AD43-2
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

MAY 18 1990

Date

From Carl C. Peck, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration (HFD-1)
Paul D. Parkman, M.D., Director, Center for Biologics Evaluation and Research, Food and Drug Administration (HFB-1)

Subject

To Comments on Nuclear Regulatory Commission's March 9, 1990 draft interim final rule to revise NRC's radiopharmaceutical licensing requirements

Bill M. Morris, Director, Division of Nuclear Applications, Office of Nuclear Regulatory Research, Nuclear Regulatory Commission

This memorandum conveys the views of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) with respect to the Nuclear Regulatory Commission's (NRC's) March 9, 1990, draft interim final rule to revise NRC's radiopharmaceutical licensing requirements. This follows a March 23, 1990, letter to you from Gerald F. Meyer, Assistant Director, CDER, which was intended as a provisional response to your March 9 letter, pending careful evaluation of your draft.

Presently, NRC regulations restrict deviations by licensees from the product's approved labeling. NRC inspects nuclear pharmacies to assure compliance with its rules. FDA regulations require that all drugs, including radiopharmaceuticals, have approved NDAs in order to be marketed. Pharmacies and physicians are not required to register with FDA; however, pharmacists and physicians are not relieved of the statutory requirements regarding formulating, labeling, and marketing drug products.

As you know, a petition for rulemaking dated June 5, 1989, which was filed with the NRC by the American College of Nuclear Physicians and the Society of Nuclear Medicine, requests NRC, inter alia, to (1) modify its regulations to permit licensees who elute generators and prepare reagent kits to deviate from the manufacturer's instructions for preparation in the approved labeling, and (2) modify its regulations to permit the use of approved radiopharmaceuticals for therapy for unapproved uses and unapproved routes of administration. NRC staff provided copies of that petition to CDER and CBER staff, and staff members of CDER, CBER, and NRC have met a number of times and have had a series of telephone conversations in the past several months to discuss the issues raised in the petition and NRC's projected response.

The March 9, 1990, draft interim final rule, developed by NRC as a partial response to the issues raised in the petition, addresses the two issues described above. We appreciate the opportunity you have given us to examine the draft interim final rule.

In the cover letter which accompanied your March 9 draft, you asked for comments on safety issues of concern to FDA. Since that letter was issued, NRC has provided additional information to CDER and CBER and asked the two Centers to examine the

draft interim final rule in light of the additional information provided. The two Centers have done so.

Based on this information and on a number of discussions with members of your staff, we believe that the major concerns expressed in CDER's March 23 letter have been met. Accordingly, CDER and CBER do not object to NRC's issuance of an interim final rule based on the March 9 draft.

While we do not now object to issuance of the interim final rule, we do have some suggestions that you may wish to consider in developing your document. We believe that inclusion of our suggestions in the text would make the document more consistent with the policies, goals, and missions of both FDA and NRC.

This document bypasses the notice and comment rulemaking process because it is being published as an interim final rule. The document will allow certain actions which have been prohibited and it will set forth new requirements applying to nuclear pharmacies and physicians. Accordingly, CDER and CBER suggest that NRC might wish to add a specific provision to the document providing for a comprehensive re-evaluation of the interim final rule and its impact on nuclear pharmacists and practitioners of nuclear medicine, prior to its being converted into a final rule. One mechanism that compels such a re-examination is a sunset provision, which, after a specified period, requires such a re-evaluation, necessitating a positive action to extend the rule, make it permanent, or revise it. Other mechanisms requiring re-examination of rules are also available. We would suggest that the review of this interim final rule -- whether through a sunset provision or some other provision -- take place after 3 years, because that period would be consistent with your inspection cycle.

The draft interim final rule requires licensees to record deviations, and we agree that suitable recordkeeping requirements should be part of this rulemaking. Appropriate recordkeeping requirements should enable NRC to gather comprehensive data for review and analysis of the experiences of nuclear pharmacies and practitioners of nuclear medicine under the revised regulation. If a sunset clause or other mechanism requiring a re-examination of the interim final rule after a specific period is added, the review and analysis could take place at the time of the activation of the provision (and, if the mechanism is a sunset provision, prior to the expiration of the interim final rule). Such a database would provide NRC with sufficient information and support to convert the rule into a final rule, modify it, or terminate it.

In our opinion, the codified recordkeeping requirements should be consistent with the language of the preamble and should yield information that will provide a reasonable basis for further consideration of the form and content of the final rulemaking document. The preamble indicates that the record of deviations is intended to provide information on "the types of, reasons for, and frequency and patterns of deviation from the package inserts." However, the codified section states that the directive should (1) direct a specific deviation for a particular patient, patients, or radiopharmaceutical, and (2) state the reasons why the deviation from the manufacturer's instructions would be in the patient's best interest. Of course, each directive need not include every data

element; however, we believe that the directives should include descriptions of the nature of deviations in the directives that are sufficiently detailed to allow extraction and analysis of the data elements described in the preamble.

We suggest that directives for deviations include the following data elements: (1) a specific direction for a patient, patients, or radiopharmaceutical for a particular deviation from the manufacturer's instructions for preparation in the approved labeling for a radiopharmaceutical for diagnostic purposes, or the indications or method of administration in the approved labeling for a radiopharmaceutical for therapy, (2) a precise description of the modification, and (3) a statement describing why the deviation is in the best interests of the patient (e.g., deviation from the manufacturer's instructions in the approved labeling will obtain results not otherwise attainable or reduce other risks to the patient). Ideally, we would find it helpful if NRC could devise a methodology by which directives and the prescriptions prepared pursuant to the directives could be related to one another, so that data could show more clearly the number of patients who are administered drugs prepared or administered under deviations. We understand that this may not be feasible in every case.

While we believe that, optimally, you might wish to require periodic reporting of deviations, we understand that the constraints under which you operate may make such reporting impracticable.

Another part of the draft commits NRC "to work closely with FDA to share the information obtained on licensees' deviations from the manufacturers instructions" after the interim final rule becomes effective. While CDER and CBER are interested in reviewing information that NRC derives from the recordkeeping requirements in the interim final rule, we do not believe that the details for the sharing and use of such information are appropriate for this rulemaking. This agency's staff would be pleased to meet with NRC to develop a process that would assure that information derived from the recordkeeping required by NRC under the rulemaking is shared with FDA, and that FDA provides NRC with the results of any review it undertakes as the result of information provided to it by NRC. A memorandum of understanding (MOU) would be one way of memorializing the process developed through these meetings.

As previously discussed with your staff, the medical literature reveals that a kit for a radiopharmaceutical for therapy is currently being investigated. CDER and CBER are concerned about the potential adverse clinical impact that might ensue if a kit for a radiopharmaceutical for therapy were approved and there were deviations from the manufacturer's instructions for preparation in the approved labeling for eluting generators and preparing reagent kits for radiopharmaceuticals for therapy, whether or not deviations are at the direction of a physician. Specifically, we are concerned that the therapy dose of radiation in such a kit, if approved, could go to a site in the body other than that intended in the event of such deviation. Substantial morbidity or, perhaps, mortality could be an outcome. We understand that the interim final rule will not authorize any deviation from manufacturer's instructions for preparation of radiopharmaceutical therapy kits and that the preamble to the rule and the regulatory text will reflect our concerns about such deviations.

While the responsibility for regulating radiopharmaceuticals lies primarily with CDER, we expect CBER to have an increasing role in regulation of these products. CBER's area of responsibility involves radiolabeled monoclonal antibody products, which are subject to licensure under the Public Health Service Act, 42 U.S.C. 262. When CBER evaluates the purity and potency of a biological product for approval, the determination of the product's biological effect is based solely on labeling instructions. If the product is part of a kit, approval is based on the use of the kit's components. Because no radiolabeled monoclonal antibody products have been licensed by CBER, we have no first-hand experience upon which to predict the other ways that these products may be used by nuclear physicians; nor can we predict future safety concerns that will result from unapproved uses, particularly where a modification would involve using products that are not part of an approved kit. The products subject to CBER's responsibility have a much shorter track record than the ones which have prompted the petition, and radiopharmacists will also have less experience modifying these products.

