FDA Audits and Inspections for PET:
A Personal Perspective

Steve Zigler, PhD and Nancy Taylor, MS, RAC
Siemens PETNET Solutions

The regulation of PET in the United States was the subject of much debate until the passage of the 1997 Food and Drug Administration (FDA) Modernization Act (FDAMA). Section 121 of this act defined PET drugs as those that are compounded on the order of a practitioner in accordance with state law (i.e., practice of pharmacy/medicine). In addition, FDAMA required that PET drugs be compounded in conformance with the United States Pharmacopeial Convention standards and monographs. FDAMA further required the FDA to develop good manufacturing practice (GMP) regulations as well as appropriate review procedures for the approval of PET drugs. The act also prevented the FDA from requiring approved applications for commercial PET drugs until two years after completion of these tasks. On December 11, 2009, the FDA completed its FDAMA obligations, with the creation of GMP regulations for PET drugs, which then became effective on December 11, 2011. Thus, we have now entered the “post-FDAMA era” of PET drug production—all commercial PET drugs must now be produced under the new PET GMP regulations.

Although the PET GMPs have been in print for more than two years, recent inspections have started to reveal a new level of detail in FDA expectations regarding the new regulations. FDA inspectors are familiar with traditional GMPs, but more and more inspectors are using the new PET GMP regulations for the first time. The FDA has addressed this by writing new guidance documents and a new manual for PET inspections. The FDA has also implemented a field training program for inspectors; however, the PET manufacturing model is still a new entity to most of them. It is inevitable that inspection standards in PET will take time to evolve to the same level of consistency as those in the traditional pharmaceutical industry. In the meantime, the potential exists for variation from one inspection to the next.

The new regulations and a lack of inspection standards have led to a challenging, and often confusing, environment for PET drug manufacturers. The distributed PET manufacturing model adds to the challenge since multiple, simultaneous inspections at numerous facilities are a new experience for PET drug manufacturers. FDA inspections typically require staff with experience in operations, quality and technical matters to address the breadth of issues raised during the inspection. This requires on-site support from teams with appropriate expertise to attend inspections on short notice and to follow through on any responses required after completion of the inspection.

Continued on page 2. See FDA Audits and Inspections
The history of drug regulation in the United States is well-documented on the FDA’s website. GMPs for traditional pharmaceuticals have their roots in manufacturing and quality standards created in the early 1940s. GMP regulations were first finalized in 1963 and then expanded in the late 1970s. In conjunction with the advances in the regulations, FDA inspections matured over the years simultaneously with industry standards. This has resulted in well-established regulatory standards for finished pharmaceuticals, supported by recognized inspection and industry standards. The commercial PET industry is still in its early stages of development and, as a result, there is a lack of mutually-recognized standards for the production of these drugs. As with traditional pharmaceuticals, inspection and industry standards are required to provide well-known guidelines for the new PET GMP regulations. A similar situation will evolve with PET drugs, but it will take some time. It would be a mistake to expect the same level of maturity for inspection and industry standards that required decades to develop with traditional pharmaceuticals.

This is a unique period in the history of PET. New imaging biomarkers and new regulations have the potential to dramatically reshape the PET landscape. The FDA and the PET industry must learn from each other during this critical time as we undergo the first wave of inspections under the new regulations. As a PET community and industry, we must work together to ensure an orderly progression to mature regulated industry standards.

CTN has always recognized that NMTs play a vital role in research imaging, but rarely receive recognition for their achievements. Additionally, there are no official pathways or curricula available with formal research training for technologists. Given current economic conditions and workforce issues, employment opportunities for NMTs are becoming fewer. To that end, CTN has been working with SNMTS leadership to investigate ways in which CTN can assist our technologists and, therefore, benefit the molecular imaging community as a whole. Current SNMTS president, Ann Marie Alessi, BS, CNMT, NCT, RT(N), and SNMTS president-elect, Brenda King, CNMT, FSNMTS, have been spearheading an initiative to provide a formal research training pathway for NMTs and to ensure that the membership is aware of these professional growth opportunities. Alessi notes, “This training is a great ‘spoke’ to add to the nuclear medicine career wheel ‘hub’ to which our members will benefit from in moving their careers along.”

