On December 9, 2009, the U.S. Food and Drug Administration (FDA) issued a regulation (21 CFR Part 212) establishing current Good Manufacturing Practices (cGMP) for positron emission tomography (PET) drugs. All PET drugs, such as $^{18}$F-FDG, $^{18}$F-NaF and $^{13}$N-Ammonia, used in the clinical practice of molecular imaging, regardless of whether they are obtained from a commercial vendor or an academic facility, must be manufactured in compliance with 21 CFR Part 212 by December 12, 2011. The rule requires the submission of a new drug application (NDA) or abbreviated new drug application (ANDA) for any PET drug product marketed for clinical use in the United States. Production of research PET drugs under an Investigational New Drug application (IND) or under the authority of an institutional Radioactive Drug Research Committee (RDRC) may follow either the cGMP regulations 21 CFR Part 212, or the current United States Pharmacopeia (USP) 32nd Edition, General Chapter <823> titled “Radiopharmaceuticals for Positron Emission Tomography–Compounding.”

Since the announcement of the rule, considerable discussion has taken place among molecular imaging societies, including SNM, PET drug manufacturers, and academic institutions, to try and determine what exactly needs to be done before the deadline; however many questions went unanswered. As a result, FDA held a public meeting on March 2, 2011, to discuss the process and other cGMP-related issues. The day-long meeting, “Preparing NDAs or ANDAs for fludeoxyglucose (FDG) F-18 injection, ammonia N-13 injection, and sodium fluoride F-18 injection used in PET imaging,” brought together industry and regulatory professionals at the FDA White Oaks Campus in Silver Spring, Md. Meeting presentations covered drug registration and the general inspection process as well as the following topics:

- Chemistry, Manufacturing and Controls (CMC) – Submission Information for ANDs/NDAs
- Microbiology/Sterility Assurance Information for PET Applications
- PET Products and User Fees
- Submitting PET IND/PET NDA Applications

The complete archived webcast of the meeting is available at http://www.fda.gov/Drugs/NewsEvents/ucm236825.htm

SUBMITTING AN APPLICATION

When submitting applications, the FDA prefers the use of the electronic Common Technical Document (eCTD) format and submission through the agency’s electronic portal. The agency also accepts hybrid applications in .pdf format submitted on CD/DVD; it is recommended that the documents be in...
FDA New Rule for cGMP Continued from page 1.

CTD format with hyperlinks. Paper submissions will also be accepted; however, it is discouraged because of the complexity of handling paper documents. All applications must be validated and accepted for review by the December 12, 2011, deadline. The FDA will allow those facilities that have submitted an ANDA or NDA before this deadline to continue to market and sell their products during the review and approval of their application. Failure of an existing facility to file an ANDA or NDA prior to the December deadline means the facility must stop marketing and selling their PET products until their applications are approved by the FDA, which may take up to three years.


MANUFACTURING FACILITY INSPECTIONS

After the December 12, 2011, deadline for submission of the NDA or ANDA, the FDA will gradually increase the number of inspections of all registered PET facilities to verify conformance with the new Part 212 rule. The agency has indicated special training will be provided to inspectors so they will be familiar with the unique characteristics of PET products and how to inspect Part 212.

CTN, through its Manufacturer’s Registry, works with SNM and the Coalition for PET Drug Approval to keep members informed about PET cGMPs. As the deadline nears, CTN will update its Web site and provide additional support where possible so that clinical trials using PET research drugs will not be interrupted.

Excerpts from JNM Newsline – May 2011: Jeffrey P. Norenberg, PharmD, BCNP, FASHP, FAPhA; Sally Schwarz, MS, BCNP, FAPhA; Henry Van Brocklin, PhD

CTN Relaunches Programs

Molecular imaging is a powerful tool for drug discovery, allowing faster, cheaper, more efficient therapeutic development to speed access to patients. Effectively employing molecular imaging requires expertise and vision to be successful. Research is not handled like clinical practice; specialized training and resources must be provided for imaging to meet required research standards and conformity. CTN has developed programs to facilitate drug development and is now ready to re-introduce the molecular imaging community to our proven resources.

