Commentaries

Radiopharmaceuticals and FDA: a Clinician's Perspective

The Food and Drug Administration is a scientific federal regulatory agency charged with the responsibility for ensuring that (1) foods are safe, pure, and wholesome; (2) cosmetics are safe; (3) drugs, biological products, and medical devices are safe and effective; (4) radiological products and their uses do not result in unnecessary radiation exposure; and (5) all these products are properly and honestly labeled. The FDA's regulatory actions—through its National Center for Drugs and Biologics (which, after the 1982 reorganization of FDA, represents the merger of the Bureau of Drugs and the Bureau of Biologics) and its National Center for Medical Devices and Radiological Health (which similarly represents the merger of the Bureau of Medical Devices and the Bureau of Radiological Health)—affect most aspects of radiology and nuclear medicine, and profoundly influence the rate at which new advances in diagnostic imaging become available to the medical community.

This article will focus on the National Center for Drugs and Biologics and its role in the regulation of radiopharmaceuticals. It is not intended to be a comprehensive review; rather, it will discuss the key features of the new drug approval process, as well as selected problems that exclusively affect this special class of drugs. It is written from the perspective of a practicing nuclear medicine physician who has had the opportunity to participate in the investigation of new radiopharmaceuticals, to observe FDA in action as a consultant to that agency, and to form opinions about some of the problems in our system of drug development and regulation.

Under the provisions of the Federal Food, Drug, and Cosmetic Act, the National Center for Drugs and Biologics performs a number of functions that regulate the marketing of prescription drugs in the United States. Most important is its role in determining that a drug is safe and that there is substantial scientific evidence of its effectiveness for its intended use in accordance with the proposed labeling. Further, the agency sets standards that will ensure that a drug is properly manufactured. This scientific evaluation must be accomplished before marketing of the drug is permitted. In addition, FDA monitors the quality of marketed drugs through product testing, post-marketing surveillance, and compliance programs; collects information on the manufacture, use, and adverse effects of drugs; and enforces requirements for accurate, balanced advertising and promotion of drugs.

Historical Considerations

During the formative years of nuclear medicine, radioactive drugs containing byproduct radionuclides were distributed chiefly under the regulatory supervision of the Atomic Energy Commission (*1*). This arrangement was formalized in 1963 (*2*), when the Investigational New Drug Regulations, which followed the 1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act, were promulgated. By agreement between FDA and AEC, reactor-produced radiopharmaceuticals for investigational use were exempted from the new drug regulations if they were shipped in compliance with AEC regulations. However, as nuclear medicine matured and as "investigational use" merged with routine clinical use, FDA actively entered the arena and in 1971 called for the submission of new drug applications (NDAs) for those radioactive drugs considered to be "well established" in nuclear medicine and therefore not appropriately distributed under investigational-use labeling (*3*). In response to this, a large number of radiopharmaceutical NDAs were submitted and approved (52 from 1971 through 1975 vs 31 from 1951 through 1970) (*4*).

On July 25, 1975, FDA fully took the reins, totally revoking the exemption of radipharmaceuticals from the new drug regulations (*5*). This action established the same regulatory requirements for radiopharmaceuticals (including radiolabeled biological products) as for all other prescription drugs. Hence, the submission of a notice of claimed investigational exemption for a new drug was required before initiating clinical studies, and the submission and approval of an NDA was required before marketing the drug. The transition (at least on paper) was now complete. Fostered by AEC, and perhaps even more by the FDA exemption, the nuclear medicine infant had grown rapidly, but not quite to full maturity. As the years after 1975 have shown, "big-league" headaches often accompany "big-league" status. The nuclear medicine adolescent was faced with the task of unlearning the comfortable radiopharmaceutical development techniques of the previous 25 years and learning new skills to cope with the more stringent requirements of the FDA regulations. This learning process has not been entirely easy, and although progress has been made, further maturation is still necessary.

Are Radiopharmaceuticals Different?

