Over the past 10–20 years, there has been a dramatic proliferation of genomic and proteomic data with a concomitant increase in the number of therapeutic and imaging targets. However, this intensified activity in therapeutic drug and imaging agent research has yet to fill the drug or tracer pipelines. In fact, submissions and subsequent approvals of new molecular entities and biologics by the U.S. Food and Drug Administration (FDA) peaked in the mid-1990s, followed by a steady decline, reaching a historic low in 2007, with only 18 approvals (Fig 1). This occurred in a period where expenditures on drug discovery and development research dramatically increased and new mandated FDA initiatives, such as the widely touted Critical Path Initiative (CPI; 2004), were implemented. Where did all the money go? According to the Tufts Center for the Study of Drug Development, the money went into the rising cost of bringing a drug successfully to market. In 2003, that cost was estimated to be between $0.8–1.7 billion.

Since 1975, radioactive diagnostics and radiotherapeutics (collectively radiopharmaceuticals) have been approved by the FDA following the same regulatory paradigm as new drugs, regardless of their unique attributes. Despite increased federal funding and the rapid evolution of molecular imaging, there remains a lack of new tracers, especially PET radiotracers, being brought to market. From 1995 until the present, there have been only five FDA-approved radiopharmaceuticals, and only one was a PET radiotracer: nitrogen-13 ammonia.

BARRIERS TO SUCCESS

Several barriers exist that contribute to the limited number of approved tracers. These may be broadly classified in three categories: tracer discovery/development, regulatory aspects and clinical development. Molecular imaging research funding from the major federal agencies (NIH, DOD and DOE) has increased over the last decade; however, the amount of funding has not kept pace with the overall growth of the molecular imaging field and the cost to bring a radiotracer from the bench to the bedside. In 2006, Adrian Nunn authored a paper (Invest. Radiol. 41:206-12, 2006) estimating the cost of new tracer development at $100–200 million. Since the majority of the new tracers were being discovered at single academic institutions, there was clearly not enough funding or resources available to bring these tracers through the full development process. Additionally, the number of companies specifically engaged in
Radiotracer development was limited.

Radiotracer development is very different from therapeutic drugs but, as indicated above, they are approved based on criteria similar to that of a new drug. One of the larger expenses in the development process is determining the toxicity. A full therapeutic toxicology package on a single entity may cost up to $200–400 million today. The clinical trials are also very expensive and often involve multiple centers. Short-lived isotopes, such as fluorine-18, have to be produced by distributed manufacturers located near the clinical trial imaging centers, and each of the manufacturing sites must produce the tracer in a standardized fashion to qualify for the clinical trial phases.

Reimbursement for approved tracers is tightly controlled by the U.S. Centers for Medicare & Medicaid Services (CMS). The cost to produce an experimental radiotracer for a few patients a week is greater than $1,000 per dose, but reimbursement is often below this cost. An additional barrier is the limited acceptance of new tracers by referring physicians, and the “new” nuclear scare being widely reported in the lay press. Most nuclear scans are now combined with a CT scan, and the exposure to ionizing radiation from the tracer and the CT has been characterized as excessive, with no real assessment of the actual benefit-to-risk ratio for medical imaging procedures.

These barriers represent significant hurdles to relieving the backlog of radiotracers in the pipeline. Significant changes in the regulatory requirements will help reduce the cost and increase the commitment to produce these valuable tracers. Outreach and advocacy are needed to educate and to assuage the fears of referring physicians and patients.

RISEING ABOVE THE CHALLENGES

A number of solutions are currently being pursued to overcome the described barriers. Some companies now have radiopharmaceutical pipelines, and several startups have been spun out of academic centers with radiotracers in their portfolio. This growth helps provide the resources and infrastructure needed to move tracers from the preclinical phases into human development with funds for full toxicology packages. Because of the devastated pharmaceutical pipeline, the Congress and the FDA are eager to reinvigorate the development process. The timing is right to engage the FDA in efforts for regulatory relief capitalizing on the differences between drugs and tracers.