As the first step in that direction, CTN and SNMTS presented a joint session at the SNM Mid-Winter Meeting in Orlando, Fla., this past January geared towards NMTs and how they can possibly transition into research positions. In addition, CTN and SNMTS will host a joint categorical seminar on June 9 at the SNM Annual Meeting in Miami Beach, Fla., to expand on this novel career direction. It will include a speaker from the Society of Clinical Research Associates (SoCRA) who has experience in nuclear medicine and has worked with NMTs in the research arena. “The SNMTS is excited to work with CTN to help our NMTs discover new career pathways in research,” stated Alessi. “By doing so, clinical research imaging will only improve. It is a win-win situation!”

CTN supports this collaboration and we are confident that, by working together, the quality of our research imaging will improve, allowing new molecular imaging agents and therapeutic drugs to move forward and ultimately benefit patients worldwide.
Positron emission tomography (PET) myocardial perfusion imaging (MPI) has been technically feasible for many years, but its wide application has been hindered by currently available tracers that require an on-site cyclotron (13NH3 and H215O) or a costly generator (rubidium-82). F-18 flurpiridaz is a novel myocardial perfusion tracer in clinical development. This tracer has promising characteristics that may be very favorable for MPI including high myocardial extraction, longer half-life, and availability in unit doses from regional cyclotrons. F-18 flurpiridaz is a structural analog of pyridaben (Figure 1) and binds to mitochondrial complex I with high affinity(1,2).

Phase 1 investigations(1,3) showed there were no tracer-related adverse events; dosimetry was within the clinically acceptable range, using up to 14 mCi combined rest-stress dose; stress imaging was feasible with both treadmill exercise and pharmacologic vasodilation; and myocardium was clearly visualized for several hours after rest and stress injection with good myocardial to background ratio.

In the Phase 2 clinical trial(4), F-18 flurpiridaz injection had a favorable safety profile and showed an improvement as compared to Tc-99m-labeled SPECT with respect to rest-stress image quality, certainty of image interpretation, and sensitivity for detection of coronary artery disease. We observed that in myocardial segments supplied by diseased coronary arteries, perfusion defects appeared more severe on F-18 flurpiridaz PET than Tc-99m-labeled SPECT MPI (Figure 2). Preliminary single-center studies at the University of California, Los Angeles have shown promising results for absolute quantification of myocardial blood flow(5). F-18 flurpiridaz is currently undergoing Phase 3 clinical trials.

References

Figure 1. Chemical structure of F-18 flurpiridaz

Figure 2. Rest-stress F-18 flurpiridaz PET and Tc-99m tetrofosmin SPECT images in a patient with significant LAD disease (adapted from Maddahi, J; J Nucl Cardiol 2012; 19(1):30-37 with permission).
New Draft Guidance Issued on INDs for PET Drugs

On February 14, 2012, the U.S. Food and Drug Administration (FDA) published a draft guidance document entitled, “Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs.” This guidance is intended to assist PET drug manufacturers when submitting investigational new drug applications (INDs); it summarizes the IND process, makes recommendations for how to submit an IND and provides advice on expanded access options for investigational PET drugs. Comments to the FDA were accepted through May 14, 2012. To view the draft guidance, visit http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf.

Additional updates on PET drug manufacturing can be found at http://coalitionforpetdrugapproval.org/.

CTN Establishes Presence at Molecular Med Tri-Con 2012

Jeffery Yap, PhD

This past February, CTN co-sponsored the 2012 Molecular Medicine Triconference held in San Francisco. As nuclear medicine and molecular imaging are integral components of molecular medicine, imaging was a relevant topic in all of the four core conference sessions: diagnostics, drug discovery and development, informatics, and cancer. Scientists and executives of pharmaceutical and biotechnology companies, academic physicians and scientists, and representatives of government agencies attended the conference. This unique audience and platform allowed CTN to promote the role of imaging with key thought leaders and early adopters of advanced technology in drug development.

The participation of CTN included a booth in the exhibit hall and a presentation of “Molecular Imaging—Advancing Drug Development from Preclinical Studies to Global Multicenter Trials” in the plenary session on “Emerging Technologies and Industry Perspectives.” In the panel discussion, it was discussed how molecular imaging shared the same challenges with other advanced technologies, such as the high cost of development, barriers to obtaining regulatory approval and clinical reimbursement. However, imaging may also be considered a “disruptive technology” that can positively alter and ultimately replace conventional approaches for evaluating the efficacy of new therapeutics and identifying the patient population that would receive clinical benefit.

Given the high failure rate and lengthy development time for bringing new drugs to market, molecular imaging is well-positioned to address these challenges. CTN provides a means to improve the performance of quantitative imaging and increase the availability of imaging biomarkers in global multicenter trials.

