

PHYSICIANS PAN FDA PLAN FOR PET

THE U.S. FOOD AND DRUG Administration remains intent on regulating radioactive tracers used in positron emission tomography, or PET scanning, despite assertions from health professionals and medical companies that state regulations are adequate to assure the safety and effectiveness of the products. FDA officials at a March 5 hearing made it clear that some form of federal oversight is inevitable.

At issue in the dispute between regulators, industry groups, and physicians and scientists is the advance of clinical PET in the U.S. health care market. Reimbursement for PET studies hinges on efforts by the FDA to regulate PET radiopharmaceuticals, efforts that have made scant progress in over four years. While many private insurance carriers, including Blue Cross and Blue Shield, are paying for various uses of PET scanning, the government is holding off on reimbursement by Medicare until the FDA approves the radiopharmaceuticals. With over 35 million eligible beneficiaries, Medicare is the single largest payer in the U.S. medical care system.

The reimbursement stalemate has outraged physicians, many of whom attended the recent FDA hearing with the message that thousands of patients with heart disease, brain cancer, and epilepsy who would benefit from PET studies are being denied these services.

The companies that make PET equipment, facing a current sales slump, also were well represented at the hearing at FDA headquarters in Rockville, Maryland. Analysts say the market has dropped off considerably since 1991 when the industry sold \$76.5 million in PET scanners and cyclotrons. But analysts predict that annual equipment sales could exceed \$110 million by 1996 if the industry can overcome regulatory and marketing hurdles.

A few weeks before the hearing, the

FDA released a proposed scheme for regulating PET tracers as "new drugs." The proposal, which has caused consternation in the PET community, would impose the following requirements:

- Filing of New Drug Applications (NDA) or abbreviated NDAs by hospitals and PET centers for every PET tracer used.
- Compliance with Good Manufacturing Practices (GMPs) at PET centers similar to those for drug manufacturers.
- Filing of Investigational New Drug (IND) applications by clinical researchers to conduct trials of unapproved PET tracers.
- Allowance of the use of PET tracers under the auspices of a Radioactive Drug Research Committee (RDRC), but only in basic research on human physiology or biochemistry.
- Filing of separate 510(k) or Pre-Market Approvals for cyclotrons and automated synthesis equipment.

Medical professionals and industry groups are largely united in opposition to the FDA's latest proposal. Not only does the proposal mean hospitals would have to pass GMP inspections, but they might also have to pay drug manufacturers' user fees. The FDA adopted the fees last year to help speed approval of new drugs by passing on to manufacturers the costs of hiring extra reviewers. The FDA hasn't clarified how user fees would be applied to PET centers.

'Death Sentence' for PET

"I think the NDA proposal is a sentence of execution for PET radiopharmaceutical research and development," testified John W. Keyes, Jr. MD, professor of radiology at the Bowman Gray School of Medicine and PET director at North Carolina Baptist Hospital.

Henry N. Wagner, Jr., MD, renowned professor of medicine and radiology at Johns Hopkins University and president of the Institute for Clinical PET (ICP),

told FDA officials that the PET community "agreed unanimously that the end users of positron-emitting radiotracers should not be regulated as drug manufacturers."

Neither Dr. Wagner nor any others who testified before the FDA offered any specific alternatives for regulating PET tracers, evidently because of the lack of a consensus. Clinical experts and industry representatives throughout the meeting referred to Dr. Wagner's recommendation that the FDA appoint a "working group" of agency staff and experts from academic institutions, professional societies, and the public to develop specific recommendations on how the FDA can be assured of the safety and effectiveness of PET tracers. "Such a group would be charged with the development of standards of practice to ensure a high quality product," said Dr. Wagner.

Making the claim that adverse reactions to PET tracer are "largely unknown and unstudied," the FDA's written proposal says the agency considers PET tracers "new drugs" because they are "not generally recognized among qualified experts as safe and effective."

The experts testifying at the hearing, however, overwhelmingly agreed that PET tracers have proven to be remarkably low-risk agents. "Our 25 years of experience have shown that the risks of adverse reactions are non-existent," said Micheal J. Welch, PhD, director of the division of radiation sciences at Washington University's Mallinckrodt Institute of Radiology in St. Louis.

Since 1988, when the FDA began formulating regulations for PET, professional associations and the medical industry have fought hard to minimize the impact of the FDA's efforts. These groups contend that federal jurisdiction is limited to new drugs intended for interstate commerce.

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PET Approval
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Food and Drug officials, however, insist that all clinical PET radiopharmaceuticals are subject to FDA regulation, because agency authority extends to drugs if any ingredient is traded across state lines.

