Part II FDA Involvement in PET: Help or Hindrance?

As PET gains widespread acceptance in the clinical world, it must face regulatory and reimbursement hurdles. How will PET adapt to these new realities?

Up until a few years ago, the PET community dealt largely with the world of research: how to get funding for a new study; how to radiolabel particular ligands; where to publish the latest results. Although still dealing with these issues, the community is now facing the realities of the clinical world. Physicians and hospitals must reconcile offering these clinically valuable studies with little chance of reimbursement by insurance companies and Medicare. Reimbursement issues have been thrust into the spotlight as PET enters more and more hospitals due to the advent of SPECT-PET.

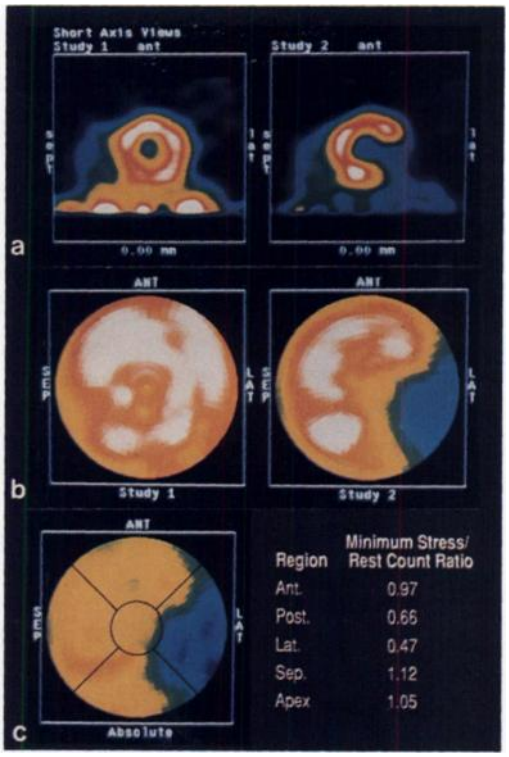
"We now need to approach managed care providers and inform them about the accuracy of PET and how PET can save them money over standard surgeries," said Richard L. Wahl, MD, director of general nuclear imaging at the University of Michigan in Ann Arbor. "We're also trying to get Medicare to reimburse for PET, which is tied into regulations from the Food and Drug Administration (FDA)." New FDA regulations concerning the production and use of PET radiopharmaceuticals have been a nightmare for many PET facilities. On the other hand, reimbursements for PET have been more forthcoming. Whether revenue from reimbursements will justify the increased costs of regulations remains to be seen.

FDA Regulation of PET Facilities

Although radiopharmaceuticals have been regulated by the FDA for decades, PET radiopharmaceuticals with their extremely short half-lives were not under FDA regulation when they were introduced in the 1980s. PET facilities were free of FDA regulations both in terms of seeking approval for existing imaging agents and investigating promising new agents.

This all changed two years ago when the FDA published a notice in the *Federal Register* forbidding the onsite compounding of PET radiopharmaceuticals. In essence, the FDA had decided that individual PET facilities that compound PET radiopharmaceuticals locally would need to follow the same standards called "Good Manufacturing Practice Guidelines" as large pharmaceutical companies. Even a university lab manufacturing PET tracers for research will now need to meet FDA standards. Moreover, all PET radiopharmaceuticals must be approved by the FDA before they are sold and distributed. Also, any radiolabeled ligands used in clinical trials must now be registered with the FDA as investigational new drugs.

The FDA's move to regulate PET spurred a joint lawsuit filed by Syncor International, the American College of Nuclear Physicians (ACNP), the Society of Nuclear Medicine (SNM) and the American Pharmacy Association against the Department of Health and Human Services. The organizations challenged the FDA's authority to regulate PET tracers. In the lawsuit, Alvin J. Lorman, counsel for the plaintiffs, argued that the FDA overstepped its bounds in setting a new regulation that forbids a procedure central to the practice of radiopharmacy.



—Reprinted from "Detection of Coronary Collaterals Using Dipyridamole PET Myocardial Perfusion Imaging with Rubidium-82" by Garza et al. *J Nucl Med* 1994;38:39–43.

PET myocardial perfusion images. (a) Short-axis tomograms, (b) polar maps and (c) count ratio maps. There is a lateral/inferoposterior perfusion defect with count ratio maps, suggesting collateral circulation blood supply.

Counsel for the FDA argued that PET compounds were always considered new drugs by the FDA and thus were always subject to regulation. The *Federal Register* notice merely reflected a change in policy, not a new regulation, said the FDA counsel. In October 1996, the federal judge presiding over the case ruled in the FDA's favor saying the agency is entitled to regulate PET compounds under the Food, Drug and Cosmetic Act.

