FDA RDAC Meeting:

Regulation of PET Radiopharmaceuticals, NDA for ^{99m}Tc HMPAO, and the Gastric Emptying Petition

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At its annual meeting last November, the Radiopharmaceutical Drugs Advisory Committee (RDAC) of the U.S. Food and Drug Administration (FDA) discussed the regulation of PET radiopharmaceuticals, and the long-standing petition for use of technetium-99m (^{99m}Tc) sulphur colloid for gastric emptying. The RDAC also reviewed the new drug application (NDA) for ^{99m}Tc HMPAO as a cerebral imaging agent. Subsequently that agent was approved by the FDA (see box, page 138).

PET Proposals

Carol Marcus, PhD, MD, director of the nuclear medicine outpatient clinic at Harbor-UCLA Medical Center, proposed a plan, endorsed by various SNM/ACNP members involved in leadership or radiopharmaceutical activities, that divides the responsibilities of ensuring safety and efficacy of radiopharmaceutical agents among the FDA, state boards of pharmacy, and the United States Pharmacopoeial Convention, Inc. (USP). In the proposal, according to Dr. Marcus, "the FDA would retain its customary responsibilities" for commercially-sponsored Investigational New Drugs (IND) and NDAs; the USP would set standards for PET radiopharmaceuticals and recommend procedures for "black boxes" (the automatic devices for radiopharmaceutical synthesis); and "state boards of pharmacy would expand their regulatory role and institute increased inspection of PET and other radiopharmacies. FDA, as the regulatory arm of the USP, can ensure that products produced by nuclear pharmacies meet USP specifications." Dr. Marcus said the practice of radiopharmacy under a pharmacy or medical license is exempt from the Food, Drug and Cosmetic Act (FDCA) and falls under state regulatory purview. She added, as of 1988, 28 to 30 states had adopted regulations for the practice of pharmacy using the National Association of Boards of Pharmacy Model Regulations for the Licensure of Nuclear Pharmacies. Dr. Marcus said state regulation has not been extensive for two reasons: states do not see the need for increased regulation because "radiopharmaceuticals are one of the safest groups of drugs in use today," and nuclear medicine and radiopharmacy practitioners have regulated themselves adequately.

The FDA developed a somewhat different proposal, which was described at the meeting by Robert West of the FDA staff. The goals of the proposal, according to Dr. West, are as follows:

- To establish consistency among the final drug products that are administered to patients.
- To provide guidance to the nuclear medicine community regarding the FDA's role in regulation.
- To exercise flexibility in the regulatory posture towards PET. While PET radiopharmaceuticals "are new drugs subject to regulation" under

FDCA, FDA is willing to break its "traditional regulatory approach" in recognition that PET is "an emerging technology."

• To provide a mechanism for reimbursement. "For PET to continue to flourish," said Dr. West, "there must be some mechanism provided for reimbursement of these procedures." The FDA proposal would "pave the way for reimbursement for at least certain of the PET agents that have demonstrated clinical efficacy."

The FDA plan is three-staged. Stage I—Exemption from IND Requirements—entails identifying PET radiopharmaceuticals that are likely to be clinically effective. A clinical plan would be devised among PET centers to develop the drug and determine its efficacy. With input from the nuclear medicine community and the USP, the FDA would establish chemistry, manufacturing, and controls guidelines to ensure that final drug products meet acceptable standards for identity, strength, quality, and purity and to ensure reproducibility among centers. Patient protection would be assured through institutional review boards and radiation safety committees.

The following conditions apply to Stage I: existing regulations must be amended; when used in research, PET drugs will be "generally recognized as safe and effective and not misbranded under conditions published in regulations and guidelines"; exemptions are limited to in-house production and use; and exemptions end "when clinical utility is demonstrated or when the study exceeds limitations under the exemption."

Stage II—Application to FDA to Establish Safety and Effectiveness—requires submission of an IND if the data do not already exist. The FDA will assist in protocol development and at least two centers must study the drug under the same protocol.

Stage III—Presentation of Application for FDA Approval—involves submission of data to the FDA for review. The FDA will then publish a *Federal Register* notice stating the conditions of approval, and, based on that notice, individual PET centers will be invited to submit abbreviated new drug applications with chemistry, manufacturing, and controls data.

Exemptions to the FDA proposal are regional distribution and generator products, which require NDA approval; "black boxes"; and PET radiopharmaceuticals which exceed radiation limits or which produce a pharmacologic effect.

The basic difference between Dr. Marcus' and the FDA's proposals, remarked Barry Siegel, MD, director of the nuclear medicine division at the Mallincrodt Institute of Radiology, and consultant to the RDAC, is over "whether or not an exemption exists in the Food, Drug and Cosmetic Act for the types of activities involved in the production of PET radiopharmaceuticals," that is, the practice of pharmacy. Dr. Marcus' proposal includes such an exemption; FDA's proposal does not. If the exemption exists, then FDA need not have a role in the regulation of PET radiopharmaceuticals.

Other RDAC members expressed concerns that the FDA proposal was time-consuming and cumbersome and could slow PET development. The FDA proposal allows only preliminary use without IND review. Subsequently, essentially the full process leading to an NDA would need to be completed. Hence the proposal provides minimal relief.

