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NUCLEAR REGULATORY COMMISSION

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UNITED STATES OF AMERICA

NUCLEAR REGULATORY COMMISSION

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AFFIRMATION/DISCUSSION AND VOTE

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PUBLIC MEETING

Nuclear Regulatory Commission
One White Flint North
Rockville, Maryland

Wednesday, July 18, 1990

The Commission met in open session, pursuant to notice, at 4:33 p.m., Kenneth M. Carr, Chairman, presiding.

COMMISSIONERS PRESENT:

KENNETH M. CARR, Chairman of the Commission
KENNETH C. ROGERS, Commissioner
JAMES R. CURTISS, Commissioner
FORREST J. REMICK, Commissioner

STAFF SEATED AT THE COMMISSION TABLE:

WILLIAM C. PARLER, General Counsel

ANDREW BATES, Office of the Secretary

P-R-O-C-E-E-D-I-N-G-S

4:33 p.m.

CHAIRMAN CARR: Good afternoon, ladies and gentlemen.

This is an affirmation session. We have one item to come before us this afternoon.

Before I ask the Secretary to lead us through the item for affirmation, do any of my fellow Commissioners have any opening comments they would like to make?

If not, Mr. Secretary, please proceed.

MR. BATES: Mr. Chairman, before we vote on the item, we need to vote to hold this on less than seven days notice. The notice to this went out last Thursday. The affirmation session this week is being held on Wednesday.

CHAIRMAN CARR: Aye.

COMMISSIONER ROGERS: Aye.

COMMISSIONER CURTISS: Aye.

COMMISSIONER REMICK: Aye.

MR. BATES: Mr. Chairman, Commissioners, the item today is SECY-90-193, the Interim Final Rule to Amend 10 CFR Parts 30 and 35.

The Commission is being asked to approve an interim final rule that amends Part 30 and 35. The

rule will be effective for three years and it allows licensees to depart from the radiopharmaceutical manufacturers instructions and package inserts regarding indications and method of administration if certain requirements and limitations are met.

Chairman Carr, Commissioners Rogers and Curtiss and Remick have approved the final rule with some modifications by Chairman Carr and Commissioner Rogers.

Would you affirm your votes, please.

CHAIRMAN CARR: Aye.

COMMISSIONER ROGERS: Aye.

COMMISSIONER CURTISS: Aye.

COMMISSIONER REMICK: Aye.

CHAIRMAN CARR: Is there anything else to come before us today?

If not, we stand adjourned.

(Whereupon, at 4:35 p.m., the above-entitled matter was adjourned.)

CERTIFICATE OF TRANSCRIBER

This is to certify that the attached events of a meeting of the United States Nuclear Regulatory Commission entitled:

TITLE OF MEETING: AFFIRMATION/DISCUSSION AND VOTE

PLACE OF MEETING: ROCKVILLE, MARYLAND

DATE OF MEETING: JULY 18, 1990

were transcribed by me. I further certify that said transcription is accurate and complete, to the best of my ability, and that the transcript is a true and accurate record of the foregoing events.

Carol Lynch

Reporter's name: Peter Lynch

RULEMAKING ISSUE
(Affirmation)

May 30, 1990

SECY-90-193

For: The Commissioners

From: James M. Taylor, Executive Director for Operations

Subject: INTERIM FINAL RULE TO AMEND 10 CFR PARTS 30 AND 35

Purpose: To obtain Commission approval of an interim final rule amending 10 CFR 30.34--Terms and Conditions of Licenses, 10 CFR 35 Subpart E--Imaging and Localization, and Subpart F--Radiopharmaceuticals for Therapy.

Background: Under its 1979 Medical Use Policy Statement, the Commission stated that it would regulate the medical use of byproduct material in order to protect the health and safety of workers and the public, which includes patients. In general, NRC regulatory requirements in 10 CFR Parts 30 and 35 are oriented to ensuring that a properly prepared radiopharmaceutical is administered to the correct patient as prescribed by an authorized user physician. Specific requirements, such as the use of dose calibrators, are intended to ensure that the correct dose is administered. The proposed medical quality assurance rule (55 FR 1439, January 16, 1990) is aimed at preventing errors between what is prescribed and what is administered to patients.

License conditions require commercial nuclear pharmacy licensees to follow the manufacturer's instructions, which are approved by the Food and Drug Administration (FDA), 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 manufacturer's 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

Contact:
John Telford, RES
492-3796
Marjorie Rothschild, OGC
492-1633

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of administration (e.g., to limit the disease states to be treated with each radiopharmaceutical to those listed in its package insert).