New NIH Website on Clinical Research Trials

Clinical trials are essential for identifying and understanding ways to prevent, diagnose and treat disease. The National Institutes of Health (NIH) supports clinical research trials in the United States and throughout the world and provides information to raise awareness about the importance of clinical research.

To this end, NIH has created a new website, NIH Clinical Research Trials and You, to explain what clinical trials are and why they are so important for moving medical discovery forward to ultimately improve health outcomes and long-term survival. Research has shown that among the greatest challenges to recruitment of volunteers in clinical trials is the lack of general knowledge about what trials involve and who may participate. This website, www.nih.gov/health/clinicaltrials/, provides important information and education materials for health care professionals and potential clinical trial participants alike.

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CTN Educational Offerings at the 2012 SNM Annual Meeting

CTN/SNMTS Joint Categorical
SATURDAY JUNE 9 (8:00 am – 4:15 pm)
Career Development Options and Research Essentials for Nuclear Medicine Technologists
The nuclear medicine technologist (NMT) is a very specialized position. NMTs face some challenges in today’s workplace; specifically, available opportunities for new hire and further career development. This session provides viable options that technologists can consider, including positions in the clinical research environment.

CTN/Radiopharmaceutical Sciences Council Joint CE Sessions
MONDAY JUNE 11 (2:30 pm – 4:00 pm)
Radiopharmaceutical Development and the IND Process
Presentations in this session will discuss current U.S. Food and Drug Administration regulations governing what an IND sponsor and its imaging site investigators are required to document and record. Instructions for developing and practical applications in using INDs for PET imaging agents will be provided.

TUESDAY JUNE 12 (2:30 pm – 4:00 pm)
F-DOPA in Clinical Research
This session offers valuable information on the background of F-DOPA: its evolution, chemical synthesis and proposed use in the clinical setting. Both basic scientists and clinical researchers will benefit from this timely and highly relevant session.

Emerging Technologies Sessions
SUNDAY JUNE 10 (4:15 pm – 5:45 pm)
New Molecular Imaging Technologies/Hardware

MONDAY JUNE 11 (10:00 am – 11:30 am)
Translating Imaging Agents into the Clinic
(12:30 pm – 2:00 pm)
FDA Update on 212 Regulations for PET Manufacturing
(2:30 pm – 4:00 pm)
New Amyloid Imaging Agents
(4:00 pm – 5:30 pm)
UPICT FDG PET/CT Protocol Presentation and Comments

Clinical Trials Network
WEBINAR SERIES 2012
CTN is pleased to present its third year of webinars to help sponsors, manufacturers and imaging personnel deal with regulatory and practical nuances of participating in clinical research. These bimonthly presentations by experts in the field offer CME credit and provide valuable information to the community. Please check the CTN website, www.snm.org/ctn, for ongoing information and updates.

JUNE 21
Title: Radiation Risks in Clinical Research: Putting It in Perspective
Speaker: Frederic Fahey, DSc

AUGUST 23
Title: Comparison of PET Performance Phantoms
Speaker: Ronald Boellaard, PhD

OCTOBER 18
Title: New Molecular Imaging Agents and Their Potential Clinical Role
Speaker: Mark Travin, MD

DECEMBER 6
Title: Phases of Drug Development
Speaker: Eileen Smith, MBA, CNMT

What’s Happening
CTN and EARL: Moving Standardization Forward
At the SNM Mid-Winter Meeting in January 2012, leadership from the European Association of Nuclear Medicine (EANM) and SNM continued discussions initiated at the International Atomic Energy Agency meeting on November 12, 2011, on a potential collaboration between the CTN and EANM Research Ltd (EARL) aimed at advancing standardization of PET imaging in clinical research. Both groups recognize the importance of ongoing scanner validations, dose calibrator assessment and the harmonization of vendor reconstruction protocols in meeting this goal.

Ideas for joint projects have focused on developing a worldwide standardized protocol for FLT PET imaging as well as working with equipment vendors to create a “clinical trial protocol” that can be harmonized across all system platforms to further standardization efforts. Although no specific project has been initiated, teleconference calls have been scheduled to set up working groups that will meet at the SNM Annual Meeting in Miami Beach, Fla., in June.
Tech Talk:
New Career Direction for Nuclear Medicine Technologists

Brenda J. King, CNMT, FSNMTS

The historical career pathways for the nuclear medicine technologist (NMT) have been from imager to supervisor or manager, imager to application or clinical specialist, and imager to radiopharmaceutical or instrumentation sales representative. Although this has worked in the past, the ever-changing job market now requires us to identify additional pathways that can utilize the NMTs current skills and knowledge as a strong foundation for a new career.

