Advisory Committee Looks at Quality Assurance for PET Radiopharmaceuticals

FDA Justifies Limiting Physician-Sponsored INDs To Hasten Drug Approval Process

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Although the United States (US) Food and Drug Administration (FDA) has instituted changes designed to shorten the review process for radiopharmaceuticals, no one can judge the success of those changes until recently submitted new drug applications (NDAs) are approved or denied. In the meantime, the nuclear medicine community hears about the FDA's improved drug review process, but remains skeptical because the results are not yet apparent.

One strategy encouraged by the FDA to shorten review time—limiting physician-sponsored investigational new drug (IND) exemptions—has generated some resentment and frustration among clinical investigators in the US. The tensions of this transition period are heightened by the rapid development of new technologies—particularly positron emission tomography (PET)—that don't fit into established regulatory policies.

"As you develop a regulatory posture for PET radiopharmaceuticals, I would urge that you do not come down too hard, too fast, lest the field get wiped out in the process," said Barry A. Siegel, MD, to FDA staff at the last Radiopharmaceutical Drugs Advisory Committee (RDAC) meeting, held November 16, 1987, in Bethesda, Maryland. Some time in the future, "it's entirely reasonable for PET agents and automated synthesis devices to be regulated as drugs, but we're not there yet," said Dr. Siegel, of the Mallinckrodt Institute of Radiology in St. Louis, Missouri.

[Often called a "black box," an automated synthesis device produces positron-labeled compounds for PET. The regulatory question centers on whether this device, to be used in conjunction with a cyclotron, produces radiochemicals or radiopharmaceuticals.]

The Atomic Energy Act of 1946 encouraged the medical use of by-product radioactive materials, and these materials were not regulated by the FDA until 1976, noted Dr. Siegel, who is a consultant to the RDAC and its immediate past chairman. "The growth of nuclear medicine was probably helped by the absence of FDA regulation for all those years," he added.

John F. Palmer, MD, director of the FDA Division of Oncology and Radiopharmaceutical Drug Products, asked Dr. Siegel why he believed that FDA regulation could harm the development of PET. "It's too early to establish drug quality standards for PET agents," explained Dr. Siegel. "There are 10 or 12 ways to make fluorine-18 fluorodeoxyglucose (FDG), for example, and we don't know which is the best method. The FDA needs to give the nuclear medicine community time to sort out these questions."

Quality Assurance

To give the RDAC an overview of quality assurance concerns that arise during the synthesis of PET tracers, Ronald D. Finn, PhD, related some of his experiences at the Radiopharmaceutical Chemistry and Cyclotron Section, National Institutes of Health (NIH), and the Cyclotron Center at Mount Sinai Medical Center in Miami Beach, Florida.

When a research hospital acquires PET capability, it can draw upon the expertise of its chemists and pharmacologists. "If PET becomes a diagnostic tool in a clinical setting that has no academic affiliation, who will be doing quality assurance on these finished radiopharmaceuticals?" asked Dr. Finn, a newly appointed consul-

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tant to the RDAC. In addition, PET facilities may need someone with expertise in cyclotron maintenance: although manufacturers offer service contracts, a hospital may have to wait a day or more for service if the manufacturer is located in another country. "I treat the cyclotron as an air-sensitive, moisture-sensitive reagent, and it takes delicate care to make sure it runs properly," said Dr. Finn.

A PET image depends on the cyclotron operation, radiochemistry unit, pharmacy unit, technologists running the PET cameras, and computer systems. "One glitch in this system can prevent your obtaining the proper image," noted Dr. Finn.

For example, if nitrogen-14 happens to contaminate the nitrogen-15 target used for making oxygen-15, the system would accidentally produce oxygen-14, a positron emitter. "On-line radionuclide checking is essential," said Dr. Finn. Different methods of synthesizing fluorine-18 FDG produce widely varying levels (5%–88%) of deoxymannose impurities, noted Dr. Finn, and no one yet knows the minimum acceptable purity of FDG for PET. "Quality assurance programs for PET agents need to address chemical, radiochemical, and radionuclidic purities, as well as the pharmacy problems of sterility, nontoxicity, and apyrogenicity," added Dr. Finn.