Discussion: Information submitted by the American College of Nuclear Physicians and the Society of Nuclear Medicine (ACNP-SNM) in a petition for rulemaking (54 FR 38239, September 15, 1989), provided by the public comments, and obtained during subsequent discussions with licensees, indicates that the requirements of 10 CFR 35 Subparts E and F, in some cases, may prevent authorized user physicians from providing certain nuclear medicine procedures to some patients. For some uncommon disease states or individual patient's medical condition, it may be necessary to depart from the FDA-approved labeling (including manufacturer's instructions and package inserts) to obtain diagnostic or therapeutic medical results not otherwise attainable, or to reduce medical risks to particular patients.

The ACNP-SNM petition, among other things, requests relief from strict adherence to the manufacturer's instructions for radiopharmaceutical preparation and the package insert for therapeutic uses. Although there are provisions in the regulations for exemptions from these requirements, authorized user physicians often have to make decisions about administration of radiopharmaceuticals on a time scale that is not compatible with obtaining prior clearance from a Federal agency.

Proposal: The staff proposes to adopt an immediately effective interim final rule to allow departures from the FDA-approved manufacturer's instructions and package inserts. The amendment is characterized as interim because the rule will be in effect for a period of 3 years after publication in the Federal Register and that a decision will be made at the end of that 3-year period as to whether to extend the interim period for the rule, make the rule permanent, or revise it. This interim rule would only apply to radiopharmaceuticals for which FDA has approved a New Drug Application (NDA). The rule would continue to provide reasonable assurance of radiological safety as well as a balance between adequate controls and avoidance of undue interference in medical judgments.

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. Therefore, these

amendments are being made effective upon publication in the Federal Register without the customary 30-day notice.

The provisions of the interim rule are as follows:

a. Medical use and commercial nuclear pharmacy licensees may depart from the manufacturer's instructions in preparing NDA radiopharmaceuticals it an authorized user physician has made a written directive for a specific departure for a particular patient, or patients, or a radiopharmaceutical. This written directive would not be required in advance in case of emergent conditions. Specific records are required. These departures are currently prohibited by license conditions and § 35.200(b).

b. A medical use licensee may depart from the package insert for therapeutic uses of radiopharmaceuticals. Specific records are required. These departures are currently prohibited by § 35.300.

The staff provided a draft of the interim final rule to the FDA for its review and received FDA comments on May 18, 1990. FDA recommendations have been incorporated into this rulemaking package. The FDA does not object to NRC issuing an interim final rule (Enclosure 6). For a period of 3 years following publication of this rule, information will be collected and analyzed on the nature of, reasons for, and frequency of the departures. The NRC will provide FDA the opportunity to review this information.

Coordination: The Offices of Administration, Enforcement, Government and Public Affairs, and Nuclear Material Safety and Safeguards concur in this rulemaking. The Office of the General Counsel has no legal objections. A copy of the Federal Register notice has been provided to the Advisory Committee for the Medical Use of Isotopes (ACMUI). The comments from the committee are expected the week of June 4, 1990. A summary of their comments will be provided to the Commission as soon as possible.

Recommendation: That the Commission:

1. After receipt of the ACMUI comments, approve the interim final rule to be immediately effective upon publication in the Federal Register for 3 years (Enclosure 1).

2. Note that:

a. A regulatory analysis (Enclosure 2) will be available in the Public Document Room.

b. An environmental assessment (Enclosure 3) will be available in the Public Document Room.

c. Congressional committees will be notified of this rulemaking by letter (Enclosure 4).

d. A public announcement (Enclosure 5) will be issued when the interim final rule is filed with the Office of the Federal Register for publication.

e. Copies of the Federal Register notice will be distributed to the petitioners, all affected Commission licensees, all states, and other interested parties.

f. Implementation of this rulemaking will increase staff resource requirements by 0.5 FTE to collect and evaluate the information on the departures from the package insert.

g. This rulemaking may require OMB approval of the information collection requirements. The staff is working with OMB in parallel with Commission review.

James M. Taylor
Executive Director
for Operations

Enclosures:
1. Federal Register Notice
2. Regulatory Analysis
3. Environmental Assessment
4. Draft Congressional Letter
5. Draft Public Announcement
6. Letter from FDA dated 5/18/90

Commissioners' comments or consent should be provided directly to the Office of the Secretary by COB Monday, June 18, 1990.

