合には、致死的な疾患で、他に方法がない、などの条件を満たすことで、上記と同様の情報をより簡略な方式でFDAに申請できる「Expanded Access-IND」という例外手続きがある。

３．２ RDRC（Radioactive Drug Research Committee）

INDの例外規定として、下記条件を満たす放射性医薬品の投与は、FDAの許可を得ることなく、FDAに認められたRDRC（放射性医薬品研究委員会、全米に70前後の委員会がある）の承認と、通常のIRB承認により実施できる。

＜投与量＞

・全身、造血組織、水晶体、生殖腺：単回 3 rem（30mSv）、年間総量 5 rem（50mSv）
・その他：単回5rem（50mSv）、年間総量 15rem（150mSv）

＜その他の条件＞

・上記の被ばく線量は、過去に人体に投与した経験による文献等による必要があるため、人体に初めて投与するfirst-in-human試験は不可である。
・診断・治療、医薬品開発の意図を持たず、人体の生理学的メカニズムや化合物の作用機序を探索する研究。
・原則として18歳以上、同意能力のある被験者を対象。

日本の「臨床研究」と似ているが、FDAが間接的に管理し、被ばく線量が法的に定義され、実施数・実施内容・被験者数等を国として統計的に把握している点が異なる。

３．３ IND/RDRCにおける製造基準：USP823

これら研究段階のPET医薬品の製造基準は、当初上述のPET-GMPが適用される予定だったが、多くの異論が寄せられ、USPにおけるPET医薬品製造基準USP823に従うこととされた。USP823はPET-GMPと整合するよう改訂されたが、基準の文書量はずっと簡潔で、品質保証

のための詳細な文書化の義務やFDAのルーチンの査察はなく、自主規制的な運用である。

4．新規制施行後2年間の動向

新規制施行から2年半が経過し、FDAは2012年6月の施行時までに承認申請した施設や企業は2015年中に査察を完了するという目標を達成しつつある。米国の核医学分子イメージング学会（SNMMI）での議論によれば、米国でFDA査察を受けて他機関にPET医薬品を供給するような企業、医療・研究機関は全米に概ね130ヵ所ある。米国でPET医薬品を供給する主な企業はPETNET Solutions、IBA Radiopharma Solutions、Cardinal Healthの3社で（他にも承認取得している小規模なラボがある）、製造施設は概ねそれぞれ40、40、10ほど、医療・研究機関の製造施設が40ほどで、計130との目安である。

表1は、2014年6月SNMMI年会でのFDA担当官の発表からの筆記であるが、新規PET医薬品のNDAの数は多くはない。通常、1回の査察に2人の査察官（1人のこともある）があたり、3日間かけて行うということである。

表1　米国PET医薬品新規制に伴うFDAによるGMP査察の実施状況

	2012	2013	2014
PAI (pre-approval inspection) for NDA	5	7	1
PAI (pre-approval inspection) for ANDA	18	17	5
Survey	37	39	9
Total	60	61	15

（2013　100% full inspection; 4 system inspections. ; 2014　10% abbreviated inspection 2 system inspections）

＊ 上の表は提供を受けていないFDA担当官の発表からの筆記である。"Survey"の意味は未確認。

医療・研究機関では、Mayo ClinicがFDG、NaF、Ammonia、Choline、MDアンダーソンがFDGとNaF、ワシントン大学がFDGについて新制度下で承認取得している。2013年、14年2月開催のSNMMI Mid Winter Meeting（MWM）では、PETNET Solutions、Mayo Clinicが、それぞれの査察経験を発表、FDAも参加して現場に密着した議論が行われた。企業と医療・研究機関では、適用されるルールは同じだが運用は異なる。SNMMIイベントでは何人ものFDA担当官が査察時の指摘事項を発表し、現場との議論が繰り返されている。承認を目指す企業、医療・研究機関では「Coalition for PET Drug Approval」という連合体が組織され、その提供するセッションでFDAの査察に不整合が指摘されFDA側が回答する場面もあり、2年間の間にFDA職員のPET医薬品製造現場への理解が深まる様子も伺われた。

2014年2月のMWMでは、FDAでPETコミュニティと議論を重ねながらPET-GMPや査察プログラムを構築してきたBrenda Uratani氏が音声参加し、直後にFDAを退官しKrishna Ghosh氏が引き継ぐと述べた。氏は、GMPシステムは10年間かけて私のbabyのように育ててきたと述べ、参加者と名残惜しそうに言葉を交わした。

