Do You Need an IND?

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An investigational new drug (IND) application is a request for authorization from the U.S. Food and Drug Administration (FDA) to administer an investigational drug to humans and be exempt from a law that prohibits transport of unapproved drugs across state lines. An approved drug is a drug with an approved marketing application (new drug application [NDA], abbreviated NDA [ANDA], or biological license application [BLA]). INDs are intended to help protect study subjects’ rights and minimize the risks to subjects and are used to study investigational drugs including diagnostic radiopharmaceuticals (DRs). Considerations regarding the IND requirement determination for DRs are described below.

What is an investigational DR?
An investigational DR is any unapproved DR used in a clinical study or research project or an approved DR used in a clinical study of an unapproved use of the drug.

In the practice of medicine, an approved DR may be used for unapproved purposes (i.e., “off label”); in this situation, the DR is not an investigational drug since the “off label” use is not part of a study or research project.

First, are you dealing with an investigational DR?
No IND is necessary if an approved DR is used for its approved purpose or in an “off label” manner in clinical practice. DRs used in these situations are not investigational drugs.

If the DR is not approved, then it is an investigational DR and it needs to be a component of either a research project or a clinical study. An approved DR used in a study to establish efficacy and/or safety of its unapproved use is also an investigational DR.

Next, is the investigational DR to be used in a research project or a clinical study?
A Radioactive Drug Research Committee (RDRC) can approve certain research projects involving investigational DRs if certain criteria (21 CFR 361.1) are met. An IND is not needed once RDRC approval is obtained for the project.

If RDRC approval is not applicable or is not obtained, then the sponsor must submit an IND or determine that the proposed clinical study is exempt from IND submission (criteria in 21 CFR 312.2). Consideration for exemption from IND submission applies only to approved DRs or those in the special consideration category outlined below.

If your study requires an IND application, you may submit an exploratory IND rather than a traditional IND if certain criteria are met.

What about the special considerations for PET drugs?
Some unapproved PET drugs may be used in the clinical practice of medicine or in clinical studies even though they are not approved and they are not the subject of an IND—these are the special considerations for certain PET drugs.

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These special considerations relate to the FDA’s phased-in approach to the submission and approval of marketing applications and INDs for PET drugs that had been used in clinical practice or clinical studies initiated prior to June 12, 2012. The FDA previously gave notice that, by June 12, 2012, an NDA, ANDA or IND must be submitted to support the use of any unapproved PET drug in clinical practice or in a clinical study. The FDA is allowing continued use of these drugs during review of the submissions. Consequently, if a marketing application has been submitted to the FDA, then these unapproved PET drugs may continue to be administered to patients for clinical purposes and the drugs may also be regarded as “lawfully marketed” such that their use in a clinical study can be considered for exemption from IND expectations. These special considerations for certain PET drugs apply through December 12, 2015.2

Are two INDs needed if the investigational DR is part of a study of an investigational therapeutic drug?

No. Information about the DR may be submitted to the therapeutic drug IND. If there is a separate IND for the DR, then the sponsor of the DR IND is responsible for reporting suspected adverse reactions for the DR to the DR IND and to the sponsor of the therapeutic drug IND who then reports all suspected adverse reactions from the entire study to the FDA.

Where can I get more information about INDs, including expanded access INDs and charging for an investigational DR?

All the preceding information is described in greater detail in currently available FDA communications. The IND webpage (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm) can be found by searching for “IND application” at www.fda.gov. The PET webpage (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm085783.htm), a particularly convenient source of information which can be found by searching for “PET manufacturing” at www.fda.gov, includes a link to an FDA guidance document3 which describes criteria for expanded access INDs and charging.