Commission Staff Office comments, if any, should be submitted to the Commissioners NLT Monday, June 11, 1990, with an information copy to the Office of the Secretary. If the paper is of such a nature that it requires additional time for analytical review and comment, the Commissioners and the Secretariat should be apprised of when comments may be expected.

This paper is tentatively scheduled for affirmation at an Open Meeting during the Week of June 18, 1990. Please refer to the appropriate Weekly Commission Schedule, when published, for a specific date and time.

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Enclosure 1

Federal Register Notice

[7590-01]

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 modifies the requirement that licensees who elute generators and prepare reagent kits do so only in accordance with 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). The interim rule will be effective for 3 years after publication in the Federal Register.

DATE: Effective date: From [insert date of publication] to [insert date 3 years from the date of publication].

Comment 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, 20555. 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

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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.

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 manufacture 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) regulations. 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.

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

On June 8, 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, the petitioners requested that the NRC amend its regulations at 10 CFR 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 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

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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.

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 466 comment letters have been received.

Comments were received from many different sources, such as hospitals, pharmacies, and medical associations. 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 timeconsuming 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 such 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 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 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 indications 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 such other regulatory action as it determines necessary to protect the public health and safety. Based on continued NRC analysis of the ACNP-SNM petition, the comments on the petition and on this interim rule, experience with the interim rule implementation, 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 the issues raised in PRM-35-9.

V. Discussion.

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

NRC believes that persons licensed by 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 radiopharmaceuticals 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 that includes (1) the specific nature of the departure for a particular patient, or patients, or for a radiopharmaceutical, (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 to 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 a delay in order to make a written directive would jeopardize the patient's health. 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 3 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.

§ 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, such use would be permitted if a record is made 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 3 years.

§ 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. 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, NRC is amending 10 CFR 30.34 "Terms and Conditions of Licenses," to permit actions within the scope of those permitted by (new) § 35.200(c). For situations not within the scope of amended § 30.34, a commercial nuclear pharmacy licensee may file an

application to have its license amended to permit specific departures 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 there is a written directive made by an authorized user physician directing a specific departure for a particular patient, or patients, or for a radiopharmaceutical, which includes a precise description of the departure and why the departure from the manufacturer's instructions would obtain medical results, not otherwise attainable or to 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 order to obtain the written directive would jeopardize the patient's health. In this case, the commercial nuclear pharmacy licensee shall obtain the written directive made by the authorized user physician after the emergency has passed. The directive must contain the information regarding the emergency and all of the other required information. Licensees shall keep those records in an auditable form and available for inspection for 3 years.

These amendments to § 30.34 take precedence over the restrictive conditions (i.e., on eluting generators and preparing reagent kits) in the licenses of commercial nuclear pharmacies. Therefore, these license conditions no longer apply during the 3-year period when the interim rule is in effect. However, NRC reserves the right to take such regulatory action as it determines necessary to protect the public health and safety. 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.

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 exists at this time and neither is authorized by current regulations. Therefore, there is no need to include a prohibition in this rule.

Radiation Safety Responsibilities of Medical Use Licenses

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 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 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 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.

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, 20555. Single copies of the Assessment are available from Dr. Tse (see ADDRESSES heading).

Paperwork Reduction Act Statement

The information collection requirements contained in this interim final rule have been submitted to the Office of Management and Budget for appropriate review under the Paperwork Reduction Act (44 U.S.C. 3501 et seq.). Accordingly, the information collection requirements will not become effective until after OMB's approval.

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 St. 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 specifically requested on or before [TO BE INSERTED]. 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 and thus a backfit analysis is not required for 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 proposing to adopt 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. 2112, 2201, 2232, 2233, 2236, 2282); secs. 201, as amended, 202, 206, 88 Stat. 1242, as amended, 1244, 1246 (42 U.S.C. 5841, 5842, 5846).

Sections 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 secs. 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 [insert date of publication] to [insert date 3 years from the date of publication], 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 in 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 a record of the number of prescriptions dispensed under the departure in an auditable form and available for inspection for 3 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 (i) above within 3 working days after the emergency has passed. The licenseee shall keep these records in an auditable form and available for inspection for 3 years.

(2) The actions authorized in paragraph (i)(1) 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, 1132, 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), 35.22, 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), 35.645 (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, 35.670, 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. 1610., 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 [insert date of publication] to [insert date 3 years from the date of publication], 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 in 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 emergent 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 emergency has passed.