SNMMI（2012年6月以前はSNM）のイベントでは、2010年頃まではFDAからはRDRCプログラムの状況が報告されていたが後にGMP、IND、NDAをめぐる議論へとシフトし、2014年には承認取得後の安全性報告、ラベル修正、プロモーション規制など、「製造販売業者」の義務に関する議論が増えた。5年間あまりの間に、米国PETコミュニティが、探索研究から、FDAに申請して臨床試験を行い、承認を目指してGMP査察を受け、さらに承認取得後の責任を果たす立場へと、成長した様子は著しい変化である。

5．NCIとSNMMIの開発戦略

よく知られたPET医薬品の承認に向けた開発は、NCI（米国国立がん研究所）とSNMMIが、規制当局FDAや診断薬・治療薬企業とも協力しながら様々な戦略を展開している。

5．1　NCIのshared-IND戦略

NCIは、新規制施行前の2011年に、NaFのNDAを取得し、直後にNDA不継続をFDAに通知した。NCIは、政府機関の果たすべきミッションとして、政府機関であればNDAの申請費用が無料なので豊富な経験に基づき困難なNDA作業を担い、承認を得た後は自ら権利放棄した。これにより他の企業や医療・研究機関がジェネリックとしてのANDA手続きでより簡略な承認申請を行えるし、PET医薬品に限ってANDA申請は企業でも無料になる。これを踏まえてNCIが意図的に計画した戦略であった。

これ以外にもNCIは多くのINDを保有している。米国ではIND申請が認められた状態をIND-holderと表現する。NCIがIND保有者として他機関とLetter of Authorization（LOA）を交わすと、INDの完全な情報はNCIが保有したまま、他の機関は、NCIのIND情報に基づき、新たに完全なINDデータをFDAに提出することなく、当該医薬品を用いた臨床試験を開始できる。NCIはこれを「Shared-IND」と称し、余分な安全性試験のために動物を犠牲にすることなく、業界全体として費用も節約できる、と述べている。

5．2　SNMMIの臨床試験ネットワーク（CTN）

SNMMIは、NCIが先にIND取得したFLTの情報を「shared-IND」方式でNCIと共有し、自らIND申請しFDAから承認を得て、学会が主導する多施設共同臨床試験を展開している。SNMMIは、PET医薬品の製造施設の登録、撮像施設の登録と認証のシステムを立ち上げ、2015年2月1日現在、全世界中（米国、カナダ、オーストラリア、ドイツ、スイス、オランダ、ベルギー、英国、韓国、台湾、日本）の163施設の241のスキャナーがバリデーションを終えている（1年半前の前回報告[3]より10施設・27スキャナー増加。166スキャナーは米国内、日本は3スキャナー）。治療薬の製薬企業は、SNMMIが一定レベルの体制整備をしていることとPET医薬品によるバイオマーカー評価をSNMMIが担うことで、開発費用を節約できることから、SNMMIに寄附金を供与する。この戦略によりSNMMIは全世界規模で臨床試験ネットワークを展開している。

5．3　SNMMIによるDota製剤開発支援

最近になってSNMMIはDotatoc、Dotatate、Dotanoc製剤の開発支援に力を入れている。これは転移を有する神経内分泌腫瘍（NET）に対するソマトスタチン受容体結合放射性医薬品で、診断後の治療も放射性医薬品であるため関係者の関心が高く、患者の要望も強い。

^{68}Ga-Dotatoc PETは^{111}In-pentetreotide SPECTより検出力が高いとするデータが出てきている。2013年8月、

CTNはFDAに68Ga-Dotatocのオーファン指定を申請し同年10月NETマネジメントについて指定を受けた。その適用はOrphan Drug Act （ODA）と関連規則による条件（患者数が20万人以下、または米国市場で利用可能にするまでの開発費に見合う収益が期待できない、など）による。指定を受けると、検証試験の症例数が小さくてよい、NDA申請料免除、FDA助成金に申請できる、などのメリットがある。実際のNDA申請は、開発を進めた後に、プレカーサ、キットなどの企業が行うことが期待される。

CTNではDOTA臨床試験実施施設を支援するため、使用基準、撮像マニュアル、症例報告書の書式、などの共同開発を進めている。2015年3月にはこれをテーマにした国際会議がSNMMIとジョンズホプキンズ大学の共催で開催され、日本からは京都大学が参加する。