The FDA recently formed a new division, the Division of Medical Imaging, offering an opportunity to interface with this group whose focus is entirely based on molecular imaging. In 2006, the FDA also introduced the exploratory

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**SAVE the DATE**

**CTN Workshop**

January, 2011

The CTN will host its mid-winter workshop January 20 and 21, 2011, during the SNM Conjoint Mid-Winter Meetings in Palm Springs, Calif. This two-day conference will cover a variety of topics dedicated to current issues and interests identified by members of the imaging research community. The agenda has not been finalized, but following is an overview of proposed topics for the workshop.

**Day 1: PET Manufacturing Regulations and Implementation for Clinical Research**

- Update on FDA Guidance for PET cGMP (Part 212)
- Electronic Registration and Submission Process
- NDA, aNDA or IND: Which Pathway to Use
- Audits and Inspections Under Part 212

**Day 2: Clinical Trials Regulations and Implementation**

- Recording and Reporting Adverse Events
- The IRB and RDRC Review Process
- 21CFR312 and GCP Training
- PET Biomarkers: A Clinical Discussion

Visit [www.snm.org/clinicaltrials](http://www.snm.org/clinicaltrials) to view presentations from past meetings and to learn about our monthly educational webinar series.
Expanding on topics presented at the CTN Workshop in Albuquerque earlier this year, the CTN presented categorical and CE sessions on the FDA 212 regulations for PET radiopharmaceutical manufacturing and promoting standardization in clinical trials. A new CE course on the roles and responsibilities of the Institutional Review Board was launched, expanding the excellent educational program already in place for investigators and technologists. Additionally, CTN leaders met with pharmaceutical companies, biomarker developers, equipment manufacturers and representatives from Asian imaging centers over the course of the five-day meeting to further advance support and collaborative opportunities for the network. The CTN is taking a multifaceted approach to move the field forward, including working with major vendors to develop standard image reconstruction settings for PET/CT scanners, as well as building relationships with our Asian counterparts to assist in facilitating global multicenter clinical trials.

The following educational events at SNM’s 57th Annual Meeting provided valuable information that attendees could use in their research practice or radiopharmaceutical manufacturing.

CTN CATEGORICAL

In a standing-room-only morning session, FDA representatives, including Dwaine Rieves, MD, director, Division of Medical Imaging Products (CDER/OND/ODEIV), updated attendees on FDA’s thoughts relative to 21 CFR Part 212, “current Good Manufacturing (cGMP) for PET drugs.” Other renowned speakers addressed some of the issues related to implementing the regulation and discussed considerations for CMC. SNM and the Clinical Trials Network are working to keep the community informed through a dedicated webpage with links to FDA presentations, http://interactive.snm.org/index.cfm?PageID=9740, and a community forum at http://interactive.snm.org/index.cfm?PageID=5867. Manufacturers must stay abreast of regulatory activities, as an updated FDA guidance document is expected in fall 2010. The afternoon session concentrated on the clinical site’s responsibilities regarding regulatory compliance, audits and ethical oversight of human subjects in clinical trials. Excellent speakers from industry and academia presented valuable insight and guidelines when using imaging in therapeutic trials, the ABCs of source documentation and how study data is handled and transferred offsite while protecting the privacy and welfare of the subject at all times.

CE SESSIONS

Over the course of the meeting, the CTN offered three continuing education sessions. The lectures spanned the development cycle of a new molecular imaging tracer, from discovery through clinical testing. Some of the key points included the need for precisely written and closely followed clinical and imaging protocols through all phases of development. A key component of performing standardized research is to perform scanner validation at predefined time points before and during participation in a multicenter trial. Once the trial has begun, it is critical for all data, including the actual study images, to be collected and analyzed in a standardized fashion. The Clinical Trials Network has been working toward these goals through our focused committees: Trial Design, which assists with protocol development; Scanner Validation via CTN phantoms, to standardize equipment and harmonize images; and Site Orientation, which has developed a wide range of courses to train all personnel at clinical research imaging sites as well as the nuclear medicine community as a whole.