A complaint frequently voiced by both nuclear medicine practitioners and radiopharmaceutical manufacturers is that FDA does not perceive the obvious differences between radiopharmaceuticals and other drugs; as a result, FDA unfairly uses the same criteria to evaluate the manufacturing controls, safety, and effectiveness of these drugs as it does for other drugs. To these practitioners and manufacturers, however, radiopharmaceuticals obviously are safe because they are given in only trace quantities and have limited potential for traditionally conceived adverse reactions. Further, most patients will receive these drugs only once or a few times, thereby obviating the need for long-term safety studies. It is further argued that the effectiveness criteria by which other drugs are evaluated cannot apply to diagnostic radiopharmaceuticals because these drugs do not (intentionally) produce a pharmacological effect that can be validated by conventional controlled clinical trials. During the transition period from 1971 to about 1976, an argument commonly heard was that the scintillation image resulting from use of a radiopharmaceutical was ipso facto evidence of effectiveness.

There certainly is some truth in these arguments for specific radiopharmaceuticals, and it is unfair to state that FDA has not recognized this. Relatively limited information documenting safety and effectiveness was accepted in NDAs for the well-established radiopharmaceuticals; this policy quite rationally was based on the long use of these drugs in routine practice prior to the partial revocation of the exemption in 1971. Certainly the safety problems with radioactive drugs have been very few (*6,7*). However, it is not justifiable to accept these drugs' safety records as evidence for no need to be concerned with new radiopharmaceuticals, particularly new chemical entities for which little toxicological information is available. In addition, assurance of acceptable radiation exposure is a critical and unique part of the pharmacological evaluation of a new radiopharmaceutical.

The criteria used by FDA for evaluating the effectiveness of diagnostic radiopharmaceuticals have changed considerably over the past decade, but these changes did not originate at FDA. Rather, they have derived from the increased understanding throughout the medical community of the methods for validating the efficacy of diagnostic tests (*8,9*), and recognition of the need for such validation before widespread dissemination of new technologies (*10–12*). Although diagnostic drugs may not have a pharmacological effect, the information derived through use of these drugs may profoundly influence the subsequent course of a patient's health—beneficially if the information is correct, and negatively if the information is incorrect. The capacity to generate an image is not documentation of the effectiveness of the radiopharmaceutical employed in a diagnostic test. Rather, the test must provide accurate, reproducible, and *useful* information, and this can only be established by a controlled, unbiased comparison of test results with other objective criteria of diagnostic "truth."

In summary, radiopharmaceuticals (and particularly diagnostic radiopharmaceuticals) differ in many ways from conventional therapeutic drugs. Nonetheless, there is a need to assess the safety

and efficacy of these drugs fully before their commercial distribution. In general, FDA has understood the unique properties of radioactive drugs (but perhaps has not been as responsive to these differences as many would like). This understanding is reflected well in the *Guidelines for the Clinical Evaluation of Radiopharmaceutical Drugs*, developed by the Radiopharmaceutical Drugs Advisory Committee and FDA staff. The guidelines serve as an informal model of the requirements for approval of a radiopharmaceutical NDA (*13,14*). These requirements are clearly different from those for other drug classes.

New Drug Investigation and Approval

The Food, Drug, and Cosmetic Act requires that FDA may approve an NDA only if the sponsor of the application first shows that the drug is safe, by substantial evidence that it is effective for the conditions prescribed in its labeling, and that it is properly manufactured. By statute, substantial evidence of effectiveness must consist of adequate and well-controlled investigations, including clinical investigations, by experts qualified to evaluate the effectiveness of the drug under the conditions of use listed in the proposed labeling.

Before initiating clinical trials, the sponsor of a new drug must submit to FDA a notice of claimed investigational exemption for a new drug. This document, the IND, is reviewed by the professional staff (including a chemist, a pharmacologist, and a physician) in the responsible division of the National Center for Drugs and Biologics. The primary purpose of this review is to evaluate potential safety problems in the proposed clinical trial. Unless notified to the contrary by FDA, the sponsor may initiate clinical trials 30 days after FDA receives the IND.

