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

MAR 28 1985

MEMORANDUM FOR: William J. Dircks
Executive Director for Operations

FROM: John G. Davis, Director
Office of Nuclear Material Safety and Safeguards

SUBJECT: AMENDMENT TO 10 CFR 35.14(b)(7) TO ALLOW USE OF CERTAIN RADIOPHARMACEUTICALS FOR PROCEDURES NOT LISTED ON THE FDA-APPROVED LABELS

Attached for your signature is a proposed rulemaking that would amend 10 CFR 35.14(b)(7) of 10 CFR Part 35, "Human Uses Of Byproduct Material."

The purpose of this proposed amendment is to allow physicians or hospitals that are now permitted by NRC to use other radiopharmaceuticals to use certain radiopharmaceuticals for recently developed diagnostic imaging procedures that are not listed on their respective package labels. The amendment will reduce NRC and licensee administrative costs by eliminating the need for licensees to request a license amendment if they want to use one of the radiopharmaceuticals for one of the new diagnostic imaging procedures.

Currently, if a physician uses a radiopharmaceutical approved by the Food and Drug Administration (FDA) for a diagnostic imaging procedure not listed on the package label, the physician is required by NRC regulation to follow the label instructions for (1) chemical and physical form, (2) route of administration, and (3) dosage range. Physicians who use radiopharmaceuticals for diagnostic imaging procedures listed in §35.14(b)(7) of 10 CFR Part 35, "Human Uses of Byproduct Material," do not have to follow this requirement. This regulatory policy is described in an NRC Federal Register notice published on February 3, 1983 (48 FR 5217).

The Office of Nuclear Regulatory Research conducted an independent review of this rulemaking and you approved continuation in a memorandum dated February 20, 1985.

This proposed rulemaking would amend 35.14(b)(7) to allow licensees to use the following FDA-approved drugs for the following new diagnostic imaging procedures: technetium-99m labeled sulfur colloid for gastroesophageal imaging; technetium-99m labeled sulfur colloid, pertechnetate, or macroaggregated human serum albumin for LeVeen, ventriculo-atrial, and ventriculo-peritoneal shunt imaging; and technetium-99m labeled pertechnetate for cystography and dacryocystography.

This minor amendment to Part 35 can be incorporated in the proposed revision of Part 35 when the latter is published as a final rule. There would be no need for a major editing of the revision or for additional public comment.

The Office of the Executive Legal Director has no legal objection and the Offices of Administration and Nuclear Regulatory Research concur in the proposed amendment to 10 CFR Part 35.14(b)(7).

John G. Davis, Director
Office of Nuclear Material
Safety and Safeguards

Enclosures:
1. Federal Register Notice
2. Federal Register Notice (48 FR 5217)

NUCLEAR REGULATORY COMMISSION

10 CFR PART 35

Physician's Use of Radioactive Drugs

AGENCY: Nuclear Regulatory Commission.

ACTION: Proposed rule.

SUMMARY: The Nuclear Regulatory Commission (NRC) is proposing to amend its regulations to allow physicians to use technetium-99m labeled sulfur colloid for gastroesophageal imaging; technetium-99m labeled sulfur colloid, pertechnetate, and macroaggregated human serum albumin for LeVeen, ventriculo-atrial and ventriculo-peritoneal shunt imaging; and technetium-99m labeled pertechnetate for cystography and dacryocystography. Without this amendment, each NRC licensee that wants to use these radioactive materials in these ways would have to apply to the NRC for permission to do so. The proposed rule will allow physicians or hospitals that are now licensed by NRC to use other similar materials to use these drugs without making an application to NRC.

DATE: Comment period expires [***30 days from date of publication***] Comments received after this date will be considered if it is practical to do so, but assurance of consideration cannot be given except as to comments received on or before this date.

ADDRESSES: Send comments to: The Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, DC 20555, ATTN: Docketing and Service Branch. Hand deliver comments to: Room 1121, 1717 H Street, NW, Washington, DC between 8:15 am and 5:00 pm. Examine comments received, environmental and regulatory analyses and the requests for exception at: The NRC Public Document Room, 1717 H Street, NW, Washington, DC.