Because PET facilities produce most of their own radiopharmaceuticals, which are not distributed across state lines, these drugs do not require NDA approval. Instead, physicians and chemists at those institutions take responsibility for the quality of the PET tracer, which is considered part of the practice of medicine or pharmacy under the Food, Drug, and Cosmetic Act. The advent of automated synthesis devices for PET agents, however, forces the FDA to scrutinize this issue and decide whether these machines should be regulated as medical devices, drugs, or combinations of both. (At present, the FDA does not classify hospital cyclotrons as medical devices.)

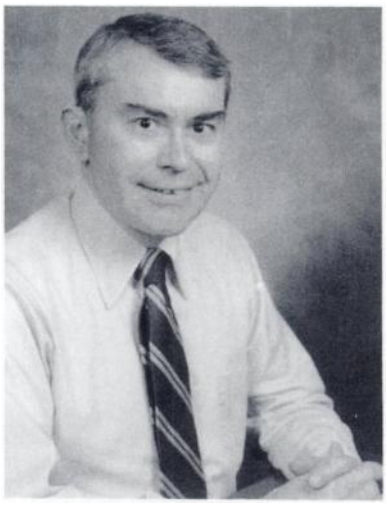
Black Box or "Remote Handling Device"?

"I think there's a misconception about what cyclotron manufacturers build and supply to users," said Maria Straatmann, of Computer Technology & Imaging (CTI), a cyclotron manufacturer in Berkeley, California. She asked the FDA to "differentiate between a black box, which is deliberately limited to producing a single specific radiolabeled compound, independent of operator judgments, and a 'remote handling device,' which can be used to produce several radiolabeled compounds, depending on chemicals and conditions chosen by the user."

Investigators at the Mallinckrodt Institute of Radiology use a robot made by the Zymark Corp. in Hopkinton, Maryland, to make fluorine-18-labeled tracers for PET, noted Ms. Straatmann. "I don't think that the FDA would say that Zymark could not sell its robot without FDA approval, even though it's used to make a radiopharmaceutical," she said.

"CTI sells a remote handling device that can be used to produce several radiochemicals. We do not claim that it produces radiopharmaceuticals, or that the end product is sterile or pyrogen-free, and we don't call it an FDG box. I think this is an important idea to fold into your discussions when you decide how to handle this issue," said Ms. Straatmann, addressing members of the RDAC and FDA staff.

About 300 organic compounds—50–100 of which have been used as potential drugs—have been labeled with positron-emitting radionuclides, "and that number probably represents the tip of the iceberg" for potential PET radiopharmaceuticals, said Norman D. LaFrance, MD, of the Johns Hopkins Medical Institutions, Baltimore, Maryland. If compounds produced by automated synthesis devices are not considered radiochemicals, can the FDA regulate so many radiopharmaceuticals?, asked Dr. LaFrance, a member of the RDAC.



A. Eric Jones, MD, group leader of the FDA Radiopharmaceutical Drug Products

FDA Seeks Guidance

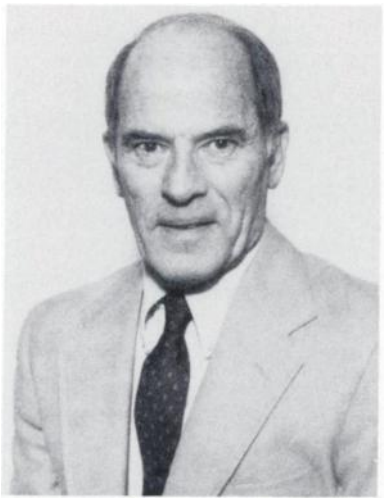
"This issue is very complex and entangled. Somehow, though, one needs to be sure that what you're giving to patients is pure, sterile, safe, and efficacious," said Paula Botstein, MD, deputy director (medical affairs) of the FDA Office of Drug Research and Review. Drs. Botstein and Palmer said that the FDA is looking for advice from the RDAC on the future regulation of PET products.