The IND contains information concerning the manufacturing of the new drug, a summary of all preclinical studies, and the plans for the clinical investigation. The required manufacturing information includes a description of the quantitative composition of the product formulation, the complete manufacturing procedure, the manufacturing controls, and analytical tests of product quality. For radiopharmaceuticals, information pertaining to radionuclidic and radiochemical purity is required in addition to the other descriptive information required for all drugs.

The summary of preclinical data provides both the rationale for the decision to conduct human trials and the results of toxicity studies. Evaluation of the toxicity of radiopharmaceuticals must include estimates of radiation dosimetry, as well as more conventional studies of pharmacological toxicity. The initial estimates of the radiation dosimetry of a new radiopharmaceutical are usually based on conventional biodistribution studies in rats or mice. These studies should be designed so that it is possible to account for virtually all the administered activity at various points in time after injection of the tracer and to characterize adequately the translocation of the drug within the animal, as well as its routes and extent of excretion. These studies are usually supplemented by limited biodistribution or imaging studies in large animals to evaluate interspecies differences and to estimate, by extrapolation, the administered activity necessary to obtain scintigrams of acceptable quality in clinical trials. In addition, the results of biodistribution studies in one or more animal species, with experimentally induced disease conditions simulating those in which use of the radiopharmaceutical is intended, may be necessary to demonstrate differences in dosimetry under abnormal conditions, as well as to document the likely effectiveness of the agent. The FDA prefers that dosimetry calculations be made with use of the Medical Internal Radiation Dose Committee scheme; estimates are generally required for the critical organ or organs, the whole body, gonads, and bone marrow. The assumptions underlying all dosimetry calculations must be documented clearly.

Toxicological evaluation generally consists of both acute and subacute toxicity studies performed in two animal species (*15*). Ideally, the final formulation of the product intended for administration to human subjects should be used in these studies. For radiopharmaceuticals, however, this requirement may create difficulties related to radiation safety. Accordingly, there has been a tendency to perform such toxicity studies with a formulation equivalent in all respects to the clinical product except that a radionuclide of lower specific activity has been substituted (e.g., Tc-95m for Tc-99m) or the product's radioactivity has nearly completely decayed. In recent years, FDA staff members

have discouraged the use of only unlabeled ("cold") products for toxicity testing, based on the assumption that the labeling step may alter the final product formulation and thus its toxicity. The objective of acute toxicity testing is to determine the acute LD_{50} of the radiopharmaceutical or, where this is not practical, to show that no acute toxicity occurs with doses of the agent that are several orders of magnitude greater on a per kilogram basis than those intended for human use. Subacute toxicity studies involve the daily administration for two to three weeks of the radiopharmaceutical in doses at least several-fold greater than those intended for human use. In addition to observing the animals for overt signs of toxicity, the objective endpoints of these studies usually include conventional laboratory studies (blood chemistry, urinalysis, and hematological profile) and necropsy with both gross and histological evaluations. When properly conducted, subacute toxicity studies are rather expensive. Fortunately, preclinical documentation of the safety of radiopharmaceuticals generally has not required chronic toxicity testing or studies of carcinogenesis, teratogenesis, or ophthalmological toxicity.

The clinical protocol section of the IND contains the detailed plans for the clinical studies and must document that these studies will be well controlled and of sufficient quality to establish the safety and effectiveness of the radiopharmaceutical. The clinical investigation is typically divided into three phases. Phase I comprises study of a limited number of human subjects to obtain information chiefly related to the pharmacokinetics of the radiopharmaceutical. Hence, for diagnostic radiopharmaceuticals such studies typically include quantitative imaging, evaluation of blood clearance and the rate and routes of excretion, an attempt to define the optimal administered dose for subsequent imaging studies, and clinical and laboratory observations to evaluate safety. The number of normal subjects studied in phase I investigations of radiopharmaceuticals typically has been quite small, based on appropriate ethical concerns related to unnecessary radiation exposure to normal individuals.