References

Message from the Co-Chairs: JSNM & SNMMI: Collaboration Becomes Official

Michael Graham, PhD, MD, and John Hoffman, MD

A unique partnership between the Japanese Society of Nuclear Medicine’s (JSNM) Molecular Imaging Strategic Committee (MISC) and SNMMI’s CTN became official when representatives from the two groups signed a proposal of collaboration during a special meeting held June 28, 2012, at the SNMMI Annual Meeting in Miami Beach, Fla. This collaboration supports activity to promote the participation of Japanese sites in global therapeutic clinical trials using PET imaging and provides informative support to Japanese PET centers (imaging and/or radiopharmaceutical production). The key elements of this collaboration include:

- Ongoing communication regarding optimizing the conduct of efficient and effective domestic and/or international multicenter clinical trials,
- Information exchange on PET drug regulations that exist in the United States and Japan to promote overall standardization,
- Continued development of standardized biomarker imaging protocols in which all research populations are represented and differing intrinsic and extrinsic factors are considered, and
- Promotion of ongoing collaboration with international clinical trials groups.

“As the first step in confirming this collaboration, we will continue to hold closed and open meetings, both in the United States and in Japan, to reinforce our goal in facilitating global clinical trials using PET for the benefit of public health,” said Michio Senda, MD, president of the JSNM MISC.

This is a major step in an international effort to promote standardization of PET imaging in clinical trials and to move the development and use of PET imaging biomarkers forward.

CTN Numbers at a Glance

- 207 Validated PET/CT Scanners
- 144 Sites with Validated PET/CT Scanners
- 29 Fully Qualified Sites
- 24 Countries Represented in the CTN Registries
- 355 Registered Sites in the CTN Database
Amyloid deposition is a hallmark of brain changes seen in Alzheimer’s disease (AD). Initial development of C-11 Pittsburgh Compound B (PIB) by William Klunk, MD, PhD, and Chester Mathis, PhD, of the University of Pittsburgh, has been translated to worldwide applications in dementia research. Their work unveiled how amyloid deposition occurs in the course of the disease, how this information can be used in potential diagnostic workup and how amyloid deposition can be altered by targeted therapeutic approaches. Through their efforts and enthusiasm, academia and industry moved forward in developing F-18-radiolabeled compounds to further investigate their value in dementia-related diseases. An F-18 labeled tracer, [F-18]FDDNP, was developed by Jorge Barrio, PhD (University of California, Los Angeles) and demonstrated increased brain uptake in patients with mild cognitive impairment before clinical onset of dementia, indicating preclinical evidence of amyloid and tau pathologies. Another compound, F-18-florbetapir, was initially investigated by Hank Kung, PhD, at the University of Pennsylvania, and then later developed by Lilly/Avid Pharmaceuticals as AV-45. The tracer is currently distributed through PETNET Solutions and Cardinal Health in the United States.

F-18-AV-45 (Amyvid™) received approval for PET imaging of beta-amyloid neuritic plaques from the U.S. Food and Drug Administration (FDA) in April 2012 and a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in Europe in October 2012. Per FDA approval, negative amyloid PET indicates sparse to no amyloid plaques—inconsistent with a neuropathological diagnosis of AD—and reduces the likelihood that a patient’s cognitive impairment is due to AD. Positive amyloid PET indicates that moderate to frequent amyloid plaques are present—the amount of amyloid plaques typically seen in patients with Alzheimer’s disease—but a similar amount of amyloid plaques may also be present in patients with other neurologic conditions and even in older people with normal cognition.

The FDA approval emphasizes that amyloid PET is an adjunct to other diagnostic evaluations, and a positive amyloid PET does not establish a diagnosis of AD. While determination for clinical reimbursement is currently under review by the U.S. Centers for Medicare and Medicaid Services (CMS), the tracer has already been used for investigational research and in clinical trials as diagnostic and surrogate biomarkers. SNMMI is currently working on various activities to support amyloid PET, including the development of the appropriate use criteria in collaboration with the Alzheimer’s Association; a procedure guideline for amyloid PET imaging in collaboration with the European Association of Nuclear Medicine; the development of an amyloid PET imaging learning module; and increased patient awareness with the SNMMI Brain Imaging Outreach Working Group.