"Right now, we believe that it's prudent for the FDA to develop proper guidance on PET. We intend to work with the RDAC, The Society of Nuclear Medicine (SNM), the NIH, and others. We'll keep the advisory committee apprised of where we are and what we're going to do," said Dr. Palmer.

During an interview with *Newsline*, Dr. Palmer said he's not convinced that FDA involvement will stifle the development of PET. Automated synthesis devices pose a regulatory problem beyond the aspects of a drug's safety and efficacy. "This is a different product, a different regulatory problem. We need to make sure that these black boxes make a uniformly consistent product. Without any regulation, who is going to make sure that this happens? This is a rare opportunity for the FDA to take a nonstandard problem and work out a benevolent, yet effective, way of regulating it. All of us are interested in the potential of PET. FDA approval of PET products—with the force of law behind it—could actually help, rather than hinder, the development of clinical PET," said Dr. Palmer.

Carol S. Marcus, PhD, MD, of the Harbor-University of California at Los Angeles (UCLA) Medical Center, raised the issues of radiochemicals versus radiopharmaceuticals and PET products in a letter sent on July 20, 1987, to Robert J. Temple, MD, director of the FDA Office of Drug Research and Review (see pages 142–144).

"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," said Dr. Marcus, a former RDAC member and consultant. "Ideally, the drug monographs should contain or refer to appropriate quality control procedures for the drugs, and these would become the 'standard of practice,' " she added.



John F. Palmer, MD, director of the FDA Division of Oncology and Radiopharmaceutical Drug Products

Standardizing PET Tracers Through Drug Monographs

Ms. Straatmann also raised the possibility of standardizing PET radiopharmaceuticals through drug monographs of the *US Pharmacopeia*, a legally recognized compendium of drug standards published by the US Pharmacopeial Convention, Inc. (USP). The USP was established in 1820 and is recognized by the US Congress in the Food, Drug, and Cosmetic Act as continuing drug standards of strength, quality, purity, packaging, and labeling that the FDA is to enforce. The USP publishes proposed revisions in the *Pharmacopeial Forum*, open to public comment, before incorporating them into the *US Pharmacopeia*. Individual drug monographs delineate methods for testing finished products and provide criteria for evaluating assay and test results.]

Drugs have usually been added to the *US Pharmacopeia* after FDA approval. Capt. William H. Briner, chairman of the RDAC, is also a member of the Committee of Revision of the USP, and he has inquired about developing drug monographs for PET radiopharmaceuticals.

William M. Heller, PhD, executive director of the USP, told *Newsline* that the USP might be the appropriate route for standardizing PET products, as well as other new drugs outside of nuclear medicine. "Considering today's advances in biotechnology, it may not be feasible for all new drugs to undergo the traditional NDA review by the FDA. Some of the new drugs being developed have extremely short biological half-lives, such that they must be made at the patient's bedside," said Dr. Heller. If the USP Subcommittee on Radiopharmaceuticals of the Committee of Revision successfully develops drug monographs for PET agents, he added, they could serve as prototypes for standardizing other new drugs that cannot be distributed in final form from manufacturers to hospitals.

Role of FDA Advisory Committee

A few members of the RDAC have questioned whether the FDA is adequately utilizing the expertise of its advisory committee. [The RDAC is a body of 10 experts in nuclear medicine and radiology, appointed by the US Department of Health and Human Services (HHS), who give advice—when it's requested—to the FDA Division of Oncology and Radiopharmaceutical Drug Products. Five new members have joined the RDAC within the past year (see box, page 140).]

Dr. Botstein said that, although the FDA has discussed very few NDAs with the RDAC, the agency "would like to change that" and include more NDAs on the agenda for future meetings. (At the November meeting, the RDAC was asked to discuss two INDs in a session closed to the public to protect proprietary information.)

