ACNP
American College of Nuclear Physicians

1101 Connecticut Avenue, N.W., • Suite 700 • Washington, D.C. 20036

202-857-1100

SNM
The Society of Nuclear Medicine

DOCKET NUMBER
PROPOSED RULE PR-35 (10)
(50 FR 15752)

DOCKETED
USNRC

'85 MAY 22 P4:21

May 21, 1985

OFFICE OF SECRETARY
DOCKETING & SERVICE
BRANCH

Secretary of the Commission
U.S. Nuclear Regulatory Commission
Washington, DC 20555

ATTN: Docketing and Services Branch

Dear Sir:

The American College of Nuclear Physicians (College) and the Society of Nuclear Medicine (Society) wish to comment on NRC's proposed rule to amend 10 CFR 35 (50 Federal Register 15752) which would allow physicians to use certain radioactive materials for clinical procedures.

The College and Society have carefully reviewed this proposal and support the position expressed by the Radiopharmaceutical Drugs Advisory Committee (RDAC) in response to this rulemaking. We appreciate this opportunity to comment and please don't hesitate to contact us if you have any questions.

Sincerely,

Kenneth A. McKusick

Kenneth A. McKusick, M.D.
President
American College of Nuclear Physicians

Michael J. Welch

Michael J. Welch, Ph.D.
President
Society of Nuclear Medicine

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Add: Norman McElroy
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Acknowledged by card. MAY 28 1985

MALLINCKRODT INSTITUTE OF RADIOLOGY

AT WASHINGTON UNIVERSITY MEDICAL CENTER

BARRY A. SIEGEL, M.D.
Professor of Radiology and Medicine
Director, Division of Nuclear Medicine

DOCKET NUMBER
PROPOSED RULE PR-35 (11)
(50 FR 15752)

21 May 1985

DOCKETED
USNRC

'85 MAY 22 P1:45

OFFICE OF SECRETARY
DOCKETING & SERVICE
BRANCH

Secretary of the Commission
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555
Attn: Docketing and Services Branch

Re: Notice of Proposed Rule-Making to amend 10 CFR 35.14(b)(7) which appeared at 50 FR 15752 (Monday, 22 April 1985)

Dear Sir:

I am writing on behalf of the Radiopharmaceutical Drugs Advisory Committee of the Food and Drug Administration, of which I am chairperson, regarding the above-named Notice of Proposed Rule-Making. At its meeting of 10 May 1985 in Rockville, Maryland, the Radiopharmaceutical Drugs Advisory Committee discussed the proposed amendments to 10 CFR 35.14(b)(7) and instructed me to offer the following comments.

1. The Radiopharmaceutical Drugs Advisory Committee endorses the use of: Tc-99m sulfur colloid for gastroesophageal imaging; Tc-99m sulfur colloid, pertechnetate or macroaggregated human serum albumin for LeVeen shunt imaging; Tc-99m pertechnetate for cystography; and Tc-99m pertechnetate for dacryocystography. All of these clinical procedures have been performed at many academic medical centers for many years and have proven safe and efficacious. Accordingly, sections 35.14(b)(7)(ii), (iii), (vi) and (vii) should stand as proposed.

2. Regarding the proposed exemptions to the requirements of 10 CFR 35.14(b)(6) that would permit group medical licensees to use Tc-99m macroaggregated human serum albumin and Tc-99m sulfur colloid for ventriculo-atrial shunt imaging and ventriculo-peritoneal shunt imaging, hereinafter collectively referred to as cerebrospinal fluid (CSF) shunt imaging (proposed 35.14(b)(7)(iv) and (v), respectively), the Radiopharmaceutical Drugs Advisory Committee recommends that such exemptions not be granted. This recommendation is based on the Committee's concern that Tc-99m macroaggregated human serum albumin and Tc-99m sulfur colloid may adhere to the lining surfaces of the shunt reservoir, valve or outflow catheter, thereby potentially rendering imaging studies with these radiopharmaceuticals difficult or impossible to interpret. Additionally, the Committee noted that it was unaware of substantial data in the scientific literature or other clinical experience to document the effectiveness of these radiopharmaceuticals for CSF shunt imaging. Generally, most authorities have considered particulate radiopharmaceuticals to be unsatisfactory for CSF imaging (e.g., see McAfee JG, et al. Radioactive agents for imaging. In: Freeman LM, ed. **Freeman and**