The CTN would like to thank all of our speakers, moderators and attendees for contributing to the very successful and informative sessions. Please be sure to participate in our upcoming webinars www.snm.org/webinars and stay tuned for details on the 2011 Clinical Trials Network Workshop, January 20–21, in Palm Springs, Calif.
In the NEWS

NOPR Study for NaF-18 PET

In June 2010, the National Oncologic PET Registry (NOPR) announced it will create a data registry for NaF-18 PET similar to that now in place for many uses of FDG-PET. The development of this new registry was in response to the February 26, 2010 publication by the U.S. Centers for Medicare & Medicaid Services (CMS) of a final National Coverage Determination (NCD) to cover NaF-18 PET for identifying bone metastasis. As previously announced to NOPR facilities, CMS concluded that current evidence is not sufficient to determine that results of NaF-18 PET imaging to identify bone metastases improve health outcomes of beneficiaries with cancer. However, CMS did announce that the available “evidence is … reasonable and necessary under §1862(a)(1)(E) through Coverage with Evidence Development (CED)” (CMS Decision Memo CAG-00065R1; Feb 26, 2010).

Currently, the NOPR team is completing the application for an NaF NOPR study, hopefully to implement in Q1 2011. This process will allow the use of NaF-18 bone scans as standard treatment evaluation for patients covered by Medicare, and should facilitate the use of this tracer in studies since the scans would be paid. Until the NOPR registry (or another CMS-approved study) for NaF-18 PET is qualified, however, there is no Medicare coverage for NaF-18 PET scans.

For more information on the CMS pathway to fund trials under CED, go to: https://www.cms.gov/mcd/ncpc_view_document.asp?id=8.

What’s Happening

Worldwide Standardization of FDG PET Imaging Protocols for Multicenter Clinical Trials

Michael M. Graham, PhD, MD

F-18 fluorodeoxyglucose (FDG) is the most commonly used radiopharmaceutical in clinical oncology PET studies and is often used in numerous clinical trials. When part of a trial, it typically determines efficacy in a specific clinical setting (e.g., lung cancer staging) and as a surrogate endpoint to help make decisions regarding the efficacy of novel chemotherapy agents. In these two types of clinical trials, it is important to conduct the studies in a standardized fashion that facilitates accurate interpretation of the study data, particularly when compared to similar trials. Currently, there are several published FDG clinical trial protocols that are generally similar in content, but differ in several aspects. It is not obvious that these differences are truly significant; however, they have made it difficult to compare imaging studies done at different institutions, particularly when trying to combine data from different FDG protocols. In an effort to harmonize the existing FDG protocols and create one that would be widely acceptable and able to be used in virtually all oncology clinical trials incorporating FDG imaging, the SNM Clinical Trials Network convened a meeting with representatives from key groups around the world that currently have an existing FDG protocol. Approximately 21 participants met on June 3, 2010, for a full-day session immediately prior to the SNM Annual Meeting in Salt Lake City.

Participants at the FDG PET Imaging Protocol Summit

Continued on page 7. See FDG PET Imaging

Image Reconstruction Harmonization Group Convenes at Annual Meeting

John Sunderland, PhD

Continued growth of PET imaging in the U.S. and around the world is contingent upon well-controlled multicenter clinical trials performed according to standards dictated by the FDA and other regulatory bodies. The Image Reconstruction Harmonization Group (IRHG) was formed in early 2010 to develop a strategy to harmonize PET reconstructions used in clinical trials. The members, consisting of physicist representatives from SNM, the Quantitative Imaging Biomarker Alliance (QIBA) and the European Association of Nuclear Medicine (EANM), met with high-level physicists and engineers from each of the three major scanner vendors in Salt Lake City in June 2010, the second meeting held on this novel initiative by the SNM Clinical Trials Network.

For each PET/CT scanner model and for each vendor, the IRHG is provid-
Several decades before the introduction of modern PET systems, $^{18}$F-labeled NaF ($^{18}$F-fluoride) was recognized as an excellent radiopharmaceutical for skeletal imaging. It became widely used for skeletal scintigraphy after its introduction by Blau and others in the early 1960s and was subsequently approved for clinical use by the U.S. Food and Drug Administration in 1972. $^{18}$F-fluoride’s characteristics of high and rapid bone uptake accompanied by very rapid blood clearance results in high-quality images less than an hour after IV administration. With the arrival of $^{99m}$Tc-labeled bone-imaging agents, however, the use of $^{18}$F-fluoride decreased dramatically.