That stance has left PET centers little choice but to work with the agency or go to court. Some fear that if there weren't an attempt to gain FDA approval, the agency could take action against the more than 50 PET centers in the U.S. that currently prepare and inject tracers into patients under the authority of state boards of pharmacy.

In August 1990, the leaders of ICP, a non-profit group representing industry, physicians, and scientists, decided to develop a Drug Master File (DMF) for institutions or companies to refer to when submitting NDAs. The Methodist Medical Center in Peoria, Illinois filed an NDA for fluorine-18-fluorodeoxyglucose, but the hospital has been unable to pass inspection to meet the GMP standards imposed by the FDA.

Now the consensus at most if not all PET centers is that "using the NDA process has proven to be a failed experiment," as Howard J. Dworkin, MD, director of the department of nuclear medicine at William Beaumont Hospital in Troy, Michigan, put it on behalf of the American College of Nuclear Physicians.

"In spite of all the favorable circumstances for FDG, it has taken four years and over half a million dollars and we're still not over the hump," said Dr. Keyes, who represented the American College of Radiology.

To the directors of PET centers and radiopharmacies, one of the most worrisome aspects of the FDA plan is the prospect of inspections for compliance with GMP standards. PET center operators say GMPs are appropriate for large scale pharmaceutical manufacturing, but not hospitals that might make fewer than 10 radiopharmaceutical doses per day. Clinicians involved in PET say they feel

betrayed by assurances from the FDA that GMPs for PET centers would be slackened to account for the differences.

Methodist Medical Center, the first PET center to attempt to pass inspection, was quickly overcome in an avalanche of paperwork. Steven S. Zigler, PhD, operational director of the PET center, says the facility can meet the criteria for aseptic processing, control of raw materials, and other technical challenges, but documentation has become a Herculean task. "The paperwork does not necessarily enhance safety, and it can be a significant burden on a PET center," Dr. Zigler told the regulators. "No single PET center has the resources to put this all together." Application of user fees on top of GMPs, he said, would "kill clinical PET in its tracks."

Standards Not Enough

While the FDA seems unlikely to withdraw entirely its plans to regulate PET, the attendance at the hearing of high-level FDA officials such as Michael Taylor, deputy commissioner for policy suggests that the agency is becoming more responsive to the pleas of PET physicians and companies.

On the other hand, the agency is under a mandate from Congress and consumer groups to respond to at least two deaths last year that resulted from tainted drugs (not radiopharmaceuticals) that were manufactured under the guise of pharmacy compounding.

Thus, regulators remained unsatisfied with arguments that compounding of PET radiotracers for in-house use is adequately covered by state medicine and pharmacy law.

"How can one systematically validate these tracers rather than rely on an ad hoc, practice-of-medicine basis?" asked the FDA's Mr. Taylor.

The professional community claims to already have a "complete regulatory infrastructure to continue to assure the good quality of PET tracers," according to Dr. Dworkin of ACNP. That infrastructure includes USP monographs on FDG, nitrogen-13 ammonia, and fluo-

rine-18 fluorodopa that spell out purity limits, bacterial endotoxin limits, pH ranges, acceptable specific activity and other detailed requirements. And thorough standards for compounding PET tracers written by the American Pharmaceutical Association are in the works.

The comments of FDA officials suggest that for them it's not enough that such standards exist, rather they are interested in documentation that PET centers adhere to those standards. "Are pharmacy guidelines going to be enough given the chemistry involved?" asked David Adams, a director in the FDA's Office of Policy.

Syncor International Corp., which operates 97 nuclear pharmacies in the U.S., says its PET business is sanctioned by state boards of medicine and pharmacy and the FDA's Nuclear Pharmacy Guidelines published in 1984.

Alvin J. Lorman, an attorney representing Syncor, said, "Treating pharmacies as drug manufacturers is not only poor public policy, but also of questionable legality so long as those pharmacies do not ship their prescriptions across state lines." Mr. Lorman said that Syncor would be forced to drop its two PET radiopharmaceutical businesses if the FDA were to pursue the NDA requirement.

Syncor broke from the ICP last year with a petition to the FDA calling for regulation of the cyclotrons and automated synthesis gear as devices rather than regulation of the tracers as drugs. The petition was largely a strategic move to ward off FDA regulation of its pharmacies (see *Newsline*, September 1992, p. 24N).

Asked about the petition by Paula Botstein, MD, acting director of FDA's Division of Medical Imaging, Surgical and Dental Drug Products, Mr. Lorman said, "We are not wedded to our proposal of a year ago." Stating flatly the bottom line of many others at the meeting, he said, "We could live with any system that doesn't require a pharmacy to become regulated like a manufacturer."

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