CTN and the Society of Clinical Research Associates (SoCRA), in collaboration with the SNMTS, have moved forward to develop and present another pathway that may interest some NMTs—becoming a certified clinical research professional, or CCRP(SoCRA). There are many NMTs that have progressed to becoming a CCRP or CCRA (certified clinical research associate/ACRP) and have found personal and professional satisfaction in this field.

The SNM Mid-Winter Meeting in January 2012 offered the very first session on research career options for NMTs, and we are pleased to follow-up at the SNM Annual Meeting in Miami Beach, Fla., with a full-day joint categorical session of select presentations designed to expand on this unique potential career choice. Members from SNMTS, CTN and SoCRA also plan to continue their collaboration by developing additional educational courses and offering them through webinars, at chapter meetings and during other society proceedings.

Make this a stepping stone to a new career and register for the CTN/SNMTS joint categorical session on Saturday, June 9. See you in Miami Beach!

Research Essentials:
Avoid Protocol Pitfalls
Excerpt from CTN course #106: Following the Protocol

Reports from pharmaceutical companies indicate that, in general, imaging studies are very problematic in terms of study protocol compliance. Not following a protocol results in a myriad of problems for the study sponsor and the research site, and can range from minor typos to affecting patient safety. But, make no mistake; even the seemingly smallest error can have dire consequences on the analysis and overall merit of the study data.

So, what happens when the study protocol is not followed? Errors occur, and are then categorized as a deviation or a violation.

- Deviation: A variation from the processes or procedures defined in the protocol, such as being unable to keep a scanning timepoint due to unavoidable situations. A deviation usually does not affect eligibility of data for analysis and does not affect the safety of the human subject.

- Violation: A significant departure from processes or procedure, such as changing the technical parameters of the acquisition sequence as outlined in the protocol. Violations may affect the evaluability of the data or affect human safety.

There are a number of steps that imaging personnel can take to avoid these pitfalls:

- Carefully review the protocol prior to starting the study; ask questions and confirm that your site can follow technical procedures as written in the study protocol
- Periodically review the protocol, especially when a long period of time may occur between study scans
- Maintain a copy of the current protocol and technical imaging manual in an accessible location for easy reference
- Use worksheets and checklists; double and triple-check the protocol requirements and your work

As imaging research personnel, we must strive to follow the protocol as written. Be a great clinical research site for your patients, for the sponsor, for your organization—and for your own professional development!

Tech Tip
BE A GREAT RESEARCH IMAGING SITE

You may be a good, or even great, clinical imaging site, but being a great research imaging site involves this key factor:

- Always follow the research study protocol. If you can’t follow the protocol for a legitimate reason, call the study sponsor to find out how to proceed before the study patient arrives.

With the exception of patient safety, following the protocol supersedes imaging experience and clinical judgment! There are regulations that state exactly this, and the sponsors who hire us as imaging sites expect that everyone lives by these regulations.
The largest and most established area in the field of cardiovascular nuclear medicine is the diagnosis and workup of coronary artery disease (CAD), driven on the one hand by myocardial perfusion imaging (MPI), but also by emerging technologies in molecular imaging. Research has demonstrated the diagnostic and prognostic importance of quantitative perfusion imaging using PET technology and, especially in the United States, there has been an increasing clinical acceptance driven by the current reimbursement policy. Today’s most commonly used cardiac blood flow tracer in combination with PET is rubidium-82. It has significantly contributed to increasing utilization of PET; however, it has its limitations due to low extraction by the myocardium and high cost of the generator. After waiting so long for a much needed F-18-labeled blood flow agent, we are excited about the recent introduction of flurpiridaz (Lantheus Medical Imaging, Inc.), a new F-18 imaging agent for high-definition cardiac perfusion (Figure 1), which currently undergoes clinical evaluation. Further information on this radiopharmaceutical is provided in the Biomarker Spotlight on page 3 of this newsletter.

Very convincing data with metaiodobenzylguanidine (MIBG) supports the notion that imaging of cardiac innervations may help us select patients for new antiarrhythmic therapies. Again, 1-123-MIBG has limitations regarding image quality and quantitation. C-11 labeled PET tracers such as C-11 hydroxyephedrine (HED) have shown great potential, but the short halftime of C-11 prohibits distribution. Lamoy et al (1) and Bozek et al (2) have used F-18-LMI1195 as a novel PET cardiac neuronal imaging agent, which combines the suitable pharmacology of MIBG with the advantages F-18 PET imaging.