These comments on products regulated by CBER are intended for your information only, and, at present, we anticipate no action on your part with respect to these products. However, the issues related to the uses of radiolabeled monoclonal antibody products and any other novel products may require separate consideration as NRC evaluates the petitioner's other requests, and as we become familiar with the way monoclonal antibody products will be used. Evaluating the records of the deviations will be not only appropriate, but important in assessing safety concerns related to monoclonal antibody products.

To assure that the interim final rule, if adopted, accurately reflects the policies of FDA as well as those of the NRC, we are offering for your consideration some suggestions for specific changes in the language of the March 9 draft. We have appended these suggestions to this letter.

I hope this information is helpful. If you have any questions, please contact Richard L. Arkin in CDER's Drug Regulations Branch (HFD-362), 5600 Fishers Lane, Rockville, MD 20857, (301) 295-8046, or P. Michael Dubinsky in CBER's Division of Regulations and Bioresearch Monitoring (HFD-130), 8800 Rockville Pike, Rockville, MD 20892, (301) 295-8110.

Carl C. Peck, M.D.

for Paul D. Parkman, M.D.

Enclosure
Specific comments on NRC's March 9 draft

SPECIFIC COMMENTS

In general:

- The terms "package insert" and "labeling" are used interchangeably in the preamble. NRC use of these terms is not consistent with FDA conventions. We suggest that you consider using one term, for example, "approved labeling." If you are constrained by the use of other terms in other regulations or in other parts of this regulation, you may wish to explain the meaning of your terms in the text.

- Similarly, the terms "directions" and "manufacturer's instructions" are used interchangeably in the draft interim final rule. We would suggest that you consider using a single term, for example "manufacturer's instructions for preparation in the approved labeling." If you are constrained by the use of other terms in other regulations or in other parts of this regulation, you may wish to explain the meaning of your terms in the text.

Page 3:

- We do not believe FDA policy is accurately described by the statement that reads: "Ordinarily, FDA does not attempt to limit the manner in which a physician administers an FDA-approved drug," or by the similar statement on page 4 that reads: "However, FDA does not ordinarily limit how the physician may use the drug." Because there is no need to characterize FDA's position on this issue in order to implement the interim final rule, we recommend that both statements be deleted.

Page 4:

- We are not satisfied with the characterization of FDA's role in drug approval in the first full paragraph on the page. We would suggest substituting the following language:

  Each new drug approved for human use by the FDA, including radiopharmaceuticals, has labeling approved by FDA that includes a description of the drug, its pharmacology, indications for use, contraindications, warnings, adverse reactions, dosage and administration, and other information,. Certain drugs, including some radiopharmaceuticals, include manufacturer's instructions that specify the method of preparation. FDA reviews and approves the information in the labeling to ensure that it accurately reflects the data on safety and effectiveness on which the drug approval is based. NRC has, in the past, relied primarily on FDA's determination of a drug's safety and effectiveness when it is prepared and used according to the labeling, which some NRC regulations

refer to as the package insert, as one means of assuring protection of the public health and safety.

Page 8:

- It is our understanding that the term "medical uses" does not include in vitro diagnostics. If this is not something that the radiopharmaceutical industry would assume, we suggest adding a statement to that effect in the preamble.

Page 19, 21:

- It is our understanding that you have included the emergency provision at §30.34(f)(2)(ii) on your own initiative, and are not responding to a request in the petition. You may wish to include in your preamble an explanation for the inclusion of this paragraph.

- We believe that clarification of the paragraph requiring the determination that no IND is needed would be desirable. We are concerned that licensees may interpret this paragraph as requiring that the determination be made by FDA. We suggest that you make clear that this determination is to be made by the licensee.

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AD43-2
PDR

NUCLEAR REGULATORY COMMISSION

10 CFR Parts 30 and 35

RIN 3150-AD43

Authorization To Prepare Radiopharmaceutical Reagent Kits and Elute Radiopharmaceutical Generators; Use of Radiopharmaceuticals for Therapy

AGENCY: Nuclear Regulatory Commission.

ACTION: Interim final rule with request for comment.

SUMMARY: The Nuclear Regulatory Commission (NRC) is issuing an interim final rule amending its regulations related to the preparation and the therapeutic uses of radiopharmaceuticals. This interim rule allows licensees who elute generators and prepare reagent kits to depart from the manufacturer's instructions for elution and preparation in the package insert (a part of the Food and Drug Administration (FDA) approved labeling) provided the licensees meet certain conditions and limitations. The interim rule also permits NRC licensees using byproduct material in a radiopharmaceutical for a therapeutic use to depart from the package insert regarding indications and method of administration if certain requirements are met. This amendment is necessary to allow health professionals to provide diagnostic or therapeutic medical results not otherwise attainable or to reduce medical risks to particular patients because of their medical condition while continuing to protect public health and safety adequately. The interim rule applies only to radiopharmaceuticals for which the FDA has approved a "New Drug Application" (NDA).

DATES: *Effective date:* From August 23, 1990, to August 23, 1993.

Comment closing date: In view of the interim nature of this rulemaking, comments will be welcome at any time during the three-year period.

ADDRESSES: Submit written comments and suggestions to the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, DC 20555, Attention: Docketing and Service Branch. Hand deliver comments to 11555 Rockville Pike, Rockville, Maryland, between 7:45 a.m. and 4:15 p.m. on Federal workdays.

Copies of the regulatory analysis, environmental assessment, and the comments received on this rule may be examined at the Commission's Public Document Room at 2120 L Street NW. (Lower Level), Washington, DC. Single copies of the Regulatory Analysis are available from Dr. Anthony Tse, Office of Nuclear Regulatory Research, U.S. Nuclear Regulatory Commission, Washington, DC 20555.

FOR FURTHER INFORMATION CONTACT: Dr. Tse, see **ADDRESSES** heading, Telephone (301) 492-3797.

SUPPLEMENTARY INFORMATION:

I. Background

A. Nuclear Medicine

Radioactive materials are used in drugs in the field of nuclear medicine. Drugs labeled with radioisotopes are known as radiopharmaceuticals. In diagnostic nuclear medicine, patients receive these materials by injection, inhalation, or oral administration. Physicians use radiation detection equipment to visualize the distribution of a radioactive drug within the patient. Using this technology, it is possible to locate tumors, assess organ function, or monitor the effectiveness of a treatment. An estimated 7 million diagnostic nuclear medicine procedures are performed in this country annually. In therapeutic nuclear medicine, radiopharmaceuticals are administered to treat various medical conditions (e.g., hyperactive thyroid). An estimated 30,000 therapeutic procedures are performed each year.

B. Regulatory Program and Policy Regarding Medical Use of Byproduct Materials

In a policy statement, "Regulation of the Medical Uses of Radioisotopes," published on February 9, 1979 (44 FR 8242), the NRC stated:

(1) The NRC will continue to regulate the medical uses [1] of radioisotopes as necessary to provide for the radiation safety of workers and the general public.

(2) The NRC will regulate the radiation safety of patients where justified by the risk to patients and where voluntary standards, or compliance with these standards, are inadequate.

(3) The NRC will minimize intrusion into medical judgments affecting patients and into other areas traditionally considered to be a part of the practice of medicine.

The NRC has the authority to regulate medical use to protect the health and safety of patients, but also recognizes that physicians have the primary responsibility for the protection of their patients. NRC regulations are predicated on the assumption that properly trained and adequately informed physicians will make decisions in the best interest of their patients.