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510 South Kingshighway Boulevard
St. Louis, Missouri 63110
(314) 362-2809

Acknowledged by card. MAY 23 1985

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Add: Nuclear Medicine
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intrathecal administration (In-111 DTPA and Yb-169 DTPA). More recently, the U.S. Pharmacopeia has officially adopted the LAL tests for bacterial endotoxins and the FDA has established guidelines for their use in pre-release testing of all drugs subject to pyrogen testing requirements. In the case of drugs intended for intrathecal administration, the acceptability criteria are 25 times more stringent than they are for drugs intended for administration by other parenteral routes.

Unfortunately, the manufacturing quality control requirements for Tc-99m pertechnetate (as the eluate of a Mo-99/Tc-99m generator) and the reagent kits used to prepare Tc-99m macroaggregated human serum albumin and Tc-99m sulfur colloid are such that these drugs must meet only the apyrogenicity criteria applicable to non-intrathecal parenteral drugs. Accordingly, it is not possible to ensure, without additional pyrogen testing requirements, that any of the proposed drugs listed in 35.14(b)(7)(iv) and (v) will meet the standards necessary to ensure their safe use by a route that might cause these drugs to enter the CSF-containing spaces of the brain. During its discussion, the Committee noted that Tc-99m radiopharmaceuticals are used for CSF imaging, including CSF shunt imaging, in institutions with medical licenses of broad scope. It further noted that such institutions generally take the responsibility to ensure that the final dosage form of the radiopharmaceutical will meet the more stringent apyrogenicity criteria for intrathecally administered drugs.

In the Committee's opinion, the Nuclear Regulatory Commission does not have either the statutory authority or the appropriate expertise to: (1) make recommendations to group medical licensees concerning the necessity for additional pyrogen testing of radiopharmaceutical drug products prior to use; or (2) to change the pyrogen-testing standards in use by manufacturers of both Mo-99/Tc-99m generators and reagent kits for preparation of Tc-99m macroaggregated human serum albumin or Tc-99m sulfur colloid. Accordingly, the Committee recommends either that these proposed exemptions be withdrawn or that, for the reasons stated above, the exemption be granted only for Tc-99m pertechnetate with the following additional instructions:

> The administered volume of Tc-99m pertechnetate introduced into the CSF shunt reservoir or valve should not exceed 0.1 ml in volume to minimize the possibility of reflux of the radiopharmaceutical into the cerebral ventricles.

The Committee further noted that the studies in the published literature pertaining to quantitation of CSF flow through CSF shunts have employed administered doses of less than 500 uCi. Accordingly, the Committee questions whether the proposed dosage range of 1 to 5 mCi is necessary or even desirable when the examination is limited to a small volume injection directly into the CSF shunt system without specific intent to reflux the radiopharmaceutical into the cerebral ventricles.

4. Regarding the generic issue of CSF shunt imaging and other applications of CSF imaging where introduction of Tc-99m radiopharmaceuticals into the cerebral ventricles or subarachnoid space is desirable (e.g. detection

Johnson's Clinical Radionuclide Imaging. Orlando, Grune & Stratton, 1984: 55-179). Moreover, the Committee expressed concerns regarding the safety of this particular application of Tc-99m macroaggregated human serum albumin and Tc-99m sulfur colloid, which are addressed in the following paragraph.

3. Regarding the proposed exemptions to the requirements of 10 CFR 35.14(b)(6) that would permit group medical licensees to use Tc-99m pertechnetate (and also Tc-99m macroaggregated human serum albumin and Tc-99m sulfur colloid) for CSF shunt imaging (proposed 35.14(b)(7)(iv) and (v) respectively), the Radiopharmaceutical Drugs Advisory Committee recommends that such exemptions either not be granted or be accompanied by additional specific instructions pertaining to the proper use of **only** Tc-99m pertechnetate for CSF shunt imaging.