The phase II study, conducted by two or more independent investigators, is designed to provide the initial evaluation of safety and effectiveness under the likely conditions of clinical use of the radiopharmaceutical. The key component of phase II studies is the collection of (1) sufficient clinical and laboratory evidence to document the nature (or absence) of adverse effects from the radiopharmaceutical and of (2) adequate clinical data to demonstrate the reliability of the diagnostic information obtained with the agent. Accordingly, these studies must be carefully designed to ensure that the patients' studies will be well characterized, and that the objective endpoints of final outcome are reliable and independent of the results of the diagnostic studies performed with the radiopharmaceutical. Sophisticated clinical research methods have not been as widely adopted in evaluating the effectiveness of diagnostic tests as in proving the therapeutic benefits of conventional drugs. Many problems have been identified in the design of such studies (*16,17*), and all these errors have been committed at one time or another in the clinical evaluation of radiopharmaceuticals.

The FDA now requires evaluation conferences with sponsors at the end of phase II for those drugs that have been classified as representing a significant therapeutic (or diagnostic) advance over currently available drugs (*18*). However, it is desirable that such conferences be held at the end of phase II for all drugs as a means of identifying deficiencies in the data that must be corrected before approval is possible. Phase III, the final portion of the study, is designed to provide statistically adequate information in larger numbers of patients to document both safety and effectiveness. In the evaluation of radiopharmaceuticals, the safety evaluation during phase III usually has been abbreviated to a requirement to observe for obvious adverse effects.

Once a new drug's clinical evaluation is completed, the sponsor seeks approval to market the product by filing a new drug application. The NDA is a large and comprehensive document, often comprising hundreds of volumes, that details all the information compiled about the new drug. It includes all the manufacturing and control information and all the preclinical data submitted with the IND, supplemented by any additional information gathered during the period of investigational exemption. The results from all the clinical studies must be tabulated and summarized, and the individual case report forms completed by each investigator must be included. All adverse effects must be characterized in detail and their incidence estimated. The NDA also must contain

copies of all labeling material intended for use with the final product, including the package insert. With this information in hand, it is FDA's task to ascertain that the drug is safe, that there is substantial evidence of its effectiveness sufficient to justify its commercial distribution, and that all claims made in the labeling are scientifically documented.

Is Radiopharmaceutical Approval Too Slow?

During the past decade, the so-called drug lag has been a topic of great concern and widespread debate. Highly divergent opinions concerning its significance (or even its existence) have been expressed by members of the medical community, government bodies, and consumer protection groups (*19–21*). The drug lag is defined most simply as the longer time required to develop and approve new drugs in the United States in comparison with other technically advanced countries (*19*). From the viewpoint of most physicians, the drug lag is objectionable because it means that they and their patients are denied timely access to valuable drugs, which often represent significant gains over available agents. It is beyond the scope of this article to discuss the drug lag in detail, although there have been several recent analyses of this problem (*19,22–24*).

Does a drug lag exist for radiopharmaceuticals as well as for therapeutic drugs? There are no comprehensive studies that document slower approval of equivalent radiopharmaceuticals in the United States in comparison with other countries, but the statistics suggest that the approval process certainly has been quite slow (*4,25*). Most nuclear medicine physicians believe that the time to approve new radiopharmaceuticals for commercial distribution is excessively long, especially in light of the admirable safety record of radipharmaceuticals in comparison with other classes of drugs. The nuclear medicine practitioner wonders why it took so long for approval of gallium-67, thallium-201, and Tc-99m disofenin when the scientific literature was replete with reports documenting the value of these radiopharmaceuticals. Since 1974, the average time for approval of radipharmaceutical NDAs has been slightly more than two years (*4,25*). This approval time is very similar to that for all other classes of drugs. Although the situation may be no worse for radiopharmaceuticals, the compelling question is why isn't it substantially better?