Under the Federal Food, Drug, and Cosmetic Act, as amended, the Food and Drug Administration (FDA) regulates drug research and the manufacturer and sale of drugs, including radiopharmaceuticals. FDA has regulated the safety and effectiveness of investigational radioactive drugs since 1975, when FDA revoked its 1963 exemption of radioactive drugs from the "Investigational New Drug" (IND) regulation. The NRC withdrew from regulating radioactive drug safety and efficacy to avoid dual Federal regulation, but continues to regulate the radiation safety of workers, patients, and the public.

Each new drug approved for human use by the FDA, including radiopharmaceuticals, has labeling approved by FDA that includes a description of the drug, its pharmacology, indications for use, contraindications, warnings, adverse reactions, dosage and administration, and other information. The labeling of certain drugs, including some radiopharmaceuticals, includes manufacturer's instructions that specify the method of preparation. FDA reviews and approves the information in the labeling to ensure that it accurately reflects the data on safety and effectiveness on which the drug approval is based. NRC has, in the past, relied primarily on FDA's determination of a drug's safety and effectiveness when it is prepared and used according to the approved labeling, which some NRC regulations refer to as the package insert, as one means of ensuring protection of the public health and safety.

NRC regulations in 10 CFR 35.200(b) require medical use licensees to prepare radiopharmaceuticals in accordance with the manufacturer's instructions in the package insert (a part of the FDA-approved labeling). Similar requirements are placed on commercial nuclear pharmacies through NRC license conditions. Regulations in 10 CFR 35.300, "Use of Radiopharmaceuticals for Therapy," require, among other things, that the licensees comply with the package insert instructions regarding indications and method of administration for the therapeutic use of radiopharmaceuticals.

[1] "Medical use," as defined in 10 CFR 35.2, means the "intentional internal or external administration of byproduct material, or the radiation therefrom, to human beings in the practice of medicine in accordance with a license issued by a State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico." "Medical use" includes the diagnostic and therapeutic use of radiopharmaceuticals in the practice of nuclear medicine, but does not include *in vitro* diagnostic tests.

II. Petition for Rulemaking Filed by the American College of Nuclear Physicians and the Society of Nuclear Medicine

On June 8, 1989, the NRC docketed as PRM-35-9 a petition for rulemaking dated June 5, 1989, which was filed by the American College of Nuclear Physicians and the Society of Nuclear Medicine (ACNP-SNM). The ACNP-SNM are composed of over 12,000 individuals who participate in the medical use of byproduct materials. Members include physicians, technologists, and nuclear pharmacists. As characterized by the petitioners, the physicians supervise the preparation and administration of radiopharmaceuticals to diagnose and treat patients. Also, technologists administer radiopharmaceuticals to diagnose and perform clinical procedures under the direction and supervision of an authorized user physician.[2] Nuclear pharmacists reconstitute radiopharmaceutical kits, compound radiopharmaceuticals, and dispense radiopharmaceuticals for medical purposes.

Among other things,[3] the petitioners requested that the NRC amend its regulations at 10 CFR part 35, "Medical Use of Byproduct Material," to recognize their appropriate practice of medicine and to allow (1) departures from the manufacturer's instructions for preparing diagnostic radiopharmaceuticals and (2) the use of radiopharmaceuticals for therapeutic indications and methods of administration not included in the package insert approved by the FDA.

The petitioners stated that, under current NRC regulations, members of the petitioning organizations believe they cannot appropriately practice their professions. The petitioners also stated that authorized user physicians cannot prescribe certain radiopharmaceuticals or routes of administration for proper patient care, even though they believe they are permitted to do so by the FDA and by their State medical licenses. According to the petitioners, nuclear pharmacists have been disenfranchised as a professional entity because activities that they believe are permitted by the FDA and by the States are not allowed under NRC regulations. The petitioners stated that, although a nuclear pharmacist is authorized by State license to prepare radiopharmaceuticals upon receipt of a prescription by an authorized user physician, current NRC regulations severely restrict their activity. The petitioners believe that their professional activities are curtailed by the limitations imposed by the NRC on nuclear physicians and pharmacists.

A notice of receipt of the petition with a public comment period of 90 days was published in the **Federal Register** on September 15, 1989 (54 FR 38239). The Federal Register notice set forth the petitioners' proposed amendments to 10 CFR parts 30, 33, and 35, including the deletion of the restriction regarding the preparation of radiopharmaceuticals in § 35.200(b) and the deletion of the restriction in § 35.300, with respect to following the package insert instructions regarding indications and method of administration (54 FR 38240). The comment period closed on December 14, 1989, and 486 comment letters have been received.

Comments were received from many different sources such as hospitals, pharmacies, and medical associates. About 60 percent of the letters were similar to a form letter written for members of ACNP-SNM. These letters indicated agreement with the petition on all essential points. Fifteen percent of the comment letters were similar to a form letter written for the staff of Syncor International Corporation, also agreeing with the assertions in the petition. Twenty-five percent of the responses were letters from other individuals.

Most letters (99 percent) supported the petition and stated that the NRC should amend its regulations to relax its current restrictions on the practice of nuclear medicine and nuclear pharmacy. The majority of these letters did not provide specific supporting rationale. Some commenters provided rationale and examples of clinical cases that the commenters believe demonstrate how the relevant NRC regulations prevent physicians from providing proper care for their patients. The commenters stated that, although a licensee may request an exemption from specific requirements in the regulations on a case-by-case basis, this exemption process is time consuming and cumbersome. The commenters believe that a delay in order to obtain NRC approval for a particular departure from the package insert may, in some cases, jeopardize the patient's health. Some examples of clinical cases the commenters provided are described below:

(1) Licensees are not able to use Tc-99m macroaggregated albumin with high specific activity and low particle concentration to safely perform lung scans for patients who have pulmonary hypertension because the ranges of specific activity and particle concentration given in the package insert would be exceeded.

(2) Licensees are not able to add ascorbic acid as an antioxidant to Tc-99m-DTPA, which would increase stability and enhance image quality, because NRC regulations do not permit departure from the manufacturer's instructions for reconstituting reagent kits.

(3) When evaluating potential blood transfusions, licensees are not able to perform *in vivo* crossmatching using potential donor red cells radiolabeled with Tc-99m because this is not provided for in the package insert.

(4) Licensees are not able to use P-32 sodium phosphate to treat primary *Thrombocythemia* because this use is not specified in the package insert.

III. Need for a Rule

Information submitted by the ACNP-SNM in the petition for rulemaking and obtained during subsequent discussions with licensees indicates that the requirements in § 35.200(b) regarding preparation of radiopharmaceuticals and in § 35.300 regarding indications and method of administration for therapy procedures are preventing authorized user physicians from providing certain nuclear medicine clinical procedures. License conditions similar to § 35.200(b) currently placed on commercial nuclear pharmacies have the same effect. For some uncommon disease states or patient conditions, in order to provide proper patient care, it may be necessary to depart from the FDA-approved instructions to obtain diagnostic or therapeutic medical results not otherwise attainable or to reduce medical risks to particular patients because of their medical condition.

The NRC believes that continued application of these restrictions governing the preparation of radiopharmaceuticals and the indications and the method of administration for therapeutic use of radiopharmaceuticals would not permit proper patient care to be provided to some patients.

Under its 1979 Medical Use Policy Statement (44 FR 8242, February 9, 1979), the NRC stated that it would regulate the medical use of byproduct material in order to protect the health and safety of workers, patients, and the public. In general, NRC regulatory requirements are oriented to ensure that the properly prepared radiopharmaceutical is administered to the correct patient as prescribed by an authorized user

[2] Whenever the term "authorized user physician" is used, it means the "authorized user" or the physician working under the supervision of the authorized user.

[3] The NRC is working to resolve the remaining issues identified in the petition.

authorize departures from the manufacturer's instructions for eluting the generator or preparing the therapy kit.