THE EXPERTISE TO GET THE JOB DONE

- Successful scanner validation program to standardize image acquisition in multicenter trials
- Education and training for molecular imaging professionals performing clinical research
- Web-based imaging site and manufacturers registries to facilitate selection of qualified sites and improve access to molecular imaging biomarkers

THE VISION TO GET THE JOB DONE EFFECTIVELY

- Powerful tools and resources that have never existed before
- A novel pathway to access centralized molecular imaging biomarkers via INDs available for cross-reference for multicenter clinical trials; $^{18}$F-FLT is currently available and in use
- Unique partnerships with key groups, such as Uniform Protocols for Imaging in Clinical Trials, to enhance the use of molecular imaging biomarkers

RESULTS YOU CAN TRUST

- In multicenter clinical trials, CTN is the key to:
  - Faster study start-ups
  - Higher-quality imaging
  - Fewer queries
  - Better data

Annual Meeting Highlights

CTN CATEGORICAL
Molecular Imaging in Clinical Trials
7:30 am – 4:15 pm
Saturday, June 4 • Room 212AB

CMIIT CATEGORICAL
Lost and Found in Translation: Developing Molecular Diagnostics and Therapeutics for Human Use.
7:30 am – 4:15 pm
Saturday, June 4 • Room 209

CTN SESSIONS
Implementing Imaging in Clinical Trials and Update on PET Radiopharmaceuticals
10:00 – 11:30 am
Monday, June 6 • Room 217C

Standardization in Clinical Trials
8:00 – 9:30 am
Tuesday, June 7 • Room 217C

SNMTS RESEARCH SESSION
Research, Regulations and Policies - Why Nuclear Medicine Technologists are Essential!
2:30 – 4:00 pm • Room 203B
Sunday, June 5
The National Comprehensive Cancer Network (NCCN®) and SNM, in March 2011, announced a collaboration to advance research for cancer imaging and therapies. Through its Oncology Research Program (ORP), NCCN obtains funding to support clinical trials at their 21 NCCN Member Institutions. As a new initiative of the ORP, the NCCN Specialized Imaging Research Consortium™ (SIRC) aims to advance the treatment of patients with cancer through the clinical application of specialized imaging technologies. SNM’s CTN will lend its experience and proven programs to work with NCCN in qualifying designated imaging facilities that support their member institutions.

It is well known that using molecular imaging agents in multicenter clinical trials has been problematic partially due to a lack of qualified imaging sites and image standardization. Since its inception, the CTN’s goal has been to facilitate the use of molecular imaging biomarkers in clinical trials, with standardization of images being the key objective. To this end, CTN relies on the expertise of its Site Qualification and Monitoring Committee and Scanner Validation Phantom Program to ensure that high-quality imaging is conducted in clinical trials. Both NCCN and the CTN recognize that achieving this goal is only possible through education and training of molecular imaging professionals performing the clinical research imaging.

“As personalized medicine continues to emerge rapidly as a major force in health care, the research questions answered by studies conducted through the SIRC will be invaluable to patients,” said Diane Paul, MS, RN, vice president of the NCCN Oncology Research Program. “We are pleased to collaborate with SNM as we embrace our mission to improve the quality and effectiveness of care provided to patients with cancer.”

CTN’s collaboration with the NCCN is a key opportunity to help advance imaging in oncology research and will serve as an integral step in filling a gap in molecular imaging research. This joint endeavor is a positive step forward in promoting standardization in imaging, and the CTN is honored to be working with an organization of such high-caliber reputation. Its ongoing efforts and standing in improving the quality, effectiveness, and efficiency of oncology practice so patients can live better lives is a priority for the entire research community.

See press release “National Comprehensive Cancer Network and Society of Nuclear Medicine Join to Advance Oncology Imaging Research” (March 8, 2011)
Proposed Collaboration with the Japanese Society of Nuclear Medicine

Peter S. Conti, MD, PhD

CTN and the Japanese Society of Nuclear Medicine (J-SNM), in conjunction with the National Institute of Radiological Sciences, are considering a joint collaboration to promote standardization and harmonization using PET imaging biomarkers in multicenter clinical trials in Japan. Over the past year, Dr. Chieko Kurihara, on behalf of the interested Japanese groups, and CTN leadership have been discussing methods to help establish a structure within Japan that provides image standardization and manufacturing regulatory oversight.