FOR FURTHER INFORMATION CONTACT: Norman L. McElroy, Office of Nuclear Material Safety and Safeguards, U.S. Nuclear Regulatory Commission, Washington, DC 20555, Telephone: (301) 427-4108.

SUPPLEMENTARY INFORMATION: Physicians who want to use certain radioactive materials in the practice of medicine may do so only in accordance with a license issued by the Nuclear Regulatory Commission (NRC) or by States which have an agreement with the NRC to license the use of these materials instead of the NRC.

As new radiopharmaceuticals, radioactive sources, medical devices, and uses of radioisotopes are developed, the NRC considers adding them to one of the groups under which medical licenses are issued. The groups were designed to allow physicians and community hospitals wide access to nuclear medicine services. The groups in §35.100 contain only radiopharmaceuticals that are the subject of an FDA-approved "New Drug Application" (NDA), or a "Notice of Claimed Investigational Exemption for a New Drug" (IND) that has been accepted by FDA. A licensee authorized to use all the materials listed in a group is referred to as a "group medical licensee."

NRC regulations in §35.14(b)(6) that apply to the group medical licensees provide that when a physician uses byproduct material for clinical procedures other than those approved by FDA and specified in the product labeling or package insert, the physician must follow the product labeling regarding: (1) chemical and physical form, (2) route of administration, and (3) dosage range. The NRC has received requests to amend its regulations to allow physicians to use technetium-99m labeled sulfur colloid for gastroesophageal imaging; technetium-99m labeled sulfur colloid, pertechnetate, and macroaggregated human serum albumin for LeVeen, ventriculo-atrial, and ventriculo-peritoneal shunt imaging; and technetium-99m labeled pertechnetate for cystography and dacryocystography. These are clinical procedures that are not listed in the product labels.

(As a separate matter, the NRC recently allowed persons who are licensed to use materials in §35.100 Group II or III to also use pertechnetate for dacryocystography and sulfur colloid for gastroesophageal imaging (see 50 FR 7663, published February 25, 1985). That action was precipitated by a letter to NRC from FDA that said those two methods of use had recently been approved for listing on the respective package inserts, but that some manufacturers might not be able to print new package inserts for several months. The NRC has included those two methods of use in this proposed rulemaking so that the regulation will provide a complete list.)

It is noteworthy that NRC and FDA have sought a solution to the general problem of drug labeling, and FDA currently is considering a program to authorize additional clinical procedures that use approved radiopharmaceuticals. However, until such a program is implemented, NRC believes that this rulemaking is the most appropriate way to resolve the problem in this interim period. This policy was described in an NRC rulemaking published in the Federal Register on February 3, 1983 (48 FR 5217).

The requests that NRC received provided a description of the clinical procedure, a justification for why the regulatory action is needed, the purpose of the procedure, an analysis of the radiation dose, and additional technical and scientific information. (Each of the requests is available for inspection at the NRC Public Document Room, 1717 H Street, NW, Washington, DC.) The NRC has reviewed the requests to determine whether the requested regulatory action might result in an unreasonable risk to the health and safety of the public or might endanger life or property. The NRC specifically considered two criteria:

- o No unjustified radiation dose to the patient, and
- o Demonstration of adequacy of occupational radiation protection measures

With assistance from its Advisory Committee on the Medical Uses of Isotopes (ACMUI), the NRC has determined that the above criteria have been met for the proposed clinical procedures. Many of the committee members believe that these clinical procedures are useful, and the risk/benefit ratio for these procedures is extremely low. They also noted that these techniques will probably become routine when allowed by NRC.

Technetium-99m labeled sulfur colloid can be administered orally either as a solid or liquid test meal. Following oral administration, technetium-99m sulfur colloid goes from the esophagus to the stomach, small intestine, and the upper large intestine. This clinical procedure permits external imaging which is helpful in assessing gastric emptying, gastroesophageal reflux, and esophageal transit. The gastric emptying procedure is useful in demonstrating the presence and the severity of gastric motor disorder; the gastroesophageal reflux study may demonstrate backward flow in the digestive tract. The esophageal transit study may demonstrate obstructions or abnormal transit time. The normal dosage is 0.3 millicuries. The radiation dose to an average adult patient from 1 millicurie of orally administered technetium-99m sulfur colloid as a liquid is: 0.1 rad to the stomach wall; 0.3 rad to the small intestine; 0.5 rad to the upper large intestine; 0.3 rad to the lower large intestine; 0.1 rad to the ovaries; 0.01 rad to the testes; and 0.02 rad to the whole body. The estimated absorbed radiation dose to an average adult patient from 1 millicurie of orally administered technetium-99m sulfur colloid as a solid food is: 0.2 rad to the stomach wall; 0.2 rad to the small intestine; 0.4 rad to the upper large intestine; 0.3 rad to the lower large intestine; 0.1 rad to the ovaries, 0.004 rad to the testes; and 0.02 rad to the whole body.