Section 30.34 Terms and Conditions of Licenses

Commercial nuclear pharmacies are licensed pursuant to 10 CFR part 30, "Rules of General Applicability to Domestic Licensing of Byproduct Material." These licensees are required by a license condition similar to § 35.200(b) to elute generators and prepare reagent kits in accordance with the manufacturer's instructions. The NRC believes that authorized users obtaining radiopharmaceuticals from commercial nuclear pharmacy licensees should not be bound by this restriction in the commercial nuclear pharmacy license. Therefore, the NRC is amending 10 CFR 30.34, "Terms and Conditions of Licenses," to permit actions within the scope of those permitted by the new § 35.200(c). For situations not within the scope of the amended § 30.34, a commercial nuclear pharmacy licensee may file an application to have its license amended to permit specific departures from the manufacturer's instructions for identified products.

Under the interim rule, commercial nuclear pharmacy licensees would no longer be bound by the requirement in their licenses to follow the manufacturer's instructions for a radiopharmaceutical for which the FDA has approved an NDA if they have a written directive made by an authorized user physician directing a specific departure for a particular patient, or patients, or for a radiopharmaceutical, and which includes the specific nature of the departure, a precise description of the departure, and why the departure from the manufacturer's instructions would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. As in § 35.200(c), there is an exception to the requirement for a written directive before preparing the radiopharmaceutical in an emergency situation if an authorized user physician determines that a delay in obtaining the written directive would jeopardize the patient's health. In this case, the commercial nuclear pharmacy licensee shall obtain the written directive from the authorized user physician within 3 working days of the prescribed departure. The directive must contain information regarding the emergency and all other required information. Licensees shall keep those records in an auditable form and available for inspection for 5 years.

These amendments to § 30.34 take precedence over the restrictive conditions (*i.e.*, on eluting generators and preparing reagent kits for NDA radiopharmaceuticals) in the licenses of commercial nuclear pharmacies. Therefore, those parts of the license conditions no longer apply during the 3-year period when the interim rule is in effect. This interim rule does not address departures from IND generator elution instructions or IND protocol directions for reagent kit preparation, thus licensees shall continue to follow the IND instructions.

Continuing Applicability of Regulatory Requirements

The NRC notes that this interim rule does not relieve licensees from the requirements to comply with other applicable NRC, FDA, and other Federal or State regulations or NRC orders or license conditions concerning possession or use of byproduct material for medical use or other purposes as specified in 10 CFR parts 30, 32, 33, and 35. Moreover, if a radioactive biologic receives a product license approval (PLA), this interim rule does not authorize departures from the manufacturer's instructions for preparing the biologic. In addition, if a kit or generator for a radiopharmaceutical for therapy receives an approved NDA, this interim rule does not authorize departures from the manufacturer's instructions for eluting the generator or preparing the therapy kit. Neither of these approvals exists at this time and neither is authorized by current regulations.

Radiation Safety Responsibilities of Medical Use Licensees

NRC medical use licensees are required by § 35.21 to appoint a Radiation Safety Officer (RSO) responsible for implementing the licensee's radiation safety program. The licensee is required, through the RSO, to ensure that radiation safety activities are being performed in accordance with approved procedures and regulatory requirements in the daily operation of the licensee's byproduct material program. Nothing in this rulemaking relieves the licensee from complying with the requirements of § 35.21.

In accordance with 10 CFR 35.22, NRC medical institution licensees are required to establish a Radiation Safety Committee (RSC) to oversee the use of byproduct material. The duties of the RSC are specified in § 35.22(b) and include reviews, on the basis of safety, of numerous aspects of a licensee's use of byproduct material. Nothing in this rulemaking relieves the licensee from complying with the requirements of § 35.22.

VI. Administrative Statements

Finding of No Significant Environmental Impact: Availability

The Commission has determined under the National Environmental Policy Act of 1969, as amended, and the Commission's regulations in subpart A of 10 CFR part 51 that these amendments are not a major Federal action significantly affecting the quality of the human environment and therefore an environmental impact statement is not required. This interim rule amends NRC regulations to permit licensees who elute generators and prepare reagent kits to depart from the manufacturer's instructions if those persons have a written directive made by an authorized user physician that requests a specific departure for a particular patient, or patients, or for a radiopharmaceutical. This directive must provide the specific nature of the departure, a precise description of the departure, and the reasons why the departure from the manufacturer's instructions would obtain medical results, diagnostic or therapeutic, not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. The amendment does not address departures from IND generator elution instructions or IND protocol directions for reagent kit preparation. The NRC is also modifying its regulations to permit, if certain requirements are met, the therapeutic use of radiopharmaceuticals without following the package instructions regarding indications and method of administration. The interim rule does not affect the exemption in 10 CFR part 20 for the intentional exposure of patients to radiation for the purpose of medical diagnosis and therapy.

Although the rule may cause some patients to be exposed to higher or lower levels of radiation than otherwise expected, those exposures would be given to obtain medical results not otherwise attainable or to reduce other risks to the patient. It should be noted that current requirements do not limit the radiation dose prescribed by the authorized user physician for either diagnosis or therapy. The amendments would not relieve licensees from meeting the requirements in 10 CFR parts 20 and 35 that restrict radiation exposure to medical care personnel in the restricted area or to the general public in the unrestricted area, or radioactive effluent releases. It is expected that there would be no

physician. Aside from the requirements in § 35.200(b) and § 35.300, other requirements in part 35, such as the use of dose calibrators, are intended to ensure that the patient receives the prescribed dose. NRC's regulations need to provide a balance between adequate controls and avoidance of undue interference in medical judgments. The high level of public health and safety protection that accrues from following the FDA-approved instructions must be balanced with the need to depart from those instructions to obtain diagnostic or therapeutic results not otherwise attainable or to reduce patient risk in some uncommon disease states or patient conditions in order to provide proper patient care.

The diagnostic use of radiopharmaceuticals is, in most cases, an area of inherently low radiation risk to patients (Policy Statement, 44 FR 8242; February 9, 1979). Although there are greater risks inherent in the use of therapeutic levels of radioactive drugs, in light of the information provided with and gathered subsequent to the petition, the NRC does not believe that limiting the therapeutic use of radiopharmaceuticals in all cases to only the indications and methods of administration specified in the package insert is justified. Moreover, as stated in its 1979 Policy Statement, the NRC recognizes that physicians have the primary responsibility for the protection of their patients. The Commission believes that basic decisions concerning the diagnosis and treatment of disease are a part of the physician-patient relationship and are traditionally considered to be part of the practice of medicine.

The NRC has made a determination that continued application of the subject requirements, without exceptions, may adversely affect the public health and safety because the delivery of proper patient care may require, in certain instances, that some radiopharmaceuticals be prepared and administered in a manner different from that stated in the FDA-approved instructions. The NRC has reviewed the information on nuclear medicine clinical procedures and believes that adequate protection of the public health and safety can be maintained while, at the same time, providing proper patient care. Hence, the NRC is issuing an interim final rule that permits, on the direction of an authorized user physician, departures from the manufacturer's instructions in preparing radiopharmaceuticals and departures from package inserts for indication and method of administration for therapeutic use, provided a proper record of the departure is made. These records will be examined by the NRC to determine whether to extend the interim period for the rule, make the rule permanent, or revise it based on the nature of, reasons for, and frequency of departures. The NRC will provide FDA the opportunity to review this information.

Because these amendments involve relief from restrictions which if left in place could have an adverse impact on public health and safety, and because the NRC has received and considered public comments on the petition for rulemaking, good cause exists for omitting the notice of proposed rulemaking and the public procedures thereon as unnecessary and contrary to the public interest, and for making these amendments effective upon publication in the **Federal Register** without the customary thirty-day notice. This interim rule will terminate 3 years after the date of publication in the **Federal Register**.