A key item to furthering this effort is encouraging imaging and manufacturing sites to register in the CTN database and undergo the appropriate qualification requirements. The incentive for sites is they will be able to participate in global clinical studies using PET imaging biomarkers, not just those performed within Japan by Japanese companies. To help prepare the imaging sites, CTN could assist by providing Japan with several of the CTN chest oncology phantoms and provide training and supervision of the image review. Additionally, discussion has included a potential SNM/CTN half-day session at J-SNM 2012 with topics covering clinical research imaging, PET cGMPs and audits, and standardized imaging protocols. Based on these initial discussions, we all recognize the merits of such a union and look forward to working together on this important project. The group will meet at the SNM 2011 Annual Meeting to move this initiative forward.

Working with CTN: An Imaging CRO Perspective

Neil Stoddart
Project Manager, ICON Medical Imaging

ICON Medical Imaging (IMI) and CTN were contracted by a pharmaceutical partner to work together on an ongoing trial. This collaboration was put in place to help with the qualification of PET/CT cameras and to help improve standardization across each manufacturer’s equipment. The variability of these factors often creates difficulty in obtaining repeatable and reliable image results in a multicenter study. Some benefits IMI expects to gain from the CTN partnership are high-quality imaging, precision and accuracy of imaging statistics, along with efficiencies in site education and a decrease in site queries.

By having CTN pre-qualify sites, we anticipate smoother study execution and an increased level of consistency in patient data. The working relationship between all three companies has been seamless to date. IMI looks forward to the continued interactions and completing a successful trial.

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In the NEWS

Coalition for PET Drug Approval

Jenny Keppler, MBA, President, ImaginAb, Inc.

On December 10, 2009, the U.S. Food and Drug Administration (FDA) published 21 CFR Part 212 (current Good Manufacturing Practice requirements for PET drugs) which applies to all producers of PET drugs—academic institutions as well as commercial manufacturers. The rule requires that producers of PET drugs for clinical use complete the following prior to December 12, 2011:

• Register as a drug establishment
• File a new drug application (NDA) or abbreviated new drug applications (ANDA) for FDG, NH3 and NaF
• File investigational new drug (IND) applications for any other PET compounds, including those with a monograph in the U.S. Pharmacopeia (USP)

Meeting the new requirements and navigating the FDA system has been problematic for academic as well as commercial producers of FDG. In November 2010, SNM took a leadership role in organizing the Coalition for PET Drug Approval. The coalition represents key organizations from the nuclear medicine community and provides a mechanism for them to interact with the FDA about the challenges related to the implementation of the rule and submission of PET NDAs or ANDAs.

If you manufacture FDG, NH3 or NaF for clinical use, email coalitionforpetdrugapproval@snm.org to receive updates or visit www.coalitionforpetdrugapproval.org. The FDA and the coalition continue to address outstanding issues, as well as new ones as they arise, so check the site for ongoing updates.

LIST OF COALITION MEMBERS:
Academy of Molecular Imaging
American Association of Physicists in Medicine
American Pharmacists Association, Nuclear Pharmacy Practice Section
Council on Radionuclides and Radiopharmaceuticals
Medical Imaging & Technology Alliance
National Association of Nuclear Pharmacies
Society for Molecular Imaging
Society of Nuclear Medicine
Society of Radiopharmaceutical Sciences
United Pharmacy Partners, LLC

What’s Happening

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CTN Educational Program

It is well known that research training materials for molecular imaging technologists and investigators are limited. Ample information exists for enhancing clinical practice performance; however, clinical research is very different and requires specialized training. CTN attempts to close that gap by offering a number of options to educate and train molecular imaging personnel on the practice of clinical trials. The curriculum is developed by molecular imaging technologists and investigators experienced in performing multicenter clinical research protocols within the current regulatory framework. The courses, offered both at SNM meetings and through online presentations, are invaluable to ensure that even the very basic elements of research are performed correctly. All courses are approximately 60 minutes in length unless otherwise noted.