There are several reasons to believe that the approval rate for new radiopharmaceuticals has been hindered by some unique characteristics in the community responsible for their development, production, use, and approval. Although it is most convenient, and perhaps most appealing, to ascribe all of the blame for this situation to FDA, the record suggests that the agency is not exclusively at fault. For approval of new radiopharmaceuticals to proceed efficiently and rapidly, there must be shared responsibility and cooperation among FDA, radiopharmaceutical manufacturers, and physicians in the nuclear medicine community, particularly those in academic institutions.

Throughout much of its history, radiopharmaceutical manufacturing has had the character of a cottage industry (*26*). In past years, most new radiopharmaceuticals were discovered in academic institutions by radiopharmaceutical scientists working in collaboration with nuclear medicine physicians. This is in contrast to new developments for most other classes of drugs where innovation occurs in the research laboratories of large manufacturers. The results of new radiopharmaceutical developments are publicized in the literature and frequently are adopted into use in other academic institutions (where they are formulated by a radiopharmacist), bypassing FDA's investigational drug regulations. Because these new radiopharmaceuticals often have not been patented, a manufacturer interested in commercial development of such a new product cannot be assured of exclusive marketing rights should the manufacturer undertake the time-consuming and expensive process of NDA submission. This lack of a competitive advantage is further compounded by the fact that the total market for any new radiopharmaceutical is often substantially smaller than that for many other new drugs because most patients will receive a given agent only once in a lifetime. Simple economic considerations alone predict that radiopharmaceutical manufacturers will not be as willing to make large investments in manufacturing process control, preclinical studies, and clinical investigation as would a manufacturer with exclusive proprietary rights to a chronically administered therapeutic drug with a multimillion-dollar sales potential. As a result of these considerations, there has been corner-cutting, which certainly has contributed to the deficiencies in some NDA

submissions and to the delay in their approval.

These economic considerations have also been the impetus for the development of several strategies that circumvent the new drug approval process (*4,26*). Some manufacturers have distributed their products as radiochemicals. They have claimed that, as radiochemicals, their products are exempt from FDA jurisdiction and that the responsibility for use of these agents as radiopharmaceuticals rests with the physicians who use them in their practices. The FDA considers this strategy to be a violation of the Federal Food, Drug, and Cosmetic Act. Moreover, if the radiopharmaceutical contains byproduct material, a physician using these products as radiopharmaceuticals also may be in noncompliance with Nuclear Regulatory Commission rules.

A much more common strategy has been the commercialization of an investigational new drug; certain radiopharmaceutical manufacturers have distributed investigational products to many physicians (acting as "investigators" under the purview of an IND), but have not ensured that these investigators are performing adequate and well-controlled trials. This practice of the open-ended clinical investigation contributes to the perception that approval of a new radiopharmaceutical is slow, since many nuclear medicine physicians already have adopted these investigational drugs into their routine practice. FDA is working actively to curtail commercialization of investigational products.

A third scheme that has been widely used is the use of a new drug without an approved NDA. This is done particularly by institutional or local nuclear pharmacies that compound their own versions of already approved and marketed radiopharmaceuticals, but do not obtain approval of their products (*27*). There is considerable controversy concerning the legality of this approach because many believe that this activity is sanctioned by the pharmacy exemptions of the Federal Food, Drug, and Cosmetic Act. FDA recently drafted nuclear pharmacy guidelines (*28*) and has taken the position that this type of activity, although it represents the practice of pharmacy, may nonetheless require submission of an IND or NDA. Again, it should be noted that physicians who use such generic radiopharmaceuticals prepared by their own or local radiopharmacies may be in violation of NRC regulations.