These estimated absorbed radiation doses and the following doses are similar to other absorbed doses received from other diagnostic nuclear medicine and x-ray procedures.

A LeVeen shunt is an implanted tube that drains built-up fluid from the peritoneal cavity to a large central vein. Technetium-99m labeled sulfur colloid, pertechnetate, or macroaggregated human serum albumin can be injected into the peritoneal cavity to diagnose shunt malfunction, such as blockage by clot or valve failure, by taking images of the shunt. The normal dosage is 3 to 10 millicuries. The radiation dose from an intraperitoneal injection of a 3 millicurie dosage of technetium-99m sulfur colloid is: 0.02 rad to the whole body; 0.02 rad to the testes; 0.02 rad to the ovaries; 0.03 rad to the liver; 0.02 rad to the spleen and 0.03 rad to the red marrow.

A ventriculo-atrial shunt is a tube implanted in patients with hydrocephalus (fluid build-up in the head). It drains the fluid from the head to the atrial cavity. Technetium-99m labeled sulfur colloid, pertechnetate, or macroaggregated human serum albumin is injected into the shunt system of the patient to localize shunt blockage before surgical repair is performed. The normal dosage is 1 to 5 millicuries. The radiation dose from an injection of a 5 millicurie dosage of technetium-99m to a patient with a patent shunt is: 0.1 rad to the whole body and 0.1 rad to the brain.

A ventriculo-peritoneal shunt is an implanted tube in patients with hydrocephalus (fluid build-up in the head). It drains the fluid from the head to the peritoneal cavity. Technetium-99m labeled sulfur colloid, pertechnetate, or macroggregated human serum albumin is injected into the shunt system of patients to localize shunt blockage before performing surgical repairs. The normal dosage is 1 to 5 millicuries. The radiation dose from an injection of a 5 millicurie dosage of technetium-99m to a patient with a patent shunt is: 0.1 rad to the whole body and 0.1 rad to the brain.

Cystography is a procedure for patients with bladder problems. A tube is inserted into the bladder of a patient. Technetium-99m pertechnetate is instilled through the tube into the bladder. Images are taken during filling and voiding of the bladder to measure the amount of reflux (backward flow) into the upper tracts, bladder volume at which reflux occurs, drainage time of reflux after voiding, and the remaining urine volume. The normal dosage is 1 millicurie. The radiation dose from a 1 millicurie dosage of technetium-99m pertechnetate is: 0.002 rad to the whole body, 0.006 rad to gonads, and 0.2 rad to the bladder.

Dacryocystography is a procedure for patients whose eyes exhibit excessive teardrops (epiphora). This procedure is performed to assess tear production and drainage in patients, and for nasolacrimal system imaging. Technetium-99m labeled pertechnetate is administered as a sterile eye drop. The normal dosage is 100 to 250 microcuries. The radiation dose from a dosage of 100 to 150 microcuries of technetium-99m pertechnetate per eye drop to the germinal epithelium of the lens is: 0.01 to 0.02 rad under normal physiological conditions. With blocked lacrimal drainage, the dose to the lens is 0.4 to 0.6 rad.

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 this is not a major Federal action significantly affecting the quality of the human environment and therefore an environmental impact statement is not required. The assessment shows that any detectable effect on the environment is unlikely. The environmental assessment and finding of no significant impact on which this determination is based are available for inspection at the NRC Public Document Room, 1717 H Street, NW, Washington, DC. Single copies of the environmental assessment are available from Mr. McElroy (see "For Further Information Contact" heading).