(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 3 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 [insert date of publication] to [insert date 3 years from the date of publication], 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.

(2) The licensee shall make 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 3 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_____day of_____, 1990.

For the Nuclear Regulatory Commission.

_____

Samuel J. Chilk,
Secretary of the Commission

Enclosure 2

Regulatory Analysis

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.

Enclosure 3

Environmental Assessment

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.

Enclosure 4

Draft Congressional Letter

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

The Honorable Morris K. Udall, Chairman
Subcommittee on Energy and the Environment
Committee on Interior and Insular Affairs
United States House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

In a few days the Nuclear Regulatory Commission will publish in the Federal Register the enclosed interim final rule to the NRC's regulations in 10 CFR Parts 30 and 35 concerning the medical use of byproduct material. This interim rule is promulgated in response to a petition for rulemaking submitted by the American College of Nuclear Physicians and the Society of Nuclear Medicine.

The amendment will allow (a) medical use and commercial nuclear pharmacy licensees to depart from manufacturer's instructions (approved by the Food and Drug Administration) for preparing radiopharmaceuticals and (b) medical use licensees to depart from the FDA-approved package insert regarding indications and method of administration for therapeutic use of radiopharmaceuticals, provided certain conditions are met. Current regulations do not permit these departures. 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.

This interim rule will be in effect for three years after publication in the Federal Register. During the three-year period, the NRC will collect information on the nature of, reasons for, and frequency of departures. This information will be examined by the NRC to determine whether to extend the interim period for the rule, make the rule permanent, or revise it.

Sincerely,

Eric S. Beckjord, Director
Office of Nuclear Regulatory Research

Enclosure:
Federal Register notice

cc: Representative James V. Hansen

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

The Honorable Bob Graham, Chairman
Subcommittee on Nuclear Regulation
Committee on Environment and Public Works
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

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The amendment will allow (a) medical use and commercial nuclear pharmacy licensees to depart from manufacturer's instructions (approved by the Food and Drug Administration) for preparing radiopharmaceuticals and (b) medical use licensees to depart from the FDA-approved package insert regarding indications and method of administration for therapeutic use of radiopharmaceuticals, provided certain conditions are met. Current regulations do not permit these departures. 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.

This interim rule will be in effect for three years after publication in the Federal Register. During the three-year period, the NRC will collect information on the nature of, reasons for, and frequency of departures. This information will be examined by the NRC to determine whether to extend the interim period for the rule, make the rule permanent, or revise it.

Sincerely,

Eric S. Beckjord, Director
Office of Nuclear Regulatory Research

Enclosure:
Federal Register notice

cc: Senator Alan K. Simpson

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

The Honorable Philip R. Sharp, Chairman
Subcommittee on Energy and Power
Committee on Energy and Commerce
United States House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

In a few days the Nuclear Regulatory Commission will publish in the Federal Register the enclosed interim final rule to the NRC's regulations in 10 CFR Parts 30 and 35 concerning the medical use of byproduct material. This interim rule is promulgated in response to a petition for rulemaking submitted by the American College of Nuclear Physicians and the Society of Nuclear Medicine.

The amendment will allow (a) medical use and commercial nuclear pharmacy licensees to depart from manufacturer's instructions (approved by the Food and Drug Administration) for preparing radiopharmaceuticals and (b) medical use licensees to depart from the FDA-approved package insert regarding indications and method of administration for therapeutic use of radiopharmaceuticals, provided certain conditions are met. Current regulations do not permit these departures. 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.

This interim rule will be in effect for three years after publication in the Federal Register. During the three-year period, the NRC will collect information on the nature of, reasons for, and frequency of departures. This information will be examined by the NRC to determine whether to extend the interim period for the rule, make the rule permanent, or revise it.

Sincerely,

Eric S. Beckjord, Director
Office of Nuclear Regulatory Research

Enclosure:
Federal Register notice

cc: Representative Carlos J. Moorhead

Enclosure 5

Draft Public Announcement

D R A F T

NUCLEAR REGULATORY COMMISSION ISSUES INTERIM FINAL RULE ON MEDICAL USE 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 user 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 (FDA) 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 final rule, experience with the interim rule implementation, and other information, the NRC will make a decision whether to extend the interim period for the rule, make the rule permanent, or revise it.

Enclosure 6

Letter From FDA Dated 5/18/90

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

To 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.

# # #