As noted above, improvement in the process of new drug approval for radiopharmaceuticals will require correction of deficiencies in all segments of the system. Problems at FDA include chronic professional understaffing, an institutionalized conservatism pervading the agency, and slow communication channels with radiopharmaceutical manufacturers and nuclear medicine practitioners. (This last problem operates in both directions, however.) To these are added the significant problem that most of the professional staff responsible for review of radiopharmaceutical INDs and NDAs have had no practical nuclear medicine experience; rather, they have acquired their expertise through didactic instruction in nuclear medicine and through on-the-job training. The FDA has tried and should continue trying to recruit individuals with broad clinical experience in nuclear medicine; perhaps the agency might attempt to attract retiring nuclear medicine physicians and radiopharmaceutical scientists who may be willing to put in a stint of government service to wind down their careers. Continued and even greater reliance on the advice of the FDA's Radiopharmaceutical Drugs Advisory Committee and greater use of outside consultants also would improve the quality and rapidity of FDA decisions. Further, it seems administratively unfortunate that the division within the National Center for Drugs and Biologics responsible for the scientific evaluation of radiopharmaceuticals, which are perhaps the least toxic of all drugs, is also responsible for the review of antineoplastic agents and anti-inflammatory drugs, which are among the most toxic of drugs. It is also unfortunate that scientific decisions often seem to be made in an adversarial atmosphere (*19*). The history of marketed radiopharmaceuticals in the United States simply does not justify this attitude.

Many of the deficiencies attributable to the radiopharmaceutical manufacturers have been ameliorated as sponsors have gained increasing experience and sophistication in preparing radiopharmaceutical NDAs and in dealing with FDA. Some of these improvements have resulted from FDA policies designed to curtail drug distribution activities that circumvent the Federal Food, Drug, and Cosmetic Act. However, there are still notable problems in the adequacy of manufacturing

controls and in compliance with the Good Manufacturing Practices regulations (*26,25*). Increasingly, the radiopharmaceutical manufacturers have come to realize that a corner-cutting maneuver in any component of an NDA may cost more than it saves because of the resultant delay in drug approval. Since FDA has the statutory right and obligation to review all the clinical studies performed with an investigational new drug, marketing of a radiopharmaceutical under the guise of an IND, often resulting in nonrecoverability of clinical results or the collection of totally uncontrolled clinical observations, has proven to be self-defeating. Most clinical evaluations of new radiopharmaceuticals can be completed quickly by a few investigators, each studying limited numbers of patients. The total number of patients studied is far less important than the adequacy of the design of the study and assurance that the outcomes of diagnostic tests performed with new radiopharmaceuticals are assessable in comparison with objective endpoints. Accordingly, the radiopharmaceutical manufacturers must desist in open-ended requests of clinical investigators to "please evaluate this new agent"; rather, they must carefully plan the study in cooperation with experienced investigators and must closely monitor the clinical study throughout its progress. In most instances, this will mean seeking committed investigators and paying for a scientifically impeccable product, rather than finding voluntary investigators who have no obligation to do the job properly. Another important change is the increasing expansion of basic research departments in major radiopharmaceutical manufacturing firms, increasing the likelihood of greater profitability of new radiopharmaceuticals and the willingness of sponsors to make a greater investment in the collection of data necessary for NDA submission.

The nuclear medicine community also must recognize that the transition period has ended and that FDA fully intends to treat radiopharmaceuticals as they do all other drugs. Nuclear medicine physicians also have a responsiblity not to circumvent the new drug regulations. When we participate in the investigation of new radiopharmaceuticals, we should demand no less of the study design and expend no less effort in assuring collection of accurate, scientific data than we would in the conduct of research intended for publication in the peer-reviewed scientific literature. We cannot all expect to be investigators for every new radiopharmaceutical that is developed, nor should we expect that these agents will be available to us for use in routine practice until they have been approved for commercial distribution. In effecting these changes in attitude, professional societies, such as the Society of Nuclear Medicine, the American College of Nuclear Physicians, and the American College of Radiology, have an important responsibility to educate their members concerning the realities of the process.