IV. Future Agency Action

This interim rule amending 10 CFR parts 30 and 35 represents only one phase of NRC's resolution of the ACNP-SNM petition for rulemaking. During the 3-year period, the NRC may modify the interim rule or take other regulatory action it determines necessary to protect the public health and safety. Based on continued NRC analysis of the ACNP-SNM petition, the comments on petition and on this interim rule, experience with the implementation of this interim rule, and other information, the NRC may propose amendments to this rule or to other provisions of 10 CFR parts 30 and 35 as part of its resolution of all the issues raised in PRM-35-9.

V. Discussion

Section 35.200 Use of Radiopharmaceuticals, Generators, and Reagent Kits for Imaging and Localization Studies

The NRC believes that persons licensed by the NRC to elute generators and prepare reagent kits should not always be bound by the requirement specified in 10 CFR 35.200(b) to follow the manufacturer's instructions for radiophmaceuticals for which the FDA has approved an NDA. They should not be bound if they have a written directive (*e.g.*, prescription) made by an authorized user physician directing a specific departure for a particular patient, or patients, or for a radiopharmaceutical, and which includes (1) the specific nature of the departure, (2) a precise description of the departure, and (3) a brief statement of the reasons why the departure from the manufacturer's instructions would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. The NRC recognizes that the physician may face severe time constraints during an emergency; therefore, an exception has been provided in § 35.200(c). Under the exception, a written directive is not required before preparing the radiopharmaceutical if an authorized user physician determines that the delay in obtaining a written directive would jeopardize the patient's health. The written directive together with a statement of the emergency determination must be prepared with 3 working days of the emergency administration. The written directive and a record of the number of patient administrations under each departure must be retained by the licensee for a period of 5 years and made available for NRC inspection.

This interim rule does not address departures from "Investigational New Drug" (IND) generator elution instructions or IND protocol directions for reagent kit preparation because the departures may compromise the scientific integrity of the clinical investigation. Therefore, licensees must continue to follow the IND generator elution instructions and IND protocol directions for reagent kit preparation.

Section 35.300 Use of Radiopharmaceuticals for Therapy

For a radiopharmaceutical for which the FDA has approved an NDA, the amendments to § 35.300 would permit a licensee, under certain circumstances, to use therapeutic radiopharmaceuticals for indications or a method of administration not specified in the package insert. Specifically, these uses would be permitted if an authorized user physician makes a record of the departure which includes the specific nature of the departure and a brief statement of the reasons why the departure would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. A record of the departures from indications and method of administration and a record of the number of patient administrations under each departure must be retained in an auditable form and be available for inspection for 5 years. If a kit or generator for a radiopharmaceutical for therapy were approved by FDA (through an NDA), this interim rule does not

significant change, either increase or decrease, in radiation exposure to the public or to the environment beyond the exposures currently resulting from deliver the dose to the patient.

The Environmental Assessment and Finding of No Significant Impact is available for inspection at the NRC Public Document Room at 2120 L Street NW. (Lower Level), Washington, DC. Single copies of the Assessment are available from Dr. Tse (see **ADDRESSES** heading).

Paperwork Reduction Act Statement

This final rule amends information collection requirements that are subject to the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 *et seq.*). These requirements were approved by the Office of Management and Budget approval numbers 3150–0010 and 3150–0017.

Public reporting burden for this collection of information is estimated to average .05 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to the Information and Records Management Branch (MNBB–7714), U.S. Nuclear Regulatory Commission, Washington, DC 20555; and to the Desk Officer, Office of Information and Regulatory Affairs, NEOB–3019 (3150–0017 and 3150–0010), Office of Management and Budget, Washington, DC 20503.

Regulatory Analysis

The Commission has prepared a regulatory analysis for these amendments. The analysis examines the benefits and impacts considered by the NRC. The regulatory analysis is available for inspection at the NRC Public Document Room at 2120 L Street NW. (Lower Level), Washington, DC. Single copies are available from Dr. Tse (see **ADDRESSES** heading).

The Commission requests public comments on the regulatory analysis. Comments are welcome at any time during the three-year period that the interim final rule is in effect. Comments on the analysis may be submitted to the NRC as indicated under the **ADDRESSES** heading.

Backfit Analysis

The NRC has determined that the backfit rule, 10 CFR 50.109, does not apply to these amendments because they do not involve any provisions that would impose backfits as defined in 10 CFR 50.109(a)(1).

List of Subjects

10 CFR Part 30

Byproduct material, Criminal penalty, Government contracts, Intergovernmental relations, Isotopes, Nuclear materials, Radiation protection, Reporting and recordkeeping requirements.

10 CFR Part 35

Byproduct material, Criminal penalty, Drugs, Health facilities, Health professions, Incorporation by reference, Medical devices, Nuclear materials, Occupational safety and health, Radiation protection, Reporting and recordkeeping requirements.

For the reasons set out in the preamble and under the authority of the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974, as amended, and 5 U.S.C. 552 and 553, the NRC is adopting the following amendments to 10 CFR parts 30 and 35.

PART 30—RULES OF GENERAL APPLICABILITY TO DOMESTIC LICENSING OF BYPRODUCT MATERIAL

1. The authority citation for part 30 is revised to read as follows:

Authority: Secs. 81, 82, 161, 182, 183, 186, 68 Stat. 935, 948, 953, 954, 955, as amended, sec. 234, 83 Stat. 444, as amended (42 U.S.C. 2111, 2112, 2201, 2232, 2233, 2236, 2282); secs. 201, as amended, 202, 206, 68 Stat. 1242, as amended, 1244, 1246 (42 U.S.C. 5841, 5842, 5846).

Section 30.7 also issued under Pub. L. 95–601, sec. 10, 92 Stat. 2951 (42 U.S.C. 5851). Section 30.34(b) also issued under sec. 184, 68 Stat. 954, as amended (42 U.S.C. 2234). Section 30.61 also issued under sec. 187, 68 Stat. 955 (42 U.S.C. 2237).

For the purposes of sec. 223, 68 Stat. 958, as amended (42 U.S.C. 2273); §§ 30.3, 30.34(b), (c), (f), (g), and (i), 30.41(a) and (c), and 30.53 are issued under sec. 161b, 68 Stat. 948, as amended (42 U.S.C. 2201(b)); and §§ 30.6, 30.9, 30.34(g), 30.36, 30.51, 30.52, 30.55, and 30.56(b) and (c) are issued under sec. 161o, 68 Stat. 950, as amended (42 U.S.C. 2201(o)).

2. In § 30.34, paragraph (i) is added to read as follows:

§ 30.34 Terms and conditions of licenses.

* * * * *

(i)(1) From August 23, 1990, to August 23, 1993, each licensee eluting generators and processing radioactive material with diagnostic reagent kits for which the Food and Drug Administration (FDA) has approved a "New Drug Application" (NDA) may depart from the manufacturer's elution and preparation instructions (for radiopharmaceuticals authorized for use pursuant to § 35.200) provided that:

(i) The licensee has a written directive made by an authorized user physician that directs a specific departure for a particular patient, or patients, or for a radiopharmaceutical, and which includes the specific nature of the departure, a precise description of the departure, and a brief statement of the reasons why the departure from the manufacturer's instructions for preparing the radiopharmaceutical would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. The licensee shall keep the written directive and record of the number of prescriptions dispensed under the departure in an auditable form and available for inspection for 5 years; or

(ii) An authorized user physician determines, in accordance with § 35.200(c), that a delay in preparing the radiopharmaceutical in order to make a written directive would jeopardize the patient's health because of the emergent nature of the patient's medical condition. In this case, the licensee shall obtain the written directive made by the authorized user physician which contains the notation regarding the emergency and all the information specified in paragraph (i)(1)(i) of this section within 3 working days after the prescribed departure. The licensee shall keep these records in an auditable form and available for inspection for 5 years.

(2) The actions authorized in paragraph (i)(1) of this section are permitted notwithstanding more restrictive language in license conditions unless those license conditions specifically reference § 30.34(i).

