Proposed Peer Review of Physician-Sponsored INDs

FDA Requested To Clarify Policies on Radiochemicals and PET Products

The following letter was sent to Robert Temple, MD, director of the Office of Drug Research and Review at the FDA, on July 20, 1987. Written by Dr. Carol S. Marcus, the letter addresses several issues concerning radiopharmaceuticals—issues affecting nuclear medicine physicians and nuclear pharmacists. At this time, the FDA has not responded to Dr. Marcus's letter, the issues she raises, or to her suggestions. Dr. Temple has delegated the response to this letter to John F. Palmer, MD, director of the FDA Division of Oncology and Radiopharmaceutical Drug Products, (see box p.143). When a response is made available, it will be published in Newsline.

Dear Dr. Temple:

The purpose of this letter is to bring to your attention three categories of radiopharmaceutical problems and to obtain written clarification of the Food and Drug Administration's (FDA) policies and plans with respect to these issues.

Dr. Carol S. Marcus

Aspects of these radiopharmaceutical problems have been previously brought to your attention during meetings with members of The Society of Nuclear Medicine (SNM) and the American College of Nuclear Physicians (ACNP). However, apparent changes in FDA policy and persistent delays with some issues have continued to cause confusion and frustration in the nuclear medicine/radiopharmaceutical community.

I am therefore requesting a written commitment of the FDA's policy and plans regarding the issues itemized below. I am certain that you understand that these issues are critical to the practice of nuclear medicine.

Radiochemicals vs. Radiopharmaceuticals

For many years it has been the practice in radiopharmacy to obtain radiochemicals and chemicals, and from them prepare radiopharmaceuticals and pharmaceuticals. These drugs are used in the practice of nuclear medicine. The preparation of these drugs has been the responsibility of licensed radiopharmacists or pharmacists or licensed nuclear medicine physicians or their supervised designees. The responsibility for the quality of the drug belongs to the pharmacist and the physician. This is entirely within the bounds of laws set out by the various states regarding the practice of pharmacy and the practice of medicine. In addition, radioactive materials licenses are required, but this aspect is not the responsibility of the FDA.

Within the past year or so, the FDA has stepped in and prevented radiopharmacists and nuclear medicine physicians from receiving radiochemicals that may or may not become incorporated into radiopharmaceuticals. Such radiochemicals may be simple radionuclides (e.g., iodine-123, indium-111) or radiolabeled compounds. In addition, certain companies (e.g., Sigma) will not sell certain chemicals to pharmacists or physicians if these materials will eventually be incorporated into a drug preparation for human use. This firm refuses to do this because of FDA pressure.

This new behavior of the FDA is confusing and, I believe, inappropriate. Why has the FDA decided to regulate intermediates? Why is the FDA attempting to negate state laws regulating the practice of pharmacy and medicine? What problem is being solved? What need is being filled? I regard this action as trespassing on the territory of other regulatory agencies, and would be most grateful for an explanation.

Let us examine a few of the ramifications of this new policy, which is being implemented without discussion, consultation, or impact considerations.

First, patients are being deprived of optimal care because suppliers are being prevented from shipping intermediates to physicians for drug preparation for their own patients.

Second, the national laboratories are being shut out as suppliers of radionuclides for the practice of nuclear medicine. They do not have new drug applications (NDAs) on any of their radioactive materials or nonradioactive kits, and, furthermore, the federal government will not permit them to obtain NDAs. Therefore, everything they sell is a radiochemical or a chemical, and the sale of these materials to radiopharmacists or nuclear medicine physicians is prohibited. Does the Department of Energy (DOE) know they have been funding the national laboratories for cooperation with nuclear medicine for nothing? Does the FDA realize it is doing this?

Third, does the FDA plan to stop all use of chemicals by pharmacists in general for compounding nonradioactive

drugs, as well? Is it the agency's intent to remodel the entire practice of pharmacy in this country?

Please reconsider your actions. Albert Lavender stated in a telephone conversation with me in December 1986 that pharmacists should not compound any drugs which use any components that are not NDA-approved. I do not think this statement accurately reflects existing law.

Radiopharmaceuticals for PET Imaging

Positron Emission Tomography (PET) imaging is not a new modality. In 1974 it was described in the plenary session of the SNM Annual Meeting. It is a technique of unique capability and proven value. It is being crippled by bureaucracy and unwillingness to act. At issue is a form of approval for PET radiopharmaceuticals, all of which are made on site and none of which have NDAs. Many never will have NDAs because they will never be supplied by a manufacturer; their half-lives are too short. Yet calling many of these drugs "investigational" [e.g., fluorine-18-fluorodeoxyglucose (FDG)] is a mistake. "Investigational" also means "non-reimbursable," and this sort of economics is not practical. The preparation of these drugs in-house is simply the practice of pharmacy and medicine, and an approval mechanism must be found to make these drugs easily available and legitimate. Last year I proposed such a mechanism. Quite simply, I suggested using the old drug monograph mechanism. No "perpetual" investigational new drug (IND) exemption or NDA would be needed if this were done. We do not really care if the FDA chooses to use this mechanism or not. We do wish that the FDA would find some mechanism, however, and establish an approval basis for these drugs. This technology was supported by taxes from the people of the United States (US), and they deserve to reap its benefits.