A number of other interesting new molecular radiopharmaceuticals are being examined, such as (R)-(11)rolipram (Figure 2) for the characterization of phosphodiesterase activity after post-myocardial infarction (Kenk et al(3)). A recent study showed some promising preliminary results, but a pathophysiologic correlation is needed to actually define the utility of this agent.

Another exciting new radiopharmaceutical, C-11-KR31173, has been used with PET/CT imaging for myocardial angiotensin II subtype 1 receptor (AT1R) by Fukushima et al (4) and Higuchi et al (5). The group has demonstrated that myocardial infarction results in an overexpression of angiotensin receptors in the area of infarction, as shown by the relationship between tracer uptake and regional blood flow (Figure 3).

Our own group from the Technische Universität Munchen (Germany), led by Sherif (6), researched the early F-18 galacto-RGD uptake associated with long-term left ventricular remodeling after myocardial infarction. This tracer targets αvβ3 integrins because integrins are involved in angiogenesis and tissue repair occurring in is chemically injured myocardium. These new imaging probes are expected to increase our understanding of the development of heart failure and associated complications in patients with coronary artery disease and may be guiding future therapies to high risk patients.

Molecular imaging in the preclinical and clinical setting will play an important role in translational research and is likely to contribute considerably to the development and validation of new diagnostic and therapeutic strategies in patients. Rory Hachamovitch, MD, MSc, (Cleveland Clinic, OH), who was instrumental in establishing MPI as a prognostic marker, highlighted these challenges for new imaging technologies in a recent lecture. “When looking to the future,” he said, “we should not only emphasize new developments and applications but also concentrate on the role of imaging to aid in the diagnostic process, assessment of therapy, and tracking treatment of disease (7).”

References
CTN Cardiac Phantom Revisited
Paul E. Christian, BS, CNMT, PET, FSNMTS

Radiopharmaceutical manufacturers and device developers alike have renewed interest in PET myocardial perfusion imaging. Recent phase 3 multicenter clinical trials of F-18 flurpiridaz (Lantheus Medical Imaging, Inc.) and testing of other new F-18 cardiac imaging agents in the pipeline have revitalized interest in PET imaging of the heart. In addition, rubidium-82 returned to clinical availability earlier this year.

Multicenter testing relies heavily on obtaining images of a certain quality and ensuring similar performance from different scanners. Different vendor scanners, however, often provide unique challenges. Medical Designs Inc, which manufactures phantoms for the CTN, has introduced a new cardiac phantom design (Figure 1) that allows easy positioning of inserts for rest and stress myocardial perfusion imaging with PET or SPECT. This design evolved from many years of experience in manufacturing phantoms used at over 100 U.S. Veteran’s Administration (VA) Medical Centers.

The inserts for this cardiac phantom can simulate different disease patterns of infarct or ischemia as well as multi-vessel disease. Three standard clinical scenarios are currently available, each with a clinical vignette describing a possible clinical history that guides the physician to an appropriate interpretation of the phantom images.

- Scenario 1: Two regions of myocardial ischemia
- Scenario 2: Three defects—two regions of infarction and one area of ischemia
- Scenario 3: Transient ischemic dilatation (TID) with areas of infarction and ischemia

Customized patterns as well as location and extent of disease can be designed for study-specific protocols. This phantom lends itself to evaluate not only scanner performance but also the comparison of protocols relative to their effectiveness in detecting certain patient disease states. The phantom’s modification diversity, durability and reliability make it a perfect choice to ensure that images are standardized when using investigational cardiovascular imaging agents. To learn more about the CTN cardiac phantom, please visit www.snm.org/ctn.

Save the Dates

American Society of Clinical Oncology Annual Meeting
June 1 – 5, 2012 • Chicago, IL

SNM 2012 Annual Meeting
June 9 – 13, 2012 • Miami Beach, FL

Drug Information Association 48th Annual Meeting
June 24 – 28, 2012 • Philadelphia, PA

2012 World Molecular Imaging Congress (WMIC)
September 5 – 8, 2012 • Dublin, Ireland

Society of Clinical Research Associates 21st Annual Conference
September 21 – 23, 2012 • Las Vegas, NV

Radiological Society of North America 98th Annual Meeting
November 25 – 30, 2012 • Chicago, IL

SNM 2013 Annual Meeting
June 8 – 12, 2013 • Vancouver, British Columbia, Canada