(3) Nothing in this section relieves the licensee from complying with other applicable NRC, FDA, and other Federal or State regulations governing the elution of generators and preparation of reagent kits.

PART 35—MEDICAL USE OF BYPRODUCT MATERIAL

3. The authority citation for part 35 is revised to read as follows:

Authority: Secs. 81, 161, 182, 183, 68 Stat. 935, 948, 953, 954, as amended (42 U.S.C. 2111, 2201, 2232, 2233); sec. 201, 88 Stat. 1242, as amended (42 U.S.C. 5841).

For the purposes of sec. 223, 68 Stat. 958, as amended (42 U.S.C. 2273); §§ 35.11, 35.13, 35.20 (a) and (b), 35.21 (a) and (b), 35.22, 35.23, 35.25, 35.27 (a), (c) and (d), 35.31 (a), 35.49, 35.50 (a)–(d), 35.51 (a)–(c), 35.53 (a)–(b), 35.59 (a)–(c), (e)(1), (g) and (h), 35.60, 35.61, 35.70 (a)–(f), 35.75, 35.80 (a)–(e), 35.90, 35.92(a),

35.120, 35.200 (b) and (c), 35.204 (a) and (b), 35.205, 35.220, 35.300, 35.310(a), 35.315, 35.320, 35.400, 35.404(a), 35.406 (a) and (c), 35.410(a), 35.415, 35.420, 35.500, 35.520, 35.605, 35.606, 35.610 (a) and (b), 35.615, 35.620, 35.630 (a) and (b), 35.632 (a)–(f), 35.634 (a)–(e), 35.636 (a) and (b), 35.641 (a) and (b), 35.643 (a) and (b), 35.645 (a) and (b), 35.900, 35.910, 35.920, 35.930, 35.932, 35.934, 35.940, 35.941, 35.950, 35.960, 35.961, 35.970, and 35.971, are issued under sec. 161b, 68 Stat. 948, as amended (42 U.S.C. 2201(b)); and §§ 35.14, 35.21(b), 35.22(b), 35.23(b), 35.27 (a) and(c), 35.29(b), 35.33 (a)–(e), 35.36(b), 35.50(e), 35.51(d), 35.53(c), 35.59 (d) and (e)(2), 35.59 (g) and (i), 35.70(g), 35.80(f), 35.92(b), 35.200(c), 35.204(c), 35.300(b), 35.310(b), 35.315(b), 35.404(b), 35.406 (b) and (d), 35.410(b), 35.415(b), 35.610(c), 35.615(d)(4), 35.630(c), 35.632(g), 35.634(f), 35.636(c), 35.641(c), 35.643(c), 35.645, and 35.647(c) are issued under sec. 161o, 68 Stat. 950, as amended (42 U.S.C. 2201(o)).

4. In § 35.8, paragraph (b) is revised to read as follows:

§ 35.8 Information collection requirements: OMB approval.

* * * * *

(b) The approved information collection requirements contained in this part appear in §§ 35.12, 35.13, 35.14, 35.21, 35.22, 35.23, 35.27, 35.29, 35.31, 35.33, 35.50, 35.51, 35.53, 35.59, 35.60, 35.61, 35.70, 35.80, 35.92, 35.200, 35.204, 35.205, 35.300, 35.310, 35.315, 35.404, 35.406, 35.410, 35.415, 35.606, 35.610, 35.615, 35.630, 35.632, 35.634, 35.636, 35.641, 35.643, 35.645, and 35.647.

* * * * *

5. In § 35.200, paragraph (c) is added to read as follows:

§ 35.200 Use of radiopharmaceuticals, generators, and reagent kits for imaging and localization studies.

* * * * *

(c)(1) From August 23, 1990, to August 23, 1993, a licensee may depart from the manufacturer's instructions for eluting generators and preparing reagent kits for which FDA has approved an NDA, provided that the licensee has a written directive made by an authorized user physician that directs a specific departure for a particular patient, or patients, or for a radiopharmaceutical, and which includes the specific nature of the departure, a precise description of the departure, and a brief statement of the reasons why the departure from the manufacturer's instructions for preparing the radiopharmaceutical would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. If the authorized user physician determines that a delay in preparing the radiopharmaceutical in order to make a written directive would jeopardize the patient's health because of the emergency nature of the patient's medical condition, the radiopharmaceutical may be prepared without first making a written directive. The authorized user physician shall make notation of this determination in the written directive within 3 working days after the prescribed departure.

(2) The licensee shall keep the written directive and a record of the number of patient administrations under the departure in an auditable form and available for inspection for a period of 5 years.

(3) Nothing in this section relieves the licensee from complying with other applicable NRC, FDA, and other Federal or State regulations governing the elution of generators and preparation of reagent kits.

6. In § 35.300, the existing text is designated as paragraph (a) and a new paragraph (b) is added to read as follows:

§ 35.300 Use of radiopharmaceuticals for therapy.

* * * * *

(b)(1) From August 23, 1990, to August 23, 1993, a licensee may depart from the package insert instructions regarding indications or method of administration for a radiopharmaceutical for which FDA has approved an NDA, provided that the authorized user physician makes a record of the departure which includes the specific nature of the departure and a brief statement of the reasons why the departure would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. Licensees are not authorized to depart from the manufacturer's instructions for eluting a generator or preparing any kit for a radiopharmaceutical for therapy.

(2) The licensee shall obtain this record within 3 working days of the administration and keep this record and a record of the number of patient administrations under the departure in an auditable form and available for inspection for 5 years.

(3) Nothing in this section relieves the licensee from complying with other applicable NRC, FDA (including requirements governing the submission of an IND), and other Federal or State regulations governing the use of radiopharmaceuticals for therapy.

Dated at Rockville, Maryland, this 17th day of August 1990.

For the Nuclear Regulatory Commission.

Samuel J. Chilk,

Secretary of the Commission.

[FR Doc. 90–19901 Filed 8–22–90; 8:45 am]

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UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555

AD43-2
PDR

ASSOCIATED WITH 55 FR 34513
AUGUST 23, 1990

Regulatory Analysis
10 CFR Parts 30 and 35

Authorization to Prepare Radiopharmaceutical Reagent Kits and Elute Radiopharmaceutical Generators; Use of Radiopharmaceuticals for Therapy

1. Statement of Problem

The NRC has received and docketed a petition for rulemaking filed by the American College of Nuclear Physicians and the Society of Nuclear medicine (54 FR 38239, September 15, 1989). The petitioners stated that, under current NRC regulations, nuclear physicians and nuclear pharmacists cannot appropriately practice their professions. The petitioners requested that, among other things, the NRC (a) allow medical use and commercial nuclear pharmacy licensees to depart from package insert instructions for preparing radiopharmaceuticals using generators or reagent kits and (b) allow medical use licensees to depart from package insert instructions regarding indications or method of administration for therapeutic use of radiopharmaceuticals.

Current license conditions require commercial nuclear pharmacy licensees to follow the manufacturer's instructions, which are part of the Food and Drug Administration (FDA)[1] approved labeling, when preparing radiopharmaceuticals using generators or reagent kits. Regulations in Subpart E at § 35.200(b) require medical use licensees to follow the FDA-approved instructions when preparing radiopharmaceuticals using generators or reagent kits. Further, Subpart F at § 35.300 requires medical use licensees to comply with the FDA-approved package insert instructions regarding indications and method of administration, e.g., to limit the disease states to be treated with each radiopharmaceutical to those listed in its package insert, or to prohibit administration of an oral radiopharmaceutical by intravenous injection.

2. Objectives

In medical use, NRC's objectives are to protect the public health and safety, including patients, from radiological hazards and, at the same time, to permit the widest possible use of byproduct material in providing medical benefit to patients.