The Committee concurs with the NRC judgment that these exemptions fulfill the criteria of (1) no unjustified radiation dose to the patient, and (2) demonstration of adequacy of occupational radiation protection measures. Additionally, the Committee acknowledged in its discussions that there is a substantial body of published scientific literature and clinical experience to document the effectiveness of Tc-99m pertechnetate for CSF shunt imaging (e.g., see: Harbert JC, et al. Quantitation of cerebrospinal fluid shunt flow. **Radiology** 1974; 112: 379-387; Brendel AJ, et al. Cerebrospinal fluid shunt flow in adults: Radionuclide quantitation with emphasis on patient position. **Radiology** 1983; 149: 815-818; and Chervu S, et al. Quantitative evaluation of cerebrospinal fluid shunt flow. **J Nucl Med** 1984; 25: 91-95). However, the Committee is concerned with another aspect related to the safety of the proposed application (CSF shunt imaging) for these radiopharmaceuticals.

Specifically, the Committee is troubled by the potential for serious pyrogen reactions, including a clinical syndrome of aseptic meningitis, that might result if these radiopharmaceuticals are introduced into a CSF shunt and are refluxed either inadvertently or intentionally into the cerebral ventricles.

It is well documented that adverse reactions attributable to pyrogenic substances (e.g., bacterial endotoxin) occur at lower levels of pyrogen contamination when drugs are introduced via the intrathecal route rather than by other parenteral routes. The high frequency of minor adverse reactions and the non-negligible frequency of major adverse reactions to I-131 human serum albumin, which was used in the past for radionuclide cisternography, have been shown to be most likely the result of trace endotoxin contamination. This trace endotoxin contamination was not detectable by the conventional U.S. Pharmacopeia rabbit pyrogen test that was employed as the pre-release pyrogen test for that drug during the era of its use for radionuclide cisternography (see Cooper JF, et al. Endotoxin as a cause of aseptic meningitis after radionuclide cisternography. **J Nucl Med** 1975; 16: 809-813).

After the advent of the more sensitive Limulus amebocyte lysate (LAL) tests for bacterial endotoxins, these tests were adopted as the pre-release tests for pyrogens of FDA-approved radiopharmaceuticals intended for

of CSF rhinorrhea), the Radiopharmaceutical Drugs Advisory Committee expressed the opinion that the radiopharmaceutical generally preferred for these indications is Tc-99m DTPA. When Tc-99m DTPA is used for CSF shunt imaging, the examination often includes intentional refluxing of the tracer into the cerebral ventricles as a maneuver designed to assist in distinguishing proximal from distal shunt catheter obstruction (e.g. see Sty JR, et al. Nuclear anatomy of diversionary central nervous system shunts in children. **Clin Nucl Med** 1978; 3: 271-275).

To this end, the Radiopharmaceutical Drugs Advisory Committee agreed to undertake the preparation of a class labeling petition for submission to the Food and Drug Administration. This petition will seek approval of CSF imaging and CSF shunt imaging as supplemental indications for Tc-99m DTPA and will suggest specific alterations of the package insert for this drug to include instructions that the final dosage form of the compounded drug be tested for bacterial endotoxin with the LAL test by the user prior to use for these indications.

The members and consultants of the Radiopharmaceutical Drugs Advisiory Committee appreciate this opportunity to comment on this Notice of Proposed Rule-Making. Although the Radiopharmaceutical Drugs Advisory Committee generally supports the Nuclear Regulatory Commision's approach to permitting exemptions to 10 CFR 35.14(b)(6) in response to specific petitions, its members nonetheless believe that the surest means of maximizing the safe use of radiopharmaceuticals is by FDA-approval for each supplemental indication, thereby providing a full set of instructions in the package insert to physicians who use these drugs.

Please feel free to contact me if you require additional information concerning these comments of the Radiopharmaceