Congress Passes FDA Reform Act: Nuclear Medicine Community Stands to Gain

On November 21, 1997, President Clinton signed into law a congressional mandate for the Food and Drug Administration (FDA) to reform its rulemaking authority. Radiopharmaceutical manufacturers and PET researchers alike stand to gain from the Food and Drug Administration Modernization Act of 1997 (S. 830), which directs the FDA to issue new rules concerning the regulation of radiopharmaceutical approval, PET drugs and pharmacy compounding. The main thrust of the legislation is to streamline the drug approval process and allow science and industry leaders to have more input into how new regulations are written. "The bill writes into law many of the Reinventing Government measures introduced by the FDA a few years ago, reducing the requirements and simplifying the review process for new drugs and medical devices without compromising safety," said President Clinton in his remarks at the bill signing.

For the nuclear medicine community, FDA reform comes on the heels of two other recent victories. In October 1997, the U.S. Court of Appeals ruled in favor of Syncor International in its challenge of the FDA's 1995 notice concerning the regulation of PET radiopharmaceuticals. The appeals court found that the FDA had overstepped its authority when it issued new regulations requiring FDA approval for all PET drugs without going through the formal rulemaking-and-comment process. In November 1997, U.S. Secretary of Health and Human Services Donna E. Shalala announced that Medicare would begin paying for PET scans for the diagnosis and staging of lung cancer by the end of 1997 and committed the FDA to a fast-track review of PET for other types of cancer (including colorectal, breast and ovarian cancer and melanoma) within the next 18 months. (See "CHCCP News," page 22N.)

The new FDA reform legislation specifies that the FDA should write separate regulations for radiopharmaceuticals and PET radiopharmaceuticals to distinguish them from other drugs. For years, the nuclear medicine industry has been requesting changes in the FDA approval process to take into account the negligible risk of radiopharmaceuticals used in imaging. "We are extremely pleased with the FDA reform law," said Bill Ehmig, chairman of the Council on Radionuclides and Radiopharmaceuticals (CORAR). "We worked very hard with congressmen and senators to get specific provisions and feel the bill is a positive outcome."

The bill contains some general provisions that affect radiopharmaceutical companies, such as the reauthorization of the Prescription Drug User Fee Act for 5 more years, under which drug companies pay fees to ensure a faster review process. It also expands access to experimental therapies for cancer and other diseases whose approval is still pending. Specifically, the bill contains three provisions that pertain to nuclear medicine: a provision on PET drugs, a provision on the radiopharmaceutical approval process and a provision concerning the application of federal law to the practice of pharmacy compounding.

Regulation of PET Radiopharmaceuticals

Congress directed the FDA to recognize PET drugs as distinct from other pharmaceuticals and other radiopharmaceuticals. The bill states that the FDA is required to "take account of the special characteristics of positron emission tomography drugs and the special techniques and processes required to produce these drugs." The FDA has been given 2 years to establish both appropriate procedures for the approval of PET drugs and appropriate current good manufacturing practice requirements for PET and an additional 2 years to implement the new regulations. "In the 4-year interim period, these drugs will be considered FDA-approved, so the lack of regulations will not be a hindrance to reimbursements by insurance companies," said Jennifer S. Keppler, CNMT, MBA, executive director of the Institute for Clinical PET (ICP). Congress also specified that, within 30 days

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FDA Still Without Commissioner

As President Clinton signed into law the bill overhauling the FDA in November 1997, he still had no comment on when he would choose someone to lead the agency in its reform efforts. The commissioner's job has been vacant since David Kessler, MD, left to become dean of the Yale School of Medicine.

The Clinton administration is still trying to determine whether the nominee should come from inside or outside the agency and how connected he or she should be with the pharmaceutical industry. Perhaps the most important consideration is whether the nominee can easily win confirmation in the Senate, which recently stalled the nomination of David Satcher for U.S. Surgeon General. The President is expected to pick a nominee within the next few months.

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of the bill's enactment into law, the FDA will publish a notice terminating its two 1995 notices and one final rule concerning the regulation and manufacture of PET drugs (which was also the outcome of the Syncor appeal). The bill specified that new drug applications and abbreviated new drug applications will not be required for PET drugs that meet the U.S. Pharmacopeia (USP) standards for quality and purity for at least 4 years. Until then, the law will revert to the 1984 guideline for nuclear pharmacy, which exempts nuclear pharmacies that compound PET radiopharmaceuticals from complying with current good manufacturing practices, according to Alvin J. Lorman, the attorney who represented Syncor, the American College of Nuclear Physicians (ACNP), the Society of Nuclear Medicine (SNM) and the American Pharmaceutical Association in the suit against the FDA.

This means that university researchers who manufacture PET drugs for individual patients will no longer be required to file new drug applications with the FDA—at least until new regulations are implemented.

One intriguing requirement included in the PET provision states that the FDA "shall take due account of any relevant differences between not-for-profit institutions that compound the drugs for their patients and commercial manufacturers of the drugs" when developing procedures for new drug applications. In essence, Congress is giving the FDA the option of issuing separate guidelines for those who make PET drugs at universities and hospitals and for those who manufacture PET drugs for commercial pharmacy networks such as PETNet™. PET experts, however, are skeptical that the FDA will make this distinction. "In my past dealings with the FDA, I have found that the agency does not believe there are relevant differences between academic centers and commercial manufacturers," said Lorman. "It's up to the PET community to convince the FDA of the fact that there are differences. The legislation leaves a lot of details to be worked out between the FDA and the nuclear medicine community." Taking this into account, Congress has also ordered the FDA to consult with patient advocacy groups, professional associations, manufacturers and physicians and scientists licensed to make or use PET drugs. The ICP, in conjunction with other nuclear medicine organizations, is planning to submit a proposal for regulating PET radiopharmaceuticals to the FDA within the next year.

Requirements for Radiopharmaceutical Approval

The FDA has no more than 6 months to issue proposed regulations for the approval of radiopharmaceuticals and must consult with patient advocacy groups, professional associations, physicians licensed to use radiopharmaceuticals and industry representatives before doing so. All in all, the FDA has 18 months to come up with a final rule. In issuing the regulations, the FDA must consider how radiopharmaceuticals are used in medicine (primarily for diagnostic purposes), the pharmacological and toxicological activity of the radiopharmaceutical and the estimated absorbed radiation dose. Although the bill does not distinguish between diagnostic and therapeutic radiopharmaceuticals, "we want the rulemaking to apply to diagnostics only and to have separate proposed rules for therapeutics," said Ehmig. This distinction would allow the FDA to consider the relatively low doses and low toxicity associated with diagnostic imaging drugs in determining whether the approval process can be less stringent.

In a significant coup for the radiopharmaceutical industry, the bill also contains a provision calling for the FDA to consider approval for broader disease indications. Instead of approving a radiopharmaceutical solely for cardiac imaging, for example, the FDA should consider other organs or diseases for which the radiopharmaceutical could be useful for imaging (without requiring the requisite clinical trials). In explaining the need for broader indications for organ imaging, Ehmig cited the example of how analgesic manufacturers get approval to market their products "for the relief of pain" without having to conduct clinical trials on every type of pain from a sprained ankle to a sore neck.

"We're hoping that the FDA will recognize congressional intent under the bill calling for broader indications for labeling and the inherent safety of radiopharmaceuticals in terms of the need for more rapid review and approval," said Ehmig. CORAR is working with SNM and the ACNP to compose a "Points to Consider" document, which will be submitted to the FDA within the next 6 months. Although the details of the document are still being worked out, Ehmig said it will contain proposals outlining ways to speed the review process and broaden indications. "We'll also include some statements about clinical trial requirements and how to include nongovernment agencies, such as university consortia, in the review process," he said.

Exclusion of Nuclear Medicine from Pharmacy Compounding Regulations

The FDA reform legislation stipulates that the provisions negotiated for pharmacy compounding are too restrictive for PET drugs and radiopharmaceuticals. Thus, the 1984 FDA guideline on nuclear pharmacy compounding will still be in

(Continued on page 18N)

allowing nuclear medicine physicians to present objective evidence to hospitals, insurance companies and even federal regulatory agencies, leading to more rapid acceptance of and reimbursement for newly emerging technologies.

Carefully performed CEA involves collaboration between numerous clinicians, biomathematicians, statisticians and health economists, as well as patients affected by the disease. If the clinical problem is not well modeled, then no analysis can salvage the CEA. Alternatively, understanding the clinical problem is critical, but the mathematical modeling needs to be properly applied to arrive at useful conclusions. Many people are intrigued by the technique but fail to understand its real utility. We as physicians must be careful to provide the best quality of care possible to our patients, but we must also fight to objectively prove the utility of our imaging protocols for various management algorithms. More importantly, we must be willing to accept that some applications of our imaging studies are not cost-effective and should not be utilized purely for economic gains.

For newly emerging technologies (e.g., coincidence imaging with gamma cameras) as well as newly emerging clinical tracers, it is important that proper clinical trials and CEA be performed in conjunction with each other. One can always make a stronger case for a new imaging study if its role in patient management has been proven in a well-designed clinical trial. Many of the CEA studies available to date have been done by combining literature data with existing management algorithms, and they are therefore not as compelling as prospective trials. ADAC Corporation is currently performing a multicenter prospective study utilizing molecular coincidence detection technology for the evaluation of lung cancer staging and solitary pulmonary nodules with fluorodeoxyglucose. Similar studies, in which industry, university hospitals and community hospitals work together, should be encouraged.

Workshops at the Society of Nuclear Medicine (SNM) Annual Meeting in June 1997 presented various aspects of CEA. These included a workshop in which Dr. David Mankoff discussed CEA as it relates to breast cancer and scintimammography. There was also a workshop on the role of positron imaging in lung cancer in which I discussed CEA as it has been applied to non-small cell lung cancer staging and solitary pulmonary nodule diagnosis. A workshop that will cover CEA and lung cancer is planned for the June 1998 SNM Annual Meeting in Toronto. The Institute for Clinical PET also held a workshop on CEA in 1996 and several talks in October 1997.

I expect that there will be more workshops explaining the details of CEA with important new relevant areas of application over the next year. One of the best ways to understand CEA is to apply it to a nuclear medicine procedure of current interest. At the 1997 SNM Annual Meeting, there were 12 presentations and posters that applied CEA to various nuclear medicine procedures. Unfortunately, some of these did not model the effectiveness component, only the cost component. It is likely that articles addressing CEA will continue to increase in number and quality over the next few years. The *Quarterly Journal of Nuclear Medicine* has an issue devoted to nuclear medicine health economics and CEA planned for publication in early 1999. Guest editors for this issue include Professor Michael Maisey and Dr. Peter West (a health economist).

CEA is expected to continue to play a major role in the evaluation of current and future nuclear medicine studies. It is vital that we continue to perform CEA studies and apply the results from such studies with a proper understanding of their limitations. Nuclear medicine can be enhanced only if we continue to aggressively prove the cost-effective role of our procedures while providing the best quality care for our patients.

—Sanjiv Sam Gambhir, MD, PhD, is the director of the computational and communications sciences division at the Crump Institute for Biological Imaging and assistant professor, department of molecular and medical pharmacology, department of biomathematics, UCLA School of Medicine.

FDA Reform Act

(Continued from page 16N)

effect and will still exclude PET drugs and radiopharmaceuticals from federal laws governing compounding. However, the FDA is not forbidden from revising the guideline. "We were excluded from all restrictions in the pharmacy compounding law," said David Nichols, director of government relations for the ACNP/SNM Government Relations Office.

Compounding laws come into play when researchers and physicians prepare or alter a medication dose for an individual patient, which is almost always the case with PET radiopharmaceuticals. Each state has its own set of compounding laws to ensure quality and purity, but the FDA laws will be more specific, dictating when and if products should be compounded. In the compounding legislation, there are seven additional requirements that pharmaceutical manufacturers must meet, including obtaining chemicals from FDA-approved manufacturers and compounding only products that comply with a USP monograph or are approved by the FDA. (See "Government Relations Update," page 26N.) "These regulations could have been a severe hindrance to radiopharmaceutical manufacturers had they not been excluded from the legislation," said Nichols.

The complete text of the three provisions of the FDA Modernization Act of 1997 (S. 830) pertaining to nuclear medicine can be downloaded from the SNM home page (http://www.snm.org). To access it, click on the "Government Relations" header, and then click on "Documents." If you cannot access the home page, contact the ACNP/SNM Government Relations Office at (703) 708-9773 or e-mail David Nichols at dnichols@snm.org.

—Deborah Kotz