Paperwork Reduction Act Statement

This proposed rule contains no information collection requirements and therefore it is not subject to the requirements of the Paperwork Reduction Act of 1980 (44 U.S.C. 3501 et. seq.).

Regulatory Analysis

The NRC has prepared a draft regulatory analysis for this proposed rule. The analysis examines the costs and benefits of the alternatives considered by the NRC. The draft analysis is available for inspection at the NRC Public Document Room, 1717 H Street, NW, Washington DC. A single copy may be obtained from Mr. McElroy (see "For Further Information Contact" heading).

Regulatory Flexibility Certification

As required by the Regulatory Flexibility Act of 1980, 5 U.S.C. 605 (b), the NRC certifies that this rule, if adopted, will not have a significant economic impact on a substantial number of small entities. The NRC has prepared a draft regulatory analysis for this proposed rule that examines the economic impact of this action. The analysis notes that approximately 1900 medical licensees may experience some beneficial impact from the rule. The proposed rule would spare each medical licensee who desires to use the radioactive material in the requested manner the estimated $230 cost of preparing a license amendment request, the $120 amendment fee, and the 60 day delay associated with the amendment of the license.

The Commission is seeking comment particularly from small entities (i.e., small businesses, small organizations, and small jurisdictions as defined by the Regulatory Flexibility Act) about the ways the proposed rule will affect them and the ways it may be modified to impose less stringent requirements on them which will still adequately protect the public health and safety. Those small entities that offer comments on how the regulations could be modified to take into account their differing needs should specifically discuss:

(a) The size of their business and how the proposed regulations would result in a significant economic burden upon them as compared to larger organizations in the same business community;

(b) How the proposed regulation could be modified to take into account their differing needs or capabilities;

(c) The benefits that would accrue, or the detriments that would be avoided, if the proposed regulation were modified as suggested by the commenter;

(d) How the proposed regulation, as modified, would more closely equalize the impact of NRC regulations or create more equal access to the benefits of Federal programs as opposed to providing special advantages to any individuals or groups; and

(e) How the proposed regulation, as modified, would still adequately protect the public health and safety.

List of Subjects in 10 CFR Part 35

Byproduct material, Drugs, Health facilities, Health professions, Incorporation by reference, Medical devices, Nuclear materials, Occupational safety and health, Penalty, 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. 553, the following amendment to 10 CFR Part 35 is being considered.

PART 35 - HUMAN USES OF BYPRODUCT MATERIAL

1. The authority citation for Part 35 continues to read as follows:

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

For the purposes of sec. 223, 68 Stat. 958, as amended (42 U.S.C. 2273); §§35.2, 35.14(b), (e) and (f), 35.21(a), 35.22(a), 35.24, and 35.31(b) and (c) are issued under sec. 161(b), 68 Stat. 948, as amended 42 U.S.C. 2201(b); and §§35.14(b)(5)(ii), (iii) and (v) and (f)(2), 35.25 and 35.31(d) are issued under sec. 161o, 68 Stat. 950, as amended (42 U.S.C. 2201(o)).

* * *

2. In §35.14, paragraph (b)(7) is revised to read as follows:

§35.14 Specific licenses for certain groups of medical uses of by-product material.

* * * * *

(b)***

(7) The following radiopharmaceuticals, when used for the listed clinical procedures, are not subject to the restrictions in paragraph (b)(6) of this section:

(i) Technetium-99m pentetate as an aerosol for lung function studies;

(ii) Technetium-99m sulfur colloid as a solid or liquid for gastroesophageal imaging;

(iii) Technetium-99m sulfur colloid, pertechnetate, or macroaggregated human serum albumin for LeVeen shunt imaging;

(iv) Technetium-99m sulfur colloid, pertechnetate, or macroaggregated human serum albumin for ventriculo-atrial shunt imaging;

(v) Technetium-99m sulfur colloid, pertechnetate, or macroaggregated human serum albumin for ventriculo-peritoneal shunt imaging;

(vi) Technetium-99m pertechnetate for cystography; and

(vii) Technetium-99m pertechnetate for dacryocystography.

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Dated at Bethesda, Maryland this 5th day of April, 1985.

For the Nuclear Regulatory Commission.

William J. Dircks,
Executive Director for Operations.