On December 13, 1996, Syncor and the other plaintiffs filed a notice of appeal, which the U.S. Court of Appeals probably will not rule on for at least six months, according to Lorman. If the court rules in Syncor's favor, the lawsuit could be resumed. In the meantime, PET facilities must contend with the hoards of paperwork necessary to comply with FDA regulations.

At this point, the FDA has notified the PET community that they should be making changes to come under compliance. In about a month, the FDA

PET community is divided over whether FDA regulation of PET will be a help or a hindrance.

will hold a two-day training seminar to provide specifics on what paperwork will be required to receive an approved application for the manufacturing of PET radiopharmaceuticals. After that, the FDA has said it will begin enforcing regulations, according to Michael McGehee, executive director of the Institute for Clinical PET. The FDA could fine or even shut down PET facilities that do not file the necessary applications.

Optimistic about PET Reimbursement

Somewhat surprisingly, many in the PET community support the FDA's efforts to regulate PET tracers. In fact, Methodist Medical Center in Peoria, IL filed an abbreviated New Drug Application (NDA) with the FDA about three years ago—before the FDA made a formal move to regulate PET. Not supported by research grants or a large university, the PET facility at Methodist relies on reimbursements from its clinical studies to pay for costs. "We felt that the NDA needed to be filed to enhance our prospects for reimbursement," said Carter Young, MD, director of the PET facility at Methodist.

The PET community is divided over whether FDA regulation of PET will be a help or a hindrance. The vast majority of nuclear medicine leaders, including SNM and ACNP leadership, have taken a stand against FDA regulation because it will impose burdensome costs. "A significant minority" of PET leaders, however, have accepted the FDA's role as a necessary nuisance that will lead to reimbursements, said Young. "We figured FDA regulation was inevitable, so we tried to determine a process that would be user-friendly," he said.

This "significant minority" realizes that a nod from the FDA means a nod from the Health Care Financing Administration (HCFA), which controls Medicare reimbursements. Closely intertwined with the FDA, HCFA ties its reimbursement decisions to FDA approval for a specific pharmaceutical or procedure. Since PET facilities never had FDA approval to manufacture radiopharmaceuticals, Medicare reimbursements for PET have been virtually nonexistent. In most states, Medicare will reimburse only for PET using ^{18}F-flurodeoxyglucose (FDG) for the evaluation of epilepsy and for PET using rubidium for cardiac perfusion imaging—the only FDA-approved indications.

"Once enough facilities get FDA approval to distribute and sell FDG, HCFA may adopt the codes for several different PET procedures and begin reimbursing Medicare patients," said Kenneth McKusick, MD, chairman of the SNM Coding and Reimbursement Committee. HCFA frequently waits to adopt CPT codes until the new procedure and drug

Putting PET Cancer Tracers on the Fast Track

With the dark clouds of FDA regulation threatening to slow down the development of new PET tracers, there may be a silver lining: The FDA appears willing to fast track radiopharmaceuticals used in cancer imaging. The Council on Radionuclides and Radiopharmaceuticals, the Society of Nuclear Medicine (SNM), the American College of Nuclear Physicians (ACNP) and the Institute for Clinical PET (ICP) submitted a proposal to the FDA in December to extend the FDA's Cancer Drug Initiative to include diagnostic imaging products. "We had a preliminary meeting with the FDA, and the proposal was generally well received," said David Nichols, associate director of the ACNP/SNM Government Relations Office.

The proposal is based on a "reinventing government" initiative that accelerates the approval of cancer therapies by lowering the requirements for clinical trials and speeding the review time once an application is filed. The current proposal by the nuclear medicine community incorporates many of the same elements in the cancer initiative and applies them to radiopharmaceuticals. The FDA is currently reviewing the proposal and will make a decision within the next few months.

- Evidence of effectiveness: Instead of two controlled clinical trials, the FDA would permit approval based on evidence of effectiveness generated by a single well-controlled trial. In addition, trials could be designed using clinical endpoints other than effectiveness in diagnosing a particular disease (e.g., enhanced visualization or utility in staging a disease). For example, clinical evidence could consist of data showing that an agent localizes in or binds to a particular type of tumor. Following approval, the manufacturer could be required to confirm the effectiveness of the tracer by conducting further studies.
- Evidence of safety: Where the potential for adverse response is low, toxicology studies in limited animal models may be adequate for preclinical evaluations. The requirements for safety assessments should be based on the predicted profile.
- Supplemental applications: Accelerated procedures would be available not only for original applications but also for supplemental applications for new indications. This would ensure that the label of a diagnostic imaging agent accurately conveys information corresponding to the actual uses of the agent in clinical practice.
- Expanded access to agents approved in foreign countries: This program would be similar to the one established to expand access to therapeutic cancer drugs. If a diagnostic imaging agent under study in the U.S. is approved in a foreign country and there is no comparable agent available in the U.S., the FDA would approve expanded access protocols regardless of the length of time the agent has been under investigation in the U.S.