In addition to the above problem, there are related regulatory nightmares afoot involving cyclotrons, automated drug synthesis devices, and the purchasing of fluorine-18 as a radiochemical from a central supplier for in-house fluorine-18–FDG preparation. Again, we have the problem of regulating intermediates rather than the final product, and the purchase of a radiochemical from which to prepare a radiopharmaceutical. We urge you to stop this regulatory meddling now. The responsibility for the final drug product quality rests on the shoulders of the pharmacists and physicians who put their professional competence on the line when they prepare these compounds for human use. It doesn't matter whether they use a cyclotron, an automated synthesis machine, a centrifuge, or chromatography equipment. These are not drugs or devices. They are intermediates in drug preparation. The final drug must be adequately tested for quality, and the pharmacist, physician, and institution determine what is appropriate. The consequences of carelessness are lawsuits against the institution and malpractice charges against the pharmacist and physician. These are strong deterrents to sloppiness. They are all that

(continued on page 144)

FDA Explains Delay in Response

Dr. Robert Temple has delegated the response to Dr. Carol Marcus's letter to John F. Palmer, MD, director of the Food and Drug Administration (FDA) Division of Oncology and Radiopharmaceutical Drug Products. At the last meeting of the Radiopharmaceutical Drugs Advisory Committee (RDAC), held November 16, 1987, in Bethesda, Maryland, Dr. Palmer said that he hoped to deliver an official response "within days or weeks."

The answers to some of Dr. Marcus's questions, however, require that the FDA create policies, which takes time. "Although we realize that it's important to respond as soon as possible, we would prefer to answer correctly rather than hurriedly," Dr. Palmer told *Newsline*.

A well-thought-out answer is being developed among FDA staff in the Radiopharmaceutical Drug Products Group, the Center for Devices and Radiological Health, the Office of Compliance, and the General Counsel (legal department), he said.

The General Counsel is "quite interested in the issue of positron emission tomography (PET), and their opinions are not totally in tune with the thinking we had developed," said Dr. Palmer. This group's main concern is that FDA policies are made in accordance with United States (US) law, he pointed out.

Dr. Marcus's letter has been discussed at about 10 meetings within the FDA, said Dr. Palmer. Three of those meetings involved representatives from the four above-mentioned groups. Other issues, beyond those raised in Dr. Marcus's letter, have surfaced during these meetings, he explained—issues involving the relation between radiopharmaceuticals and medical devices, and the manufacture of drugs in a hospital setting.

"It's not often that the FDA is pressed to create unique ways of handling new technologies, and we have to be careful in trying to identify and articulate new regulatory policies," said Dr. Palmer.

(continued from page 143)
is needed. Ideally, the drug monographs should contain or refer to appropriate quality control procedures for the drugs, and these would become the "standard of practice."

Please consider this approach to PET radiopharmaceuticals. It is clean, appropriate, and adequate. The drug monographs can be provided by experts in radiopharmacy, and the FDA can simply stop there. The state laws regarding the practice of pharmacy and medicine and the use of radioactive materials are adequate regulatory mechanisms from then on.

Physician-Sponsored INDs and Outside Review of INDs

The FDA has been refusing to accept certain physician-sponsored INDs, and has even asked radiopharmaceutical companies not to allow physicians to refer to the appropriate drug master files. This effectively thwarts submission. On the one hand, I understand that the FDA is short-staffed and cannot handle a large number of IND reviews efficiently. The decision to stop certain physician-sponsored INDs in order to concentrate available manpower on a commercial IND or NDA for the same product is an appropriate approach, given the circumstances. However, it is by no means a good solution. I would like to propose an idea that the National Institutes of Health (NIH) has used successfully for many years—peer review.

Peer review of physician-sponsored INDs that the FDA does not wish to evaluate could neatly solve the problem at hand. The reviews would probably be tough and complete, as they are for grant proposals, and the final decision, of course, would still rest with the FDA. Reviewers could receive instructions on how the FDA wishes the INDs to be evaluated, just as the NIH issues instructions to reviewers as to how to evaluate grant proposals. It would not be necessary to have study sections; this could all be accomplished by mail and telephone. The SNM and the ACNP could provide a list of reviewers who could assist the FDA in choosing appropriate persons. Or, the Radiopharmaceutical Drugs Advisory Committee (RDAC) could take on some peer review functions or help distribute physician-sponsored INDs for outside peer review.

The FDA has precedence for this, of course, in the formation of Radioactive Drug Research Committees (RDRC), which review research projects involving metabolism and kinetics. The FDA has essentially delegated this category of research to peer review, while maintaining ultimate power.

Please consider this suggestion carefully, because it is unlikely that FDA manpower will ever be increased to the point where it can efficiently handle all requests for evaluation.

Thank you for your attention and consideration. I eagerly await your reply, as does the radiopharmaceutical and nuclear medicine community.

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(continued from page 141)
investigators were not even documenting data. "That type of activity clogs up the funnel at the FDA. That's what's been hurting the nuclear medicine community," he said.

Dr. Palmer sees a parallel between radiopharmaceutical development of the 1980s and drug development of the 1960s. When Congress passed the Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act in 1962, all drugs except for radiopharmaceuticals labeled with by-product radionuclides had to demonstrate effectiveness in addition to safety, the only previous requirement. By-product radiopharmaceuticals did not come under the FDA's jurisdiction until 1976.

"In the 1960s, the study of new drugs changed dramatically. The new law required adequate, well-controlled studies, and transformed drug development into a more disciplined clinical science," explained Dr. Palmer. This type of discipline is now being incorporated into radiopharmaceutical development, he added.

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