6．βアミロイドの承認と保険収載

新規PET医薬品では、アミロイド・イメージング製剤^{18}F-Florbetapir（Amyvid®）が2012年中に承認され、話題を呼んだ。この種のPET医薬品は、Avid Radiopharmaceuticals、Bayer HealthCare Pharmaceuticals、GE Healthcareの3社がそれぞれが臨床開発を進め、2008年にFDA末梢・中枢神経系医薬品諮問委員会「アルツハイマー病診断補助としてアミロイドを検出するイメージング製剤の臨床開発」と題する公聴会が開催され、公開の場で、それまでの臨床試験の結果を各社が発表、承認取得のためにさらに必要な臨床試験についてFDAとの議論が交わされた。ここで画像データと剖検データの一致性を示す試験の必要性が確認され、Avid社がいち早くこの試験結果を示し承認申請した。承認の根拠となったのは画像・剖検データの一致性を示す試験の他2試験で、読影判定の高い成績が示された。2010年末にEli Lilly社がAvid社を買収、2011年1月のFDA諮問委員会では読影の一致性のための教育プログラムを作成すべきとされた。後に教育プログラムも作成され、関連学会による使用基準も明確化され、保険適用が目指された。

米国では公的保険適用の可否は保健福祉省下のCMS（メディケア・メディケイド・サービス・センター）が諮問委員会の意見に基づき決定する。医薬品としての承認は有効性・安全性の確立によりFDAが与えるが、保険適用は、臨床的アウトカム改善のエビデンスを示さなければならない。2013年1月のCMS諮問委員会では、同検査の患者アウトカム改善エビデンスは不十分とされ、9月の最終決定では、CMSの認めた枠組みの中での一定範囲の研究（患者登録システムを含む）における1回の検査のみがメディケアによる公的保険の適用とされた。CMSの決定は個別商品ではなく「βアミロイド・イメージングPETによる認知症・神経変性性疾患」に対するものなので、Florbetapirに続き承認取得したバイエル社のFlorbetaben、GE社のFlutemetamolも、同じ条件での保険適用となる。

7．保険診療におけるイメージング施設認証

PET医薬品の規制とは別に、保険診療の条件としてのイメージング施設認証の規制が2012年施行され、既に認証更新の時期にある。これは、「患者および医療提供者のためのメディケア改善法」（MIPPA）に基づき、高度なイメージング技術（PET、SPECT、CT、MRIなど）によりメディケアの保険償還を得て画像検査を提供する施設に対する認証取得義務である。この規則は病院を除くイメージング施設に適用されるが、保険診療の条件としての病院認証は別に包括的な規制が存在するため、その対象とならないPETセンターなどを標的としたためである。

認証機関は、ACR（米国放射線協会）、IAC（Intersocietal Accreditation Commission）、JC（Joint Commission）の3機関、加えて後に認められたRadSite™の計4機関である。ACR、IACはこの制度以前から20年にわたり自発的な認証活動を行っている。JCは病院全体の活動に対する認証機関で、これの国際機関が、メディカルツーリズムで有名なJCI（（Joint Commission International）で、世界中の多くの病院が認証取得している。

2013年5月、米国会計検査院が報告書をまとめ、CMSが認証機関に関する基準を最終化していないことを批判した。また、JCは基準を十分に満たしていないとされていることが、SNMMIの2014年中の年会で議論された。JCは改訂基準を公表し、2015年7月有効になる。

8．まとめ

以上、米国におけるPET医薬品新規制の施行とその後の状況、保険診療におけるイメージング認証などについて報告した。以下に概略を要約する。

- 米国では医療・研究機関も含む施設ごとのNDA/ANDA申請・査察・承認が目標（2012年6月までの申請は2015年末までに完了）に向けて着実に進められ、NDA取得後の製造販売業者の責任へと議論がシフトしている。
- NCIのShared-IND、SNMMI-CTNのセントラルINDの活動は着実に展開、CTNではDota製剤開発を特に支援している。
- βアミロイド製剤は医薬品としての承認を得られたが、公的保険の適用はCMSの認める研究の枠組みにおける1回の検査のみである。
- イメージング認証についても規制は着実に施行され、「次の段階」として認証の更新時期に来ている。CMSの上位機関として会計検査局の監視も機能している。

こうした米国の状況に学びつつ、日本核医学会でも、PET医薬品製造施設及び撮像施設の認証活動を進めている。製造認証については、院内製造のための合成装置承認との関連で、学会認証が必要とされる体制が構築されつつある。「PET Drug Japanese Dream World」の構図は着実に描かれ、今後の展開が期待される。