Numerous recent studies have compared $^{18}$F-fluoride PET to $^{99m}$Tc-MDP scintigraphy, demonstrating that $^{18}$F-fluoride PET is more accurate than planar imaging or SPECT with $^{99m}$Tc-MDP for localizing and characterizing both malignant and benign bone lesions. The addition of correlative imaging, such as CT, MRI or hybrid imaging with PET/CT, further improves the specificity and accuracy of $^{18}$F-fluoride skeletal PET. Its clinical usefulness has shown to be effective for many clinical indications in both oncology and benign bone diseases. Although not yet used routinely in clinic, quantitative $^{18}$F-fluoride PET may prove useful to assess metabolic bone disorders such as renal osteodystrophy, osteoporosis or Paget’s disease. $^{18}$F-fluoride PET images can be obtained without attenuation correction, although some well-defined artifacts may be avoided by applying attenuation correction. Use of this agent offers additional advantages such as faster study times, improved workflow in the nuclear medicine clinic, increased convenience to the patient and rapid turnaround of results to the referring physician.

The widespread availability of modern PET scanners permits high-quality skeletal imaging with $^{18}$F-fluoride and its dosimetry is similar to that of $^{99m}$Tc-MDP. These reasons, as well as those listed previously, indicate the need to reconsider the use of $^{18}$F-fluoride PET for select skeletal application. However, obstacles to the widespread re-adoption of $^{18}$F-fluoride as a bone-imaging agent persist. The longstanding familiarity with $^{99m}$Tc-MDP scintigraphy and issues related to insurance reimbursement for $^{18}$F-fluoride PET are the key reasons. Although reimbursement is usually not a factor in clinical research trials (sponsors normally cover the costs), it does become a significant concern when used in clinical practice.

Tech Talk

CTN EDUCATION EXPERIENCE
Rebecca Sajdak, BA, CNMT

Salt Lake City, Utah, was one of the best venues for the Annual Meeting in recent SNM history. Expanding on courses offered at the 2010 SNM Mid-Winter Meeting Workshop, the Clinical Trials Network provided valuable educational sessions on the importance of performing high-quality molecular imaging in research and launched a new course on working with the Institutional Review Board (IRB). You may not realize it, but most of the CTN’s CME courses are primarily written by imaging technologists who have experience in, and a strong dedication to, promoting quality imaging in research. These volunteers, representing all aspects of nuclear medicine, spend hours developing courses used to train imaging technologists, like you, to perform at a higher level in current positions or pursue new career paths in imaging research.

Following a concept through all phases of clinical trials and knowing that the data you collected was of highest quality can be a very rewarding experience. If you are interested in being part of this evolving and exciting area and want to see your contributions showcased at an event like the SNM Annual Meeting, send an e-mail to clinicaltrials@snm.org. To view a full listing of educational courses and presentations, click on the “Education” tab from the CTN website main page at www.snm.org/clinicaltrials.

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Tech Tip
THE CORRECT WAY TO MAKE CORRECTIONS
Tina Kiss, CCRP

When recording research subject data, always sign and date the source document containing the values. If there is an error and you must correct what is written, draw one line through the original value (leaving it still legible), record the correct value to the side or above the erroneous value and then initial and date the change. Never use correction fluid, erasable ink or any other method of obliterating the original recorded value. An auditor must know what was originally recorded, when it was changed and by whom.

RESEARCH ESSENTIALS FOR TECHNOLOGISTS:
VITAL SIGN MEASUREMENTS IN CLINICAL TRIALS
LisaAnn Trembath, MSM, CNMT, NCT, CCRA

When vital signs are required as part of a clinical protocol, they tell an important story about physical responses (or non-responses) to a research intervention, whether it is a study drug or procedure. Changes in vital signs from pre- to post-dose may not signify a clinical emergency or even be notable in terms of the subject’s health and safety, but they do become part of the permanent record of the drug’s evaluation and may also indicate trends that affect monitoring of that drug. It is critical that measurements of the subject’s temperature, blood pressure, pulse and/or oxygen saturation are recorded accurately and precisely on schedule as required by the protocol. Here are some tips to follow when taking vitals as part of a study:

1. Follow the protocol schedule as precisely as possible. Be ready to take those measurements exactly at the prescribed time and record the actual time of the measurement even if it varies from the prescribed time.
2. Take vital signs in the same order during each sampling time point.
3. If the measurements are late or early due to an unpreventable issue, document exactly why the assessment deviated from the protocol.
4. If you repeat an assessment, document each and every measurement and indicate which measurement you are submitting as the protocol data.
5. Follow protocol instructions exactly. A falsely elevated blood pressure due to the subject being assessed immediately after walking into the room could potentially be categorized as a drug effect and negatively impact study analysis.
6. When vital signs significantly change after dosing, they can be considered an adverse event. Keep in mind that an individual sponsor or protocol may have different thresholds for adverse event reporting. Read the study protocol very carefully but, when in doubt, always ask the sponsor before recording an adverse event for a vital sign reading.
7. If a medical history that contributes to vital sign changes, record the pertinent information in the source document.

A complete list of research-related courses developed by the CTN can be found on the Education page at the CTN website: www.snm.org/clinicaltrials.
IND to enable first-in-man studies using microdosing. This initiative is intended to stimulate the development of both traditional therapeutics as well as imaging agents. Since most imaging agents are administered at the microdose level, this approach has already been utilized to successfully develop new PET tracers. CMS has also fostered the employment of radiotracers through the National Coverage Determination (NCD) mechanism using the Coverage with Evidence Development (CED) pathway. They are also working with the imaging community through NOPR, a national registry that led to further indications for FDG PET. However, the community still needs to have a means of developing some tracers, such as FDG or FLT, as markers of biochemical processes, not disease or indication-specific imaging agents.

PATHWAY FOR THE FUTURE
The FDA identified molecular imaging as one of the key components in the drug development process in the CPI. There are several new radiotracers, for a variety of applications, now in the pipeline, with some already in phase III clinical trials. Within the next five years, FDA approval will be sought for many of these diagnostic agents. It will be interesting to watch as these go forward through the FDA review process. Additionally, CMS is also providing means to cover more molecular imaging agents, and the community is actively working with them to take advantage of this unprecedented avenue. To engage referring physicians and patient advocacy groups, SNM is providing several educational opportunities through the CTN and the Molecular Imaging Center of Excellence highlighting the potential impact that molecular imaging offers to more personalized healthcare.

The incorporation of molecular imaging in clinical trials for new therapeutics offers opportunities to bring more tracers through the approval process. This is one example of how the community must continue to rise and overcome the barriers to success, challenging old paradigms and identifying creative solutions to bring new radiotracers to market.

FDG PET Imaging
Using the summary document developed by the Uniform Protocols for Imaging in Clinical Trials (UPICT) group, we addressed a number of key items and completed review of approximately three-fourths of the proposed topics. The discussion produced agreement on several significant points, including management of diabetic patients, using a minimum fasting time of six hours and setting the target imaging time at 60 minutes (55–75 minutes range). Additionally, blood glucose levels up to 200 mg/dl were considered acceptable, but should be < 150 mg/dl for quantitative studies. Remaining items will be reviewed by e-mail or via conference calls over the months following this meeting. Once all remaining points have been discussed and agreement reached, the final protocol will be organized into a jointly-authored document and submitted for publication in early 2011.

Image Reconstruction
Continued from page 4.

Image Reconstruction
Continued from page 4.

Continued from page 2.
Save the Dates

Be sure to attend “Clinical Trials Network: The Impact Today (AS32B),” presented by Kathy Hunt, MS, CNMT, current president of SNMTS. It is the second part of “The Clinical Impact of Molecular Imaging” session held on Tuesday, November 23, at 10:30 a.m. in Room E350.

Visit the Clinical Trials Network located in the SNM booth at RSNA 2010 and learn how the CTN can help with your research studies. Visit our website: www.snm.org/clinicaltrials for more information.

35th Annual Western Regional SNM Meeting
October 21-23, 2010, Anaheim, CA
Clinical Trials Lectures: Session IV, October 21

Breast Cancer Imaging and Treatment: State of the Art, 2011
April 21–22, 2011, Natcher Auditorium
National Institutes of Health, Bethesda, MD

Multimodality Molecular Imaging of Prostate Cancer Symposium
January 21, 2011, Palm Springs, CA
SNM Mid-Winter Meeting