CTN COURSE LIST (*CORE COURSE)

CTN101* Source Documentation in Clinical Trials
CTN102* The Language of Clinical Trials
CTN103* Introduction to GCP and 21 CFR 312
CTN104* Adverse Events and Serious Adverse Events
CTN105 Vital Signs, ECG, and Other Physical Measurements in Clinical Trials (30 min)
CTN106* Following the Protocol in Clinical Trials
CTN107 Quality Control for Standardized Clinical Trials
CTN108 The Importance of SOPs in Clinical Trials (30 min)
CTN109 A Close-up Look at the 1572: The Investigator’s Responsibilities in Clinical Trials
CTN110 Pharmacokinetic Sampling: Blood and Urine Collection Techniques (30 min)
CTN111 RECIST and Other Response Measurement Criteria
CTN112 Conflict of Interest: Financial and Otherwise (30 min)
CTN113 Institutional Review Board [IRB] and Review Process
CTN114 Site Inspections: Are You Ready?
CTN115 Phases of Drug Development

CTN Registry Data Entry Tips

The “Administer Personnel” page is the screen used to add imaging staff to the database. Pre-defined positions include: technologist, physicist, physician/investigator, research coordinator, and other. All personnel working on the study should be entered into the database.

To add a new person, click the “Add a Person” button in the top green band. Below the table, a generic list of data fields will open. All fields should be completed; however, those marked with an asterisk (*) MUST be completed to save the page.

Note: If the position box is selected to read “All Positions,” only the generic information is collected, which is helpful if you are entering basic information for others. If the position box has a particular position selected (e.g., technologist), all of the detailed questions for that position will also be available to complete. This is best left to the individual person to complete on their own.

CTN Webinar Schedule 2011

JUNE 23 Identifying and Reporting Adverse and Serious Adverse Events

SPEAKER: Eileen Smith, MBA, CNMT

AUGUST 11 Radiation Risks in Clinical Research: Putting It in Perspective

SPEAKER: John Sunderland, PhD

OCTOBER 13 Obtaining Vital Signs, ECG and Pharmacokinetic Sampling in Research Studies

SPEAKER: Marybeth Devine, BSRT, CNMT

DECEMBER 8 FDG PET – Standardized Protocols for IND

SPEAKER: Jeffrey Yap, PhD

COMING SOON: Check www.snm.org/ctn for updates on the CTN 2012 webinar schedule.
EDUCATION LEADERSHIP TRANSITION
LisaAnn Trembath, MSM, CNMT, CCRA, NCT, FSNMTS

Education is the driver for the CTN Site Orientation Committee, and we are proud of consistently providing high-quality programs for physicians, technologists and other nuclear medicine personnel involved in multicenter clinical trials. The CTN curriculum in presentation format, which started out as technologists helping other technologists learn the “ropes” in research, has developed into one of the most sought after offerings of CTN. Topics include source documentation in clinical trials; following the protocol in clinical trials; quality control for PET imaging in clinical trials; and adverse event reporting. Most of these programs offer CE credit and are recorded in webinar format for access at any time and from anywhere in the world.

As outgoing chair of this committee, I want to express my pleasure in working with so many dedicated individuals during the past two years. Their hard work helped raise the knowledge level and skills of our research colleagues around the world. At the 2011 SNM Annual Meeting, I pass the leadership of the committee and its activity to our new co-chairs, Marybeth Devine, and Raymond Taillefer, both excellent in their own professional fields and as educators. I encourage you to support them and the CTN Site Orientation Committee in their dedication to providing exceptional educational programs for the entire molecular imaging community.

Marybeth Devine, BSRT, CNMT
Lantheus Medical Imaging

Raymond Taillefer, MD
Center Hospitalier de l’Université Montréal

Research Essentials: Following the Protocol

Clinical research can be full of what ifs. What would you do if a study patient arrives two hours late for an image that is supposed to occur 24 +1 hours after the injection? Or if you are supposed to inject 10 mCi of the study drug but there is only 7.5 mCi in the syringe? What would you do if you believed you could get better looking images with higher resolution if you “tweak” the acquisition parameters just a bit?

To be a great clinical research site, the answer must always be to follow the protocol or if you can’t, call the sponsor.