Interactions of FDA and NRC Policies

The use of radiopharmaceuticals in the practice of medicine is made more difficult by the fact that these drugs are regulated not only by FDA, but also by NRC or equivalent state agencies. One particularly difficult problem arising from this interaction of distinct agencies with differing policies relates to the use of approved drugs for indications other than those specified in the labeling (package insert). The package insert is meant to be a summary of essential scientific and medical information about a drug that physicians should know to use the drug safely and effectively for the listed indications. By statute, the information presented in the package insert is supported by substantial evidence, consisting of adequate and well-controlled trials documenting the drug's safety and effectiveness. With all drugs, new indications for use often are recognized and reported in the medical literature, but these expanded indications will not be reflected in the package labeling until adequate documentation has been submitted to, and approved by, FDA. Many physicians have been concerned that it may be illegal to use an approved drug for unapproved indications. The FDA has made it quite clear that the package labeling is not meant to restrict the practice of medicine and that physicians do have the right to use drugs as they see fit, obviously with the usual professional responsibility for determining that this use constitutes proper treatment for the patient (*29*). This responsibility also reflects the potentially greater malpractice risk should an adverse outcome arise from the unapproved use of a drug.

In the case of radiopharmaceuticals, NRC has imposed an added restriction on the practice

of medicine. Before 1979, group medical licensees were authorized to use approved radiopharmaceuticals only for those indications listed in the package insert. Hence, such licensees were technically in violation of NRC regulations for such clinical practices as use of [^{99m}Tc] pertechnetate for detection of Meckel's diverticulum. In 1979, NRC regulations were modified (*30*) to permit group medical licensees to use byproduct material for clinical procedures other than those specified in the package insert as long as the licensee complied with the product labeling regarding the radiopharmaceutical's chemical and physical form, route of administration, and dosage range.

However, a number of potential unapproved indications for approved radiopharmaceuticals represent a variance in the route of administration of the drug. Examples of these types of procedures include the oral administration of Tc-99m sulfur colloid for gastroesophageal scintigraphy, conjunctival administration of [^{99m}Tc] pertechnetate for dacryocystography, and installation of [^{99m}Tc] pertechnetate into the bladder for direct radionuclide cystography. These specialized procedures have been developed in academic institutuions with broad medical licenses after approval by local institutional review committees. However, diffusion of these techniques into the nuclear medicine community at large is restricted by the existing NRC regulations. At present, NRC seems unwilling to change its posture on unapproved uses of approved radiopharmaceuticals. Therefore, the required solution may be to amend approved NDAs to include these new indications. For various reasons, the radiopharmaceutical manufacturers have been reluctant to gather the information necessary to submit amendments to their NDAs, perhaps because they perceive relatively small marginal increases in sales from these newer applications and perhaps because of an unwillingness to cast the first stone where there are many manufacturers of the same radiopharmaceutical (e.g., [^{99m}Tc] pertechnetate). The latter posture is quite reasonable, since the first sponsor to submit an NDA for a new radiopharmaceutical or a new indication is likely to have the hardest time in getting it approved. Subsequent manufacturers have the advantage of learning from the mistakes of the first. An alternative approach is the use of class labeling petitions filed by citizens' groups, professional societies, or a consortium of manufacturers, such as the Atomic Industrial Forum. This approach has been successful in effecting labeling revision for several radiopharmaceuticals to "permit" their use in children. This has been achieved without the necessity for *prospective* adequate and well-controlled clinical trials since a sufficient body of evidence could be marshalled from the open scientific literature documenting a long history of safe and effective use of these drugs in children (despite the pediatric "orphan" clause in the labeling). A similar approach may be effective in modifying the labeling of radiopharmaceuticals to include present unapproved uses as approved indications. FDA, guided by the advice of its Radiopharmaceutical Drugs Advisory Committee, has encouraged this approach.