involved have received FDA approval. Although there are codes established for PET myocardial, tumor, and brain imaging, HCFA currently will reimburse only for epilepsy brain imaging, the sole indication for which FDG is approved. Even for this indication, Medicare's reimbursement for PET varies from state to state, with some providing no reimbursement for a test they consider to be experimental.

At a recent meeting, HCFA indicated that it would grant a request to approve coverage for the use of PET in lung cancer, according to Ernest Garcia, PhD, president of the Institute for Clinical PET. HCFA may grant the approval at its September meeting but with the understanding that coverage would only be granted to those facilities that have FDA approval to manufacture FDG.

In essence, the PET community must jump through two hoops. They must get FDG's package insert expanded to include a broad use of indications such as tumor and myocardial imaging. They also must get FDA approval for how they manufacture FDG at their individual facilities.

In terms of expanding FDG's approved uses, the ICP has spent $300,000 on a multicenter trial concerning the use of FDG-PET for lung cancer diagnosis. Results will be submitted to the FDA, and an approved indication could be granted by the end of this year, according to McGehee. Approval of FDG for myocardial imaging and other types of tumor diagnosis could prove to be more difficult. The FDA has rejected previous submissions of review literature by the ICP, citing the need for more data. The trouble is, no one has yet stepped up to fund large trials of FDG—beyond the lung cancer study. In short, Medicare probably would not provide reimbursements for FDG-PET unless it is for an indication that has FDA approval.

The one glimmer of hope lies in a bill that may be introduced in Congress that would require HCFA to reimburse for oncologic PET imaging, regardless of whether the indications have FDA approval. Several senators are currently drafting such legislation which could be introduced within the next year, according to David Nichols, associate director of the ACNP/SNM Government Relations Office.

Jumping through the second hoop may require even more fancy footwork. The FDA wants all PET facilities to meet its standards for good manufacturing practices in order to receive an approved NDA to manufacture FDG. These standards are usually based on decades of data outlining the safest and most efficacious methods for manufacturing and distributing pharmaceuticals. The problem with PET is that it is fairly new. No one method for the manufacture of PET radiopharmaceuticals has been accepted by the PET community as the gold standard. In the case of FDG—the only FDA-approved PET tracer—a facility may use one of several methods to manufacture the imaging agent.

Nevertheless, the FDA is looking for certain standards to ensure that FDG is being produced in a sterile environment. So far, Methodist Medical Center is the only PET facility to have received an approved abbreviated NDA. Built in 1991, the newer facility happened to meet the FDA's good manufacturing practices guidelines. It spent roughly $25,000 on minor equipment changes such as laboratory hoods. Older PET facilities, like the one at the University of Michigan in Ann Arbor, will need to make major upgrades to receive FDA approval. Wahl estimates that Michigan's facility will spend about $200,000 on renovations, which does not factor in costs to perform the extra record-keeping required by the FDA.

Before embarking on these major improvements, facilities may want to first consider alternate approaches to the new regulations. "The FDA made it clear that they would consider petitions from facilities who wish to make modifications to the rules or obtain an exemption," said McGehee.

Success with Private Insurers

Although HCFA will not budge on its refusal to reimburse for procedures that have not received FDA sanctioning, private insurance companies have proven to be more amenable to PET. For years, the ICP has been lobbying payers to reimburse for PET by supplying them with data to support PET's efficacy and cost-effectiveness in comparison to biopsies or unnecessary treatments for metastatic cancer. Indeed, most private insurers will now pay for PET, although some more readily than others.

The Northern California PET Imaging Center in Sacramento manages to get reimbursements for about 70% of patients, according to Ruth Tesar, executive director of the center and vice president of PET-Net Pharmaceutical Services. To get this high reimbursement rate, she spends about one-third of her time discussing reimbursement issues with insurance companies. The center also employs a full-time billing person whose sole job is to obtain coverage from a patient's insurance company. "This is not a passive process," said Tesar. "Each patient requires us to negotiate with the insurance company to get them to pay." To minimize the paperwork and haggling, the Northern California PET Center and other PET centers throughout the country have negotiated contracts with individual insurance companies to get them to uniformly cover PET procedures in patients with specific indications.