To facilitate communication between the FDA and the nuclear medicine community, FDA Commissioner Frank E. Young, MD, PhD, directed

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in 1986 that representatives of three medical organizations—the SNM, the American College of Nuclear Physicians (ACNP), and the American College of Radiology (ACR)—serve as liaison members of the RDAC. Robert E. O'Mara, MD, representing the ACR, attended the last RDAC meeting. M. Donald Blaufox, MD, representing the SNM, and Letty G. Lutzker, MD, representing the ACNP, were unable to attend.

The nuclear medicine community has expressed concern in recent years about the length of time required for NDA review of radiopharmaceuticals (see *Newsline*: Jan. 1987, pp. 1-11; Jan. 1986, pp. 1-8).

"We have developed draft guidelines for the format of an NDA, which companies are just beginning to use. These guidelines recommend, for example, that companies present a succinct summary accompanied by many tables of data, rather than volumes of text. We have very high hopes that these guidelines will improve NDA review," said Dr. Botstein.

One reason for delayed NDA reviews was a staff shortage within the FDA Division of Oncology and Radiopharmaceutical Drug Products. A. Eric Jones, MD, group leader of the FDA Radiopharmaceutical Drugs Group, reported the following staff changes: two radiopharmaceutical chemists, Raj Kishore, PhD, and Florian Zielinski, PhD, joined the FDA in October 1986 and January 1987, respectively; John Leak, PhD, who had been an FDA reviewing radiochemist for 11 years, resigned in November 1987; Dominick Conca, MD, a board-certified radiologist with special competency certification in nuclear medicine, was hired in May 1987; Joseph Zolman, PhD (endocrinology), MD, a nuclear medicine physician, was hired in November 1987; Ray Farkas, who was chief of radiopharmacy at the NIH for 18 years, joined the FDA in November 1987 as a reviewing radiopharmacist. The FDA radiopharmaceutical review team consists of two pharmacists (who are consumer safety officers), six physicians, two radiopharmaceutical chemists, one radiopharmacist, and one pharmacologist (see *Newsline*, Jan. 1987, p. 9).

Dr. Jones also summarized the projects that his group worked on over the past year. As of last November, nine NDAs (six for radiopharmaceuticals, three for contrast agents) were under review: one filed in 1987, two filed in 1986, two filed in 1985, two filed in 1984, and two filed in 1983. Four NDAs were approved in 1987: iodine-123 iodoamphetamine, now called iofetamine HCl I-123 (SPECTamine,® Medi-Physics); technetium-99m mebrofenin (Choletec,® Squibb); sodium pyrophosphate (AN-PYROTEC,™ CIS-US); and technetium MAA (Techne-Scan,® Mallinckrodt). Two NDAs are approvable in the near future, and several others were reviewed in 1987 and not approved.

As of November 1987, Dr. Jones's group was overseeing 16 commercial INDs (six for diagnostic radiopharmaceuticals, four for therapeutic radiopharmaceuticals, and six for contrast agents).

From October 1986 to November 1987, Dr. Jones's group reviewed 73 INDs and provided 75 consultations to other FDA divisions, most of which involved radiolabeled monoclonal antibody products in the FDA Office of Biologic Research and Review. During this same time, 11 supplements (amendments adding new indications to a drug's package insert) were reviewed, and nine were approved.

Dr. Siegel inquired about the status of a petition, submitted by the RDAC in May 1985, to add gastric emptying as an indication for technetium-99m sulfur colloid. Dr. Jones explained that the FDA has many other priorities—INDs, for example, must, by law, be reviewed within 30 days of submission, and new drugs take precedence over supplemental indications for approved drugs—but "the supplement petition has not been lost."

"Because of this, we have advocated limited distribution of the investigative radiopharmaceutical. As a result, both the FDA and the radiopharmaceutical manufacturers have been criticized," said Dr. Jones. "We recognize the commercial advantage

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to the firm of distributing the radiopharmaceutical under multiple INDs prior to NDA approval, but the advantage is costly to all concerned—the nuclear medicine community, the FDA, the manufacturer, and the patients who will benefit from the radiopharmaceutical once it's approved," he added.