Figure 1. In negative scans, gray matter shows less cortical radioactivity than does the adjacent white matter, preserving clear borders between the two areas. In positive scans, gray-white matter contrast drops, and cortical radioactivity is more similar—or even exceeds—that of the nearby white matter. (Image credit: Eli Lilly and Company)

Figure 2. Amyvid™ is a sterile, non-pyrogenic radioactive diagnostic agent for intravenous injection and has a half-life of 109.77 minutes. The clear, colorless solution is supplied ready to use in 10 mL, 30 mL, or 50 mL multidose vials containing 500-1900 MBq/mL F-18-florbetapir. Chemically, it is described as (E)-4-(2-(6-(2-(2-[18F]fluoroethoxy)ethoxy)ethoxy)pyridine3-yl)(vinyl)-N-methylbenzamine, and its molecular weight is 359.4. (http://www.amyvid.com, http://pubchem.ncbi.nlm.nih.gov/)
CTN and SNMMI Have Strong Presence at Japanese Symposium

SNMMI president, Frederic Fahey, DSc, FACR, FAAPM, Satoshi Minoshima, MD, PhD, and Jeffrey Yap, PhD, all attended the International Symposium on PET Clinical Trials at the 52nd Annual Meeting of the Japanese Society of Nuclear Medicine (JSNM) in Sapporo, Japan. This session, which took place on October 12, 2012, was very well attended and the conference president, Nagara Tamaki, MD, PhD, as well as symposium organizers, Tomio Inoue, MD (JSNM president), Jun Hatazawa, MD, PhD, and Michio Senda, MD, were most impressed.

Dr. Yap gave a remarkable presentation on the CTN and clinical trial methodology, as well as an informative update on recent changes in U.S. PET drug regulations. He then presented an additional lecture at the University of Yokohama hosted by Dr. Inoue and Hiroshi Watanabe (JSNMT president). Drs. Fahey and Minoshima also attended a lunch with JSNM leadership and discussed ideas for strengthening the alliance between JSNM and SNMMI. The goals of the symposium and additional discussions were to harmonize the use of quantitative PET imaging to increase utilization of imaging in clinical trials in Japan, as well as promote the inclusion of Japan in global multicenter therapy trials. Despite the common goals, there are differences in quality assurance processes and regulatory requirements between Japan and the United States. For example, the regulation of radiopharmaceutical production in Japan is through the approval of synthesis devices rather than approval of processes and testing of final product.

This successful event is just one step forward in facilitating the CTN globalization of standardizing PET imaging trials and strengthening the SNMMI/CTN and JSNM ongoing relationship. Further collaborations are planned for 2013. (See page 2: JSNM & SNMMI: Collaboration Becomes Official)

CTN Coordinating Five-Year NCI-sponsored PET Reconstruction Harmonization Project

The National Cancer Institute (NCI) recently announced the funding of a $2.6 million initiative to identify optimized and harmonized PET reconstructions for use in cancer clinical trials. The research project is being spearheaded by the PET physics teams at the Universities of Iowa, Washington and Pennsylvania and has active participation from physicists at Siemens, GE and Philips. CTN, which spawned this project two years ago, will continue to play a central coordinating role over the five-year duration of the project.

Medical imaging, in general, and PET, in particular, are playing increasingly important roles in clinical trials. However, variability associated with quantitative aspects of imaging has been a target of criticism by federal regulators reviewing results of these studies. This project aims to identify reconstruction parameters specific to each of the current generation scanners from the three major vendors that will result in optimal images with quantitatively identical performances for use exclusively within the context of clinical trials. The vision is to have the clinical trial-specific reconstruction parameter set pre-loaded into the vendor’s commercial software offering for each scanner model. Sites will still be able to use their preferred reconstructions for their clinical work, but can access the clinical trial parameter set when quantitation is necessary for multicenter trials.

This research team is coordinating its work with other national and international organizations that are grappling with other image quantitation issues. These organizations include the American College of Radiology Imaging Network, Quantitative Imaging Biomarkers Alliance, the European Association of Nuclear Medicine, American Association of Physicists in Medicine and the NCI’s own Quantitative Imaging Network.

Dr. John Sunderland (Iowa) is lead investigator on this project, and the CTN is coordinating study activities including image storage and data management.
CTN Collaborates on Two Unique CE Sessions

CTN is pleased to collaborate with the SNMMI-TS once again to provide technologists with excellent presentations at the SNMMI 2013 Mid-Winter Meeting that can augment knowledge and enhance skills. In the first session, experts in PET imaging will discuss topics such as resolving artifacts in PET imaging, what impacts SUV measurements and tips to improve imaging in research. The session will take place on Saturday, January 26, from 8:00 am to 12:15 pm.

The second session joins CTN and the SNMMI Radiopharmaceutical Sciences Council in providing updates from the U.S. Food and Drug Administration, commercial entities and academic facilities Part 212 regulations, investigational new drug submissions and inspections. Join CTN on Friday, January 25, from 1:00 to 5:00 pm, to find out what has been happening since Part 212 became a rule.

Don’t miss these outstanding sessions!

Clinical Trials Network
2013 WEBINAR SERIES

FEBRUARY 14
The UPICT FDG-PET Protocol: Progress and Updates

APRIL 11
AEs and the 1572: What Imaging Professionals Need to Know

JUNE 20
PET QC: Optimizing Scanner Performance

AUGUST 8
RECIST and Other Tumor Response Measurement Criteria

OCTOBER 17
Optimizing Amyloid Imaging in Research

DECEMBER 12
Artifacts in PET Imaging: Examples and Explanations

For more information on the webinar series, please visit www.snmmi.org/ctn.

Department of Defense Prostate Cancer Imaging Grant Submitted

Four academic sites, in concert with CTN, collaborated on a Department of Defense grant submission in August 2012 under its Biomarker Imaging Award - Prostate Cancer Research Program. The proposed study’s primary objective is to have anti-F-18-FACBC approved for clinical use in identifying lymph node involvement in prostate cancer patients. Michael Graham, PhD, MD, is the study’s principal investigator, and sites include the University of Iowa, University of Utah, Washington University and Emory University. The maximum performance period is three years with total direct costs of over $2 million awarded for the entire period. Representatives from sites with the top proposals selected from 15 semi-finalists will give oral presentations in Washington, DC, in January 2013.

CTN Successful at Drug Information Association 2012 Annual Meeting

For the second year in a row, CTN was given the opportunity to present a 30-minute session on PET imaging biomarkers in clinical research at the Drug Information Association (DIA) 2012 Annual Meeting. This year, CTN’s presentation, “Quantitative PET Imaging with F-18 FDG and F-18 FLT: Using Imaging Biomarkers in Multicenter Clinical Trials,” was the first part of the three session track on novel imaging techniques held on June 26, 2012.

The presentation was well-received by approximately 20 attendees; half of whom submitted evaluations with excellent scores. In fact, it was suggested that a full session on biomarker detection techniques be offered at the DIA 2013 Annual Meeting. Based on this, and other attendee comments, CTN is collaborating with SNMMI’s Center for Molecular Imaging Innovation and Translation (CMIIT) to present a full 90-minute session in 2013 (see page 8).

In addition to this successful presentation, CTN sponsored a booth where staff answered questions and spoke with interested parties on possible future collaborations.
Tech Talk:
Strength in Numbers

Marybeth Devine, CNMT, and Kathleen Krisak, CNMT, FSNMMI-TS

Molecular imaging plays a major role in many clinical trials, especially in oncology. More and more nuclear medicine technologists (NMTs) are becoming involved in research, yet are often not properly trained on the nuances and regulations that go along with it. In June 2012, at the SNMMI Annual Meeting in Miami Beach, Fla., CTN and the SNMMI-TS collaborated on a full-day categorical that educated attendees on the unique characteristics involved with clinical research and molecular imaging. The morning panel presented personal experiences in incorporating their nuclear medicine technology training into other PET imaging-related careers, and provided helpful tips for those interested in transitioning to other positions. We were also fortunate to have a representative from the Society of Clinical Research Associates who has worked with NMTs in the research arena to discuss how becoming a research coordinator can be a novel career option for some NMTs. Experts in PET image acquisition, quality control and the drug development process shared important tips and guidelines to follow when NMTs become involved in research.

CTN and the SNMMI-TS continue to collaborate on continuing education sessions and other ventures to unify their efforts and investigate ways that we, as a joint force, can assist our technologists and, therefore, provide benefit the molecular imaging community as whole.

Research Essentials:
PK and Biodistribution Sampling in Imaging Trials

Excerpt from CTN 110 course

Pharmacokinetics (PK) is the activity of drugs in the body over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues and excreted. In clinical research—especially in Phase I and II studies—PK sampling is a crucial part of testing the safety of an investigational agent or drug. Knowledge of basic hematolgy is important, including the following:

- Whole blood clots in two to five minutes,
- Ethylenediaminetetraacetic acid (or EDTA) is a colorless compound used to keep blood samples from clotting before tests are run,
- Serum is blood plasma minus clotting components, and
- Serum and plasma samples are usually frozen in cryotubes while awaiting analysis.

Along with PK sampling, biodistribution in imaging studies is also often recorded. Biodistribution involves measuring whole blood, plasma or urine to determine radioactive levels at specific times, post-injection. A volumetric pipette is used for radiologic biodistribution where radioactivity is measured “per mL.” Samples are counted in gamma or well counters, often used in combination with imaging to determine the radioactive dose distribution.

When imaging protocols ask for biodistribution samples, PK samples or both, ensure that your site has the required laboratory equipment and supplies before doing the first study patient. Carefully read the protocol requirements and contact the sponsor with any questions. For each sampling time, draw the specimens in the same order, even if tube color is the same, and record the precise time the sample is drawn (not the protocol-defined sample time).

Finally, always follow universal precautions for venipuncture safety!

Obtaining blood samples during research imaging is a team effort!
Academic investigators in the United States hold multiple INDs for investigational and limited clinical use radiopharmaceuticals, many of which have no potential for commercialization. Some have no intellectual property rights, many are too short-lived for distribution (e.g., C-11) and others have such narrow clinical application that the substantial investment required for a new drug application (NDA) could never be recouped. There are also some radiopharmaceuticals considered “intermediate” (regarding potential use) but not sufficient to justify an NDA. However, these could possibly be viable for a commercial entity to manufacture the isotope or radiopharmaceutical, a precursor or a kit, and submit a drug master file (DMF). In recognition of this situation, the FDA has issued a draft guidance1 that details what to submit for expanded access INDs for PET drugs used in clinical care and how to apply for permission to charge for them.2

Many investigators hold, or wish to hold, INDs for the same compounds (e.g., F-18-DOPA, C-11-acetate). Each must submit their own IND containing all the required information. Some of this information is site-specific, such as the chemistry, manufacturing and control (CMC) section and the site clinical protocol. But much of the information for INDs for the same compound is identical, such as the pharmacology/toxicology, animal and/or human dosimetry and previous human exposure. If adequate studies cannot be accessed from the literature, they must be duplicated, which is a waste of time, money and the lives of laboratory animals.

“Shared” INDs

An approach to streamline filing for an IND has been called “shared” INDs. This approach uses right of reference letters to existing INDs or DMFs that are already active at the FDA; the IND itself is not actually shared. A right of reference letter (also called a letter of authorization or cross-file letter) instructs the FDA to include all the sections authorized in the letter from an existing IND or DMF in the new IND for the same drug. For example, Dr. Smith at Upstate University provides a letter to Dr. Jones at Downstate University that permits reference to the pharmacology, toxicology, dosimetry and previous human exposure data but not the CMC information in her IND for F-18-drugA. Dr. Smith submits a copy of this right of reference letter to the FDA for her IND. When Dr. Jones submits his IND for the same drug, he includes this letter and, in each of the required IND sections covered under this letter, he refers the FDA reviewers to the letter. Note the following important points:

1. No actual data are transferred. Dr. Jones has no knowledge of the actual contents that have been referenced unless Dr. Smith gives him some or all of it separately.
2. Even if the data are transferred, he does not submit them with his new IND.
3. The original IND holder, Dr. Smith, has no responsibility whatsoever for what Dr. Jones does in his clinical studies. She does not need to monitor his trials nor report his adverse events in her annual reports.
4. The new IND holder, Dr. Jones, does not need to inform Dr. Smith about his plans or results; however, they can choose to collaborate.
5. The same points apply to a right of reference letter to a DMF from a manufacturer of a kit, a precursor, an isotope, or any other item that is sourced from outside the IND institution.

The process of using the right of reference letter has several advantages. First, duplication of expensive animal studies is avoided. Second, the actual IND application is much simpler to prepare and submit. Third, the originators of the required data can share the regulatory use of the data without actually sharing the data if they prefer to hold it confidential.3 Finally, less obvious but very important, both the IND submitter and the FDA have increased confidence levels in the project. Both the submitter and the reviewers know that FDA has already reviewed the referenced sections over the lifetime existence of the original IND and found the data acceptable. That means that both can concentrate their efforts on what is different about this new IND: the clinical setting and, often, the CMC.

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**Tech Tip**

ADME is an acronym in pharmacokinetics/pharmacology that describes the disposition of a pharmaceutical compound within an organism.

- **A bsorption**: the process of a substance entering the blood circulation
- **D istribution**: the dispersion or dissemination of substances throughout the fluids and tissues of the body
- **M etabolism**: the irreversible transformation of parent compounds into daughter metabolites
- **E xcretion**: the removal of the substances from the body

These four criteria influence levels and kinetics of drug exposure to the tissues, therefore influencing the performance and pharmacological activity of the compound as a drug.

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Continued on page 8. See Special FEATURE.
Effectively employed, molecular imaging can speed development of a therapeutic agent, saving pharmaceutical companies millions of dollars and significant time in bringing a drug to market. As such, CTN and SNMMI Center for Molecular Imaging Innovation and Translation (CMIIT) joined forces to submit an abstract to the Drug Information Association (DIA) for a 90-minute session at its Annual Meeting taking place June 23-27, 2013, in Boston, Mass. Titled “Molecular Imaging: Utilizing it as an Effective Drug Development Tool,” the abstract was accepted as proposed, and final speakers have been confirmed.

Three 30-minute talks will illustrate the unique process of bringing molecular imaging agents into the clinical space. Jonathan McConathy, MD, PhD, will discuss what is involved when trying to identify and develop a molecular imaging probe, the first step in drug development. The second talk, presented by Todd Peterson, PhD, relates to in-vivo preclinical molecular imaging and how it supports therapeutic drug development. Lastly, Jeffrey Yap, PhD, will finish up the session describing the design and implementation of molecular imaging endpoints in multicenter therapeutic drug trials. Join us for this novel and informative session at the DIA 2013 Annual Meeting.

As our kindergarten teachers told us long ago, we all just need to share! Our clinical research and, ultimately, our patients will be the better for it. Feel free to contact me at jacobsp@mail.nih.gov.

References
2. Expanded access INDs and authorization to charge for investigational drugs are not limited to PET drugs.
3. Information that should be shared for the good of our community is the QC specifications; patient data can be combined for analysis between sites only if the drug is the same in quality.