The ICP has taken this concept one step further: It has approached several insurance giants in an attempt to get them to cover certain procedures

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at any PET facility throughout the country. The institute recently went to Health Source Provident—which insures 4 million patients through 14 health maintenance organizations—and asked them to uniformly cover PET scans in patients who have solitary pulmonary nodules of undetermined status. (All of these patients routinely undergo surgery even though half have benign nodules.) After reviewing data showing that PET has a high sensitivity for detecting malignant nodules, Health Source decided to provide reimbursements for all its patients. "We're cautiously optimistic that AETNA-US Healthcare, Kaiser Permanente and the United Auto Workers will also follow suit," said McGehee.

Whether PET will achieve true success as a clinical modality will depend on costs. In an article published in *Diagnostic Imaging* (December 1996), Wahl pointed out that various cost-benefit analyses of PET scans for diagnosing or staging various types of cancers all found that PET can lead to significant cost savings. One study from the University of California at Los Angeles found that PET could save $550 per patient over standard diagnostic procedures when used in solitary pulmonary nodule imaging. Another analysis from the Northern California PET Center found that PET changed the surgical management of 34% of colorectal cancer patients, with a savings of $5000 per patient. Although these results are impressive, the key is to convince insurance companies and hospitals that PET can indeed save them money. This will be the determining factor in whether the imaging modality will make the transition from the research lab to the clinical world.

—Deborah Kotz

The Cost of FDA Regulations: An Innovative Solution

Over the past few years, PET facilities have been a financial drain on hospitals and universities that own and operate the cyclotrons with little hope of reimbursements for PET procedures. Recent efforts by the Food and Drug Administration (FDA) to regulate the production of PET tracers threaten to increase operating costs to a staggering amount. Many institutions have considered closing their PET centers rather than spend tens of thousands of dollars to upgrade their facilities to the FDA's standards.

Capitalizing on these monetary difficulties, a new pharmacy network, called PETNet Pharmaceutical Services, may offer some institutions an alternative. PETNet, a limited liability corporation formed six months ago as a joint venture between Syncor and CTI to distribute ^{18}F-deoxyglucose (FDG), is offering to pay for and obtain FDA approval for PET facilities in exchange for using their cyclotrons to produce and sell FDG. "We try to make this a win-win situation," said Ruth Tesar, vice president of marketing for PETNet, which is based in Atlanta. "We do the necessary work to get FDA approval in the form of an aNDA [abbreviated new drug application], and they allow us to sell FDG outside of their institution."

As of presstime, PETNet had signed contracts with 10 sites throughout the country. They are currently negotiating contracts with 8 additional sites and plan to have 25 sites in operation within 3 years, according to Tesar. She stressed that PETNet has "no standardized agreement" with the institutions. For each site, the terms of the contract vary from PETNet owning the cyclotron outright to sharing the responsibilities of managing the cyclotron and lab with the institution. The main components of every contract is that PETNet—staffed with experts in FDA regulations—will obtain an aNDA for the production of FDG in exchange for selling FDG to its customer base. (Since FDG has only a two-hour half-life, PETNet needs access to cyclotrons throughout the country to meet its customers' demands.)

William Beaumont Hospital in Royal Oak, MI is currently negotiating a contract with PETNet to turn over the management of its PET facility in exchange for PETNet assuming all operating costs and upgrades to meet FDA guidelines. Before the prospect of PETNet, the hospital was considering closing its PET facility because of its escalating costs. Under the proposed contract, PETNet will not only sell FDG to its outside customers but to Beaumont Hospital as well (although at a slightly lower price), according to Jack E. Juni, MD, the director of Beaumont's PET Diagnostic Center.

"Our main incentive is to reduce our fixed operating costs," said Juni. He said the costs for the PET facility to come under compliance with the FDA would have been $100,000; this does not include the $50,000 annual costs for paperwork and quality control. PETNet will pick up those costs and will also pay the salary of a radiochemist currently employed by Beaumont who will operate the cyclotron. In addition, PETNet will produce the PET tracers ^{13}N-ammonia, ^{15}O-water, and ^{11}C products free of charge to Beaumont for hospital research studies. "Our operating costs will go down a little, whereas they would have gone up drastically to meet FDA requirements," Juni said. Beaumont's PET facility will still be operating in the red, but it now has a fighting chance for survival.

ERRATUM

In the December 1996 *Newsline* article entitled, "Chernobyl: 10 Years Later," (*J Nucl Med* 1996; 37:27N) David V. Becker's, MD, affiliation was printed incorrectly. Dr. Becker is the professor of radiology and medicine at the New York Hospital-Cornell Medical Center in New York, NY.