Dr. Jones said that his group has met over the past 18 months with radiopharmaceutical companies early in the IND phase to help assess whether preclinical animal studies are complete, to establish reasonable claims, and to assist in the design of clinical studies needed to support NDA approval. "The study protocol must be conducted without any deviations, since results of each study should be comparable and supportive. Replication of findings in a well-controlled study environment is the objective. We also emphasize blinded readings and require confirmatory or supportive testing," he added.

"We believe that radiopharmaceutical development should parallel the development of other drugs, which are not widely distributed to individual physician sponsors. Rather, they are tightly controlled by a commercial sponsor. We expect that this limitation will assure that adequate data will have been collected for review and approval by the FDA, thereby allowing for earlier marketing of the radiopharmaceutical. Once an NDA is under review, the commercial sponsor is encouraged to expand the investigation of the radiopharmaceutical, through controlled clinical trials, to develop additional indications and claims," Dr. Jones continued. "Our intent is to make the new agent commercially available in the shortest time possible, and to encourage the radiopharmaceutical company to conduct additional studies to expand knowledge about the drug's usefulness and, thereby, establish new indications for its use.

"On the other hand, if the company widely distributes the new radiopharmaceutical, relying only on clinical usage and any publications that appear, the data will probably not meet regulatory requirements, and the company will be frustrated in not being able to introduce these new indications for use in their package insert. The absence of this information in the package insert also prohibits the firm from advertising the new indications," said Dr. Jones.

The petition route does not seem to work well within the FDA, noted Dr. Palmer, who suggested that the RDAC discuss alternative methods of adding indications to package inserts. Dr. Siegel pointed out, however, that the petition was submitted *at the FDA's request*, and although the FDA has since realized that petitions are not the most efficient method to add claims to drug labeling, this particular petition should not have "languished" for two years in the agency.

Physician-Sponsored INDs

During an ACNP/SNM government relations seminar, held in Washington, DC, on September 18, 1987, Dr. Jones addressed the causes for delay in the FDA radiopharmaceutical review process. In the past, FDA review time for radiopharmaceuticals has been prolonged by several factors, reported Dr. Jones, such as inadequate manufacturing and controls data, clinical data collected under varying protocols or protocol violations, and too many data that were noncomparable and, therefore, nonsupportive of the radiopharmaceutical's intended use.

In addition, when an NDA contains insufficient information, the review cannot move forward. Dr. Jones said that his group has been waiting for 17 months and for 11 months, respectively, for responses from companies regarding two diagnostic radiopharmaceutical NDAs.

Large numbers of physician-sponsored INDs were also cited as a problem—not only because of the FDA staff time required to review INDs, but also because they generate a large body of uncontrolled data for NDAs. In the past, review of these large bodies of data consumed much of the FDA's time, and these studies rarely met the requirements for "two adequate and well-controlled clinical studies to demonstrate effectiveness," mandated by US law.

"FDA review time is further prolonged when, each week, additional INDs for the same agent under NDA review are submitted by physicians who intend to use the new agent for one of two purposes: to conduct a well-designed research protocol for a new use of the agent; or, more commonly, to get early clinical experience with the new radiopharmaceutical. When the commercial sponsor permits or encourages wide distribution of the new agent while it is under NDA review . . . the NDA review is prolonged," said Dr. Jones.

"A More Disciplined Clinical Science"

At the last RDAC meeting, Dr. Botstein said that "the FDA is not trying to stamp out physician-sponsored INDs." Historically, investigational radiopharmaceuticals have been used more freely than other new drugs, noted Dr. Botstein. "It's highly desirable, though, for an investigational drug to be used primarily in controlled clinical trials. It is not desirable for a drug to remain in limbo as an investigational new drug indefinitely. If it is a medically useful product, the goal should be for it to come to market," she added.

Hundreds of INDs were on file for indium-111 oxine (oxyquinoline) before it was approved in 1985, recalled Dr. Palmer, and some of the

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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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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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