謝辞

本稿は、2014年度厚生労働科学研究「院内製造PET薬剤の合成装置を用いた核医学診断技術の臨床応用に関するレギュラトリーサイエンスの研究」による。

文献

1）栗原千絵子: Rad Fan 9: 76-79, 2011
2）栗原千絵子、井上登美夫: Rad Fan 11(8): 108-111, 2013
3）栗原千絵子、井上登美夫: Rad Fan 11(9): 118-121, 2013
4）栗原千絵子、井上登美夫: Rad Fan 11(10): 86-89, 2013

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)

Rinsho Hyoka (*Clinical Evaluation*). 2015 ; 43 : W37-W45. [Epub ahead of the issue publication]

* This article is an English translation of the article originally written in Japanese and published in *Rad Fan.* 2011; 9(11): 76-9, 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.

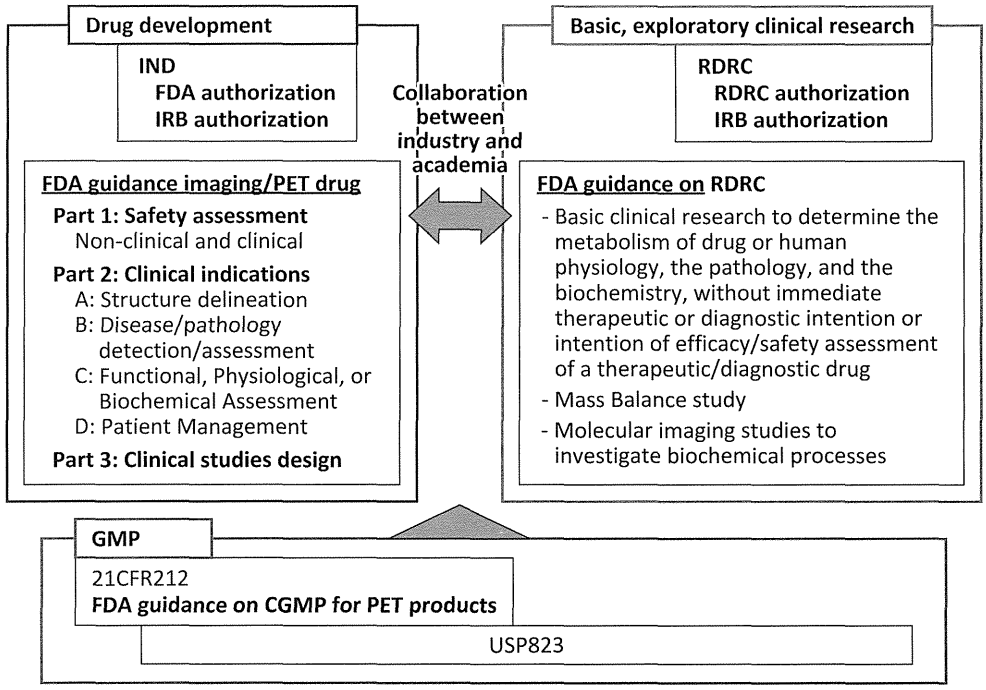
1. Regulatory framework of PET drugs

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.

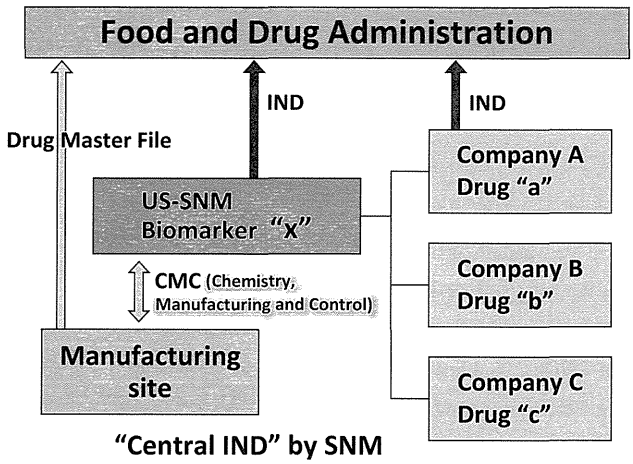
5. Clinical Trial Network

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)



•First, open protocol without detailed description of each therapeutic drug, and then protocol amendment for detailed description of each protocol.

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.

Acknowledgement

We deeply appreciate the specialists in the U.S., some of them appear in this article. This English translation and publication is supported by the following task force. Ministry of Health, Labor and Welfare, 2014 fiscal year: Regulatory science concerning clinical application of nuclear medicine diagnosis using PET drugs produced by an in-house PET drug synthesizer.

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(Published March 24, 2015)

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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.