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1 FDA is the national authority for drug safety and efficacy, including radiopharmaceuticals. Before a drug can be legally marketed in the United States, the FDA must determine that the drug is safe and effective and approve the instructions contained in the package insert, including the manufacturer's instructions for preparing radiopharmaceuticals.

3. Alternatives

Two alternatives have been considered:

(A) Maintain the status quo pending resolution of all issues of the petition.

(B) Amend Parts 30 and 35 (on an interim basis): (a) to allow medical use and commercial nuclear pharmacy licensees to depart from manufacturer's instructions for preparing radiopharmaceuticals using generators and reagent kits, and (b) to allow medical use licensees to depart from package insert instructions regarding indications and method of administration for therapeutic use of radiopharmaceuticals. The interim rule will be effective for 3 years after the date of publication.

4. Consequences

(A) The first alternative, maintaining the status quo, would continue to prohibit preparation of radiopharmaceuticals or therapeutic use not described in the FDA-approved instructions. This alternative may prevent medical use licensees from providing diagnostic or therapeutic medical results not otherwise attainable or to reduce the medical risks to particular patients because of their medical condition.

(B) The second alternative, promulgating an interim rule, would allow medical use licensees to exercise professional discretion in the selection and use of the proper diagnostic or therapeutic procedures even if these procedures are not described in the package insert.

The diagnostic use of radiopharmaceuticals is, in most cases, an area of inherently low radiation risk to patients. Although there are greater risks inherent in the use of therapeutic levels of radioactive drugs, in light of the information provided with and gathered subsequent to receipt of the petition, NRC does not believe that limiting the therapeutic use of radiopharmaceuticals in all cases to only the indications and methods of administration specified in the package insert is justified. Moreover, as stated in its 1979 policy statement, the NRC recognizes that physicians have the primary responsibility for the protection of their patients. The Commission believes that basic decisions concerning the diagnosis and treatment of disease are a part of the physician-patient relationship and are traditionally considered to be part of the practice of medicine.

No data exist on the nature of, reasons for, and frequency of the departures that would be permitted under this interim rule. While the interim rule is in effect, this information will be collected and examined to determine whether to extend the interim period for the rule, make the rule permanent, or revise it.

5. Decision Rationale

The NRC has made a determination that continued application of the subject requirements, without exceptions, may adversely affect the public health and safety because the delivery of proper patient care may require, in certain instances, that some radiopharmaceuticals be prepared and administered in a manner different from that stated in the FDA-approved instructions. The NRC has reviewed information on nuclear medicine clinical procedures and believes that adequate protection of the public health and safety can be maintained while, at the same time, providing proper patient care. Hence, the NRC is issuing this interim final rule.

6. Implementation

Because these amendments involve relief from restrictions which if left in place could have an adverse impact on public health and safety, and because the NRC has received and considered public comments on the petition for rulemaking, good cause exists for omitting the notice of proposed rulemaking and the public procedures thereon as unnecessary and contrary to the public interest, and for making these amendments effective upon publication in the Federal Register without the customary thirty-day notice. This interim rule will be in effect for a period of 3 years after publication in the Federal Register.

AD 43-2
PDR

ASSOCIATED WITH 55 FR 34513
AUGUST 23, 1990

ENVIRONMENTAL ASSESSMENT; FINDING OF NO SIGNIFICANT IMPACT FOR THE IMMEDIATELY EFFECTIVE INTERIM FINAL RULE AMENDING 10 CFR PARTS 30 AND 35 ELUTION OF GENERATORS AND PREPARATION OF REAGENT KITS IN ACCORDANCE WITH THE MANUFACTURER'S INSTRUCTIONS; USE OF RADIOPHARMACEUTICALS FOR THERAPY

I. INTRODUCTION

The Nuclear Regulatory Commission (NRC) is amending, on a three-year interim basis, its regulations at 10 CFR Parts 30 and 35 related to the preparation and uses of radiopharmaceuticals. The interim rule modifies the requirement that licensees who elute generators and prepare reagent kits do so only in accordance with the Food and Drug Administration (FDA) approved manufacturer's instructions included in the package insert; licensees would have to comply with certain conditions and limitations. The interim rule would also permit NRC licensees using byproduct material in a radiopharmaceutical for a therapeutic use to depart from the package insert instructions regarding indications and method of administration. The interim rule would only apply to radiopharmaceuticals for which FDA has approved a "New Drug Application" (NDA).

Information submitted by the American College of Nuclear Physicians (ACNP) and the Society of Nuclear Medicine (SNM) in a petition for rulemaking (54 FR 38239, September 15, 1989) and information obtained from public comments and during subsequent discussions with licensees, indicates that these requirements may, in some cases, prevent authorized user physicians from providing certain clinical procedures to some patients. Departures from the manufacturer's instructions may be necessary to obtain improved images and examination results or to diminish the risk to specific patients with uncommon disease states.

II. THE NEED FOR THE FINAL ACTION

The NRC has made a determination that continued application of the subject requirements, without exceptions, may adversely affect the public health and safety because the delivery of proper patient care may require, in certain instances, that some radiopharmaceuticals be prepared and administered in a manner different from that stated in the FDA-approved instructions.

III. THE ENVIRONMENTAL IMPACT OF THE FINAL ACTION

The regulatory action. The interim final rule does not identify specific types of departures from the manufacturer's instructions that can be made. This rule

does not authorize departures from the manufacturer's instructions for "Investigational New Drug" (IND) products.

Effects of the regulatory action. The NRC anticipates that changes in the preparation of diagnostic radiopharmaceuticals and changes in the indications and method of administration for therapeutic radiopharmaceuticals may result in increased or decreased specific activity, differences in biodistribution, and differences in solubility when compared to radiopharmaceuticals prepared according to the FDA-approved instructions. Following administration of a diagnostic or therapeutic radiopharmaceutical to the patient, other effects, such as altered target to non-target ratio, biological half-life of the radiopharmaceutical, data acquisition time, or sensitivity and specificity of the diagnostic examination may be seen. The changes may result in a minor increase or decrease in radiation exposure to the patient, physicians and technologists, medical care personnel, and the general public. Departures from the FDA-approved instructions may also cause a minor increase or decrease in radiation levels in restricted and unrestricted areas.

Impact on the patient. Although the interim rule may cause some patients' organs and tissue to be exposed to higher or lower levels of radiation than those expected if the manufacturer's instructions were followed, these exposures would be for the purpose of obtaining diagnostic results not otherwise obtainable or would reduce other medical risks to particular patients because of their medical conditions. Routine exposures for diagnostic nuclear medicine examinations are usually less that 500 millirem to the whole body and are regarded as being of low risk to the patient. The interim rule does not affect the exemption in 10 CFR Part 20 for the intentional exposure of patients to radiation for the purpose of medical diagnosis and therapy. It should be noted that current requirements do not limit the radiation dose prescribed by the authorized user physician for either diagnosis or therapy.

Licensees performing radiopharmaceutical therapy will no longer be compelled to follow the package insert instructions regarding indications and methods of administration as required under 10 CFR 35.300. Under the interim rule, authorized user physicians will be free to exercise their professional judgment regarding the appropriate use of radiopharmaceuticals for therapy.

Under the interim rule, the application of therapeutic radiopharmaceuticals may increase or decrease radiation exposure to selected patients and their organs and tissues. However, nothing in the interim final rule will diminish the licensee's obligation to comply with the provisions of 10 CFR 35.75 regarding the release of patients containing radiopharmaceuticals.

Under the interim rule, the specific departure requested by the authorized user physician must state the nature of the departure, a specific description of the departure, and the reasons why the departure would obtain medical results not otherwise attainable or would reduce medical risks to particular patients because of their medical condition. In some cases, the departure will provide improved diagnostic examinations or unique therapeutic or palliative advantages for those patients with uncommon medical conditions.