Radiopharmaceuticals in Medical Research

In addition to its role in approving radiopharmaceuticals before their commercial distribution for use in routine clinical practice, FDA also is responsible for regulating the large variety of radioactive drugs used in medical research. FDA recognizes the important role of radiolabeled tracer compounds in many types of scientific investigations, including studies of drug metabolism and basic physiological, pathophysiological, and biochemical research. To obviate the need for submission of an IND for every research study involving the use of radioactive drugs, FDA in 1975 devised a unique mechanism that would permit certain radioactive drugs to be approved for use in human research subjects by local institutional committees (*5*). These committees, known as Radioactive Drug Research Committees, are individually approved by FDA and act on its behalf. An RDRC is empowered to approve a research study with a radioactive drug after it determines that (1) the radiation exposure will be less than prescribed maximums (which are similar to the maximum permissible exposures for occupational workers); (2) the amount of active ingredient or combination of active ingredients to be administered is known not to cause any clinically detectable pharmacological effect in humans; (3) the investigator is qualified to conduct the proposed study and licensed to handle radioactive materials; (4) the rights of human subjects are protected through proper review of the research by an institutional review board; (5) the radioactive drug meets appro-

priate chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality, and purity as needed to ensure safety and significance to the research study; and (6) the research protocol is scientifically sound. An RDRC is responsible for periodically reporting its activities to FDA.

The RDRC mechanism is a significant step toward assuring unimpeded progress in research involving the use of radioactive drugs and in the initial pilot studies of new radiopharmaceuticals that may ultimately have routine clinical value and find their way into the commercial marketplace. This mechanism certainly is preferable to the alternative—namely, submission of physician-sponsored INDs for each of the hundreds of new research projects involving the use of radioactive drugs annually in the United States. The proper functioning of RDRCs is of great importance to the future of nuclear medicine since this mechanism provides the greatest latitude for rapid evaluation of potential new radiopharmaceuticals, which are so vital to the growth of this specialty.

Many of the problems in the development and approval of radiopharmaceuticals for commercial distribution relate to FDA's late entrance into regulation of radiopharmaceuticals, compared with other drugs. In addition, these problems are in part caused by the delayed understanding by FDA, radiopharmaceutical manufacturers, and the nuclear medicine community of how best to apply the complex requirements of the new drug regulations to this rather unique class of drugs with few safety problems and diagnostic rather than therapeutic effectiveness. The learning process is still not complete. The challenge to all three segments of the system is significant and must be met if diagnostic nuclear medicine is to thrive and continue to bring scientific advances arising from the power of tracer methodology into use in daily medical practice.

BARRY A. SIEGEL
Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missouri

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NOTE: On August 31, 1981, the NRC Advisory Committee on the Medical Uses of Isotopes discussed the problem of unapproved uses of approved radiopharmaceuticals involving a variance from the labeling in the route of administration. NRC staff members indicated their willingness to review requests for such uses and to approve those judged to result in acceptable radiation exposure to patients. This represents an excellent partial approach to overcoming this problem. However, I believe that efforts to amend the approved labeling of the various radiopharmaceuticals involved still should be undertaken. The labeling provides the best means for codifying the dosimetry, the acceptable dose range, and other technical details related to such procedures and thereby ensuring the safe and effective use of these radiopharmaceuticals.

FOLLOW-UP NOTE: On February 4, 1983, the NRC promulgated a final rule granting the first exemption to the "route of administration" restriction. This exemption permits the use of Tc-99m DTPA as an aerosol for pulmonary imaging. Moreover, the rule establishes a mechanism whereby similar exemptions might be approved by NRC. Additional progress in this area has resulted from FDA actions as well. NDA supplements adding direct radionuclide cystography to the list of indications for [^{99m}Tc] pertechnetate have been approved by FDA recently. Further, the Radiopharmaceutical Drugs Advisory Committee has submitted several class labeling petitions to FDA that would add indications involving different routes of administration to presently approved radiopharmaceuticals. It is hoped that these will be approved in the near future.

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