So, what does “protocol” actually mean in the context of research? According to International Conference on Harmonisation Guidelines (E6: Good Clinical Practice): Protocol is a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The U.S. Federal Code Title 21, Part 312, contains a more detailed description of what a protocol must contain:

- A statement of the objectives and purpose of the study
- The criteria for patient inclusion/exclusion
- An estimate of the number of patients to be studied (this is determined by statistical methods)
- A description of the design of the study, which must include a description of the control group (if one is being used) and methods to minimize bias of subjects, investigators and analysts

Following the protocol will minimize deviations and violations, something you should always strive towards. The two terms mean something very different and have varying degrees of affect on the study. A deviation is a variation from processes or procedures defined in a protocol, but does not preclude the overall evaluable of subject nor affect the safety of subject, whereas a violation is a significant departure from processes or procedure that may affect the evaluability of the data.

Nothing is worse than asking a patient to give their time to a study, often when they are physically or emotionally compromised, and then have the data thrown out because the protocol was not followed.

Tech Tip

KNOW THE DETAILS
Deb Gibbs, MEd, PET, CNMT

When presented with a new clinical trial, it’s a great idea to produce a teaching video or PowerPoint to ensure each step is followed in the proper sequence. This is a great way to streamline staff questions before actually starting the trial. Beginning with quality control of the phantom through patient procedures, your staff will easily overcome intimidation by demonstrating the required methods. The PowerPoint or video may also serve as documentation for staff CEU purposes as well as your institution’s accreditation documentation. Don’t get caught by the devil in the details!
SNM/CTN Outreach

CTN’s mission to facilitate the use of molecular imaging biomarkers in clinical trials includes participating in meetings that reach outside of our own molecular imaging community. We are pleased to be part of the following two symposia.

AMERICAN SOCIETY OF CLINICAL ONCOLOGY
ANNUAL MEETING 2011
Date/Time: June 3, 3:30 – 4:45 pm
Title: Molecular Imaging in Cancer Clinical Trials
Speakers: David Mankoff, MD, PhD, and Anthony Shields, MD, PhD

WORLD PHARMA CONGRESS
Date/Time: June 9, 9 am
Title: Molecular Imaging in Clinical Trials: Advancing Drug Development
Speakers: Peter S. Conti MD, PhD

DRUG INFORMATION ASSOCIATION
ANNUAL MEETING 2011
Date/Time: June 22, 10:00 – 11:30 am
Title: Quantitative PET Imaging with F-18 FDG and F-18 FLT: Using Imaging Biomarkers in Multicenter Clinical Trials
Speaker: Peter S. Conti, MD, PhD

Meet our CTN Intern and Fellow

**CTN PET FELLOW**
**AARTI KAUSHIK, MD**

The SNM PET Fellow for the 2011/2012 academic year is Dr. Aarti Kaushik, a nuclear medicine fellow at the University of Southern California in Los Angeles. As the PET fellow, she will be instrumental in helping develop a course for residents and fellows on performing clinical research using PET imaging biomarkers. Dr. Kaushik will also assist CTN on projects related to PET imaging and clinical research during this year of fellowship.

**CTN INTERN**
**XIAOFEI WANG, MD, PHD**

SNM has had an intern program for Councils and Centers in place since 2009. The purpose of the internship program is to identify and train future leaders of SNM in the structure, governance, and operations of the organization and ensure effective leadership that advances the mission and goals of the organization. This year, CTN was fortunate to be able to select one of these candidates, Xiaofei Wang, MD, PhD, who will serve as an intern of the Center for 2011-2013. Dr. Wang is currently a resident in nuclear medicine at Johns Hopkins University and is excited to expand his training to include PET imaging in clinical trials.
Save the Dates

**Society of Radiopharmaceutical Sciences**
August 28 – September 2, 2011 • Amsterdam, The Netherlands

**CMOD – Critical Markers of Disease**
September 12 – 13, 2011 • Bethesda, MD

**SNM Nuclear Medicine Week**
October 2 – 8, 2011 • www.snm.org/nmw

**AACR-NCI-EORTC: Molecular Targets and Cancer Therapeutics**
November 12 – 16, 2011 • San Francisco, CA

**RSNA 97th Scientific Assembly and Annual Meeting**
November 27 – December 2, 2011 • Chicago, IL

**SNM Mid-Winter Meeting**
January 26 – 29, 2012 • Orlando, FL

**Multimodality Cardiovascular Molecular Imaging Symposium**
April 19 – 21, 2012 • NIH, Bethesda, MD

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

CTN Web Site: **New and Improved!**
Check out our new look and enhanced information on imaging in research trials at [www.snm.org/ctn](http://www.snm.org/ctn).