Impact on medical care personnel. Medical care personnel may be exposed to increased or decreased radiation during the preparation and administration of the radiopharmaceutical and through contact with the patient, contaminated patient care materials, patient saliva, perspiration, urine, or excrement. The impact on personnel exposure is limited by the implementation of radiation safety procedures, radiation protection surveys, personnel radiation exposure monitoring, and the routine use of personal protective measures such as anti-contamination gloves and lab coats. The rule does not relieve the licensee from meeting the radiation safety requirements in 10 CFR Part 20, "Standards for Protection Against Radiation," and the administrative and technical requirements in 10 CFR Part 35, "Medical Use of Byproduct Material." These regulations provide limits for radiation dose rates and air concentrations of radioactive materials in restricted areas and impose requirements to evaluate radiation hazards, provide personnel monitoring, conduct contamination surveys, and implement waste disposal procedures. These requirements ensure that radiation doses to medical care workers who are potentially exposed to radiation are as low as reasonably achievable and are well under the maximum personal exposure levels described in 10 CFR Part 20.

Impact on members of the public. The general public might be exposed to slightly increased or decreased radiation or radioactive materials resulting from contact with the patient. The majority of nuclear medicine procedures use technetium-99m, which has a half-life of six hours. For technetium-99m procedures, the dose rate to the general public reduces dramatically within 24 hours; thus, patients undergoing diagnostic nuclear medicine examinations are generally not restricted to controlled areas after radiopharmaceuticals are administered.

NRC has regulations that protect the general public from the patient who has been administered byproduct material in quantities that may unnecessarily expose members of the general public. For example, 10 CFR 35.75 prohibits the release from confinement for medical care of a patient who has been administered a radiopharmaceutical until either the measured dose rate from the patient is less than 5 millirems per hour at a distance of one meter or the activity in the patient is less than 30 millicuries.

NRC's requirements on waste disposal by decay in storage, 10 CFR 35.92, only allow disposal to unrestricted areas after the waste has been decayed in storage for 10 half-lives and measured to ensure that there is no detectable radiation prior to release. The NRC specifically exempts contaminated excreta from individuals undergoing medical diagnosis or therapy from regulatory restrictions when it is released to sanitary sewerage systems (see 10 CFR 20.303(d)). The NRC believes that the interim rule will have little effect on the amount of radioactivity released to the sanitary sewerage systems.

Impact on the ecosystem. Under the interim rule, radiation exposure to the ecosystem will not be significantly different from the exposures under current regulations, which is small. Thus, it is likely that the interim rule will not have a significant impact on the ecosystem.

IV. ALTERNATIVES TO THE FINAL ACTION

The NRC has identified one alternative to issuing the interim final rule. It is described in the following paragraphs.

No action. The NRC could take no action and continue to require its medical use licensees to follow the manufacturer's instructions for the preparation of NDA products. This would not result in any change in radiation exposures to medical care personnel, patients, or the general public. However, it would likely result in certain patients being denied diagnostic and therapeutic clinical procedures modified to take into account their unique disease states or conditions.

If no action is taken, NRC would continue to require NRC licensees to follow the FDA-approved instructions, and NRC would be required to review and possibly approve individual licensees' amendment requests for approval of specific departures from the manufacturer's instructions for preparing each radiopharmaceutical. Although the NRC could evaluate each license amendment request on the basis of radiation safety, the NRC would not be able to make determinations about the medical safety and effectiveness of each departure without assistance. License amendment requests would have to be forwarded to the FDA for review and approval of medical safety and effectiveness. If approved, license amendments permitting the specific departure from a manufacturer's instruction for preparing each radiopharmaceutical requested by the licensee would need to be issued.

Although the review and approval process described above would inform NRC of the types of specific departures licensees want to make, the delays encountered during the license amendment process would serve to deny timely medical care to patients. If there were many requests for departures, this process could increase the NRC's licensing burden by increasing the number of individual license amendments processed every year.

In summary, if no action were taken there would be little change in radiation exposures currently received by medical care personnel, patients, and the general public. However, there would be administrative and financial burdens to licensees and to the NRC. There also might be unacceptable delays in medical care.

V. ALTERNATIVE USE OF RESOURCES

The NRC will use about 0.5 staff years to collect and evaluate the information on the departures from the package insert in the preparation of radiopharmaceuticals and additional radiopharmaceutical therapy procedures.

VI. AGENCIES AND PERSONS CONSULTED

The NRC staff has discussed this interim rule with the staff from the FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. The staff also provided a draft of the interim final rule to the FDA for review and has received and incorporated its recommendations. The FDA does not object to NRC issuing an interim final rule.

VII. FINDING OF NO SIGNIFICANT IMPACT: AVAILABILITY

The Commission has determined under the National Environmental Policy Act of 1969, as amended, and the Commission's regulations in Subpart A of 10 CFR Part 51, that these amendments are not a major Federal action significantly affecting the quality of the human environment, and therefore, an environmental impact statement is not required. This interim rule amends NRC regulations to permit licensees who elute generators and prepare reagent kits to depart from the manufacturer's instructions if those persons have a written directive made by an authorized user physician which requests a specific departure for a particular patient, or patients, or for a radiopharmaceutical. This directive must provide the specific nature of the departure, a precise description of the departure, and the reasons why the departure from the manufacturer's instructions would obtain diagnostic or therapeutic medical results not otherwise attainable or to reduce medical risks to particular patients because of their medical condition. The amendment does not address departures from IND generator elution instructions or IND protocol directions for reagent kit preparation. The NRC is also modifying its regulations to permit, if certain requirements are met, the therapeutic use of radiopharmaceuticals without following the FDA-approved package insert regarding indications and method of administration.

The interim rule does not affect the exemption in 10 CFR Part 20 for the intentional exposure of patients to radiation for the purpose of medical diagnosis and therapy. Although the rule may cause some patients to be exposed to higher or lower levels of radiation than otherwise expected, those exposures would be given to obtain medical results not otherwise attainable or to reduce other risks to the patient. It should be noted that current requirements do not limit the radiation dose prescribed by the authorized user physician for either diagnosis or therapy. The amendments would not relieve licensees from meeting the requirements in 10 CFR Parts 20 and 35 that restrict radiation exposure to medical care personnel in the restricted area, or to the general public in the unrestricted area, or radioactive effluent releases. It is expected that there would be no significant change, either increase or decrease, in radiation exposure to the public or to the environment beyond the exposures currently resulting from delivering the dose to the patient.

UNITED STATES
NUCLEAR REGULATORY COMMISSION
Office of Governmental and Public Affairs
Washington, D.C. 20555

No. 90-116
Tel. 301/492-0240

FOR IMMEDIATE RELEASE
(Friday, August 24, 1990)

NUCLEAR REGULATORY COMMISSION ISSUES INTERIM RULE ON MEDICAL USES OF NUCLEAR MATERIAL

The Nuclear Regulatory Commission is amending, on a three-year interim basis, its regulations for medical uses of nuclear material to give greater discretion to nuclear physicians and pharmacies in how they prepare, use and administer prescription drugs containing radioactive materials.

The amendments are in response to a petition filed with the NRC by the American College of Nuclear Physicians and the Society of Nuclear Medicine (ACNP-SNM).

The interim rule, which is effective immediately, permits, at the direction of an authorized physician, departures from the manufacturer's instructions in the preparation of radiopharmaceuticals to be used for diagnostic procedures, provided a proper record of the departure is made. The manufacturer's instructions are contained in package inserts that are part of the Food and Drug Administration approved labeling. The rule also permits departures from package insert instructions for indications and method of administration for their therapeutic use, provided a proper record of the departure is made.

Current NRC regulations do not permit these departures.

The interim rule represents only one phase of the NRC's response to the ACNP-SNM petition for rulemaking. Based on continued NRC analysis of the petition, comments on the interim rule, experience with implementation of the interim rule and other information, the NRC will make a decision on whether to extend the interim period for the rule, make it permanent or revise it.

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