David Adams of the FDA General Counsel responded that the FDA "does not view the use of PET technology as traditional practice of pharmacy" because more than just pharmacists are involved. He added, "there are specific exemptions within the Act from specific requirements, but there is no general exemption from all the requirements. . . .whether or not it is a diagnostic agent or something that is being used in actual treatment or for a curative effect, it is a drug." If there are no published, adequate, well-controlled studies in the literature on the agent, he added, then it is a new drug requiring an NDA or an exemption.

Review of ^{99m}Tc HMPAO

The brisk discussion of Ceretec at the meeting included a description of the use of that agent for functional brain imaging by Philip Douglas, PhD, Amersham's manager of scientific and regulatory affairs. Outlining the clinical studies in Phases 1-III, he concluded there is "good evidence the drug is safe. . ." and that the Phase II and III studies "show efficacy in stroke."

This was followed by a presentation of the clinical utility of ^{99m}Tc

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^{99m}Tc HMPAO Approved

Newsline has learned that the FDA approved the NDA for ^{99m}Tc HMPAO (Ceretec, Amersham) for cerebral imaging on December 30. According to Robert West of the FDA, ^{99m}Tc HMPAO was approved "for use as an adjunct in the detection of regional cerebral perfusion in stroke." He added that Amersham will be meeting soon with the FDA to "discuss additional indications and disease states." Philip Douglas, PhD, Amersham's manager of scientific and regulatory affairs told *Newsline* the company is "pleased as punch." He expected the agent to become generally available sometime during January, 1989. ■

long-term immobilization; for endocrinopathies known to be associated with osteopenia; for post-gastrectomy and other malabsorption states leading to osteopenia; during long-term corticosteroid therapy; for chronic renal disease, particularly in childhood or adolescence; and to monitor treatment programs for osteoporosis.

"Limiting reimbursement to these specific indications," according to the Task Force, "should assure that the diagnostic technologies used for bone density measurements will be properly and selectively applied in clinical practice. These indications are well-supported by current medical literature and practice. . . ." Medicare coverage for these indications "represents a balance between the medical needs of our patients and HCFA's need to be fiscally sound."

The SNM/ACNP asked HCFA, which is reviewing the responses to the proposed rule, to consider their comments and those of a National Osteoporosis Foundation (NOF) Task Force on bone mass measurements, as well as meet with representatives of the nuclear medicine community before making its final decision.

Some members of the SNM Task Force view the HCFA proposal as a temporary setback, but see the long-term outlook more positively. Dr. Powell told *Newsline*, "I don't think [HCFA] will be able to introduce the restriction without reviewing all the response material. This will lead to a delay in implementation" of the restrictions.

Heinz W. Wahner, MD, professor of nuclear medicine at the Mayo Clinic and Foundation, and a member of the SNM/ACNP Task Force, said new drugs are being developed to treat osteoporosis and other bone diseases. Many of these drugs require some form of measurement. If these drugs, some of which have been approved in Europe, are approved in the US, added Dr. Wahner, absorptiometry measurements will be in even greater demand.

Dr. Robinson pointed out that the OHTA assessments were, in part, based on some previous opponents of absorptiometry techniques who have reversed their opinions and now support reimbursement for clinically-indicated bone mass measurements. He also noted the magnitude of responses to the HCFA proposal, from groups such as the American College of Radiology and the NOF in addition to the SNM/ACNP. "The combined efforts of all these groups has documented the usefulness of absorptiometry procedures. . . now we are waiting—hopefully for a positive response."

Sarah Tilyou

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HMPAO in cerebrovascular disease by Richard A. Holmes, MD, chief of nuclear medicine at the University of Missouri-Columbia and the Harry S. Truman Memorial Veteran's Hospital, and president-elect of SNM. Dr. Holmes, who held the only physician-sponsored IND for ^{99m}Tc HMPAO, pointed out the agent's potential in cerebrovascular imaging, particularly transient ischemic attacks. He said, "Ceretec is what we regard as a valuable agent . . . it is technetium-labeled. . . neutral, lipophilic and will cross into the brain. . . . it. . . will be extremely valuable to the clinical practice of medicine."

Dominick Conca, MD, of the FDA staff, presented the agency's positive review of the agent, noting, however, that they did identify some differences in interpretation between the investigators and the FDA reviewers. Questions of Committee members revealed that the study design included incomplete blinding of readers, and some thought a more realistic approach would be to provide reader training.

Gastric Emptying Petition

Describing the FDA's review of the gastric emptying petition, which involves approval of the oral administration of technetium sulpher colloid mixed with food to image and quantify gastric emptying, Joseph Zolman, MD, of the FDA staff, said the agency could not find evidence of efficacy in controlled or non-controlled studies. "We do not have enough of a body of data and evidence that at this stage a labeling change would provide for significant diagnostic advantage. . . . we would prefer to get by with a broader labeling change that is in favor of gastrointestinal motility." The Committee members expressed surprise at the FDA's inability to obtain evidence of efficacy for gastric emptying and concern that the lack of a labeling change may preclude reimbursement. There were further concerns that manufacturers would not be willing to invest in the controlled trials FDA requires for the labeling change. The possibility of changing the indication to gastrointestinal motility was considered, but in lieu of a general motion in that direction, the FDA agreed to review the petition again in light of the Committee's remarks.

A discussion of safety considerations and a proposed labeling revision related to the use of nonionic contrast media was deemed premature and deferred to a future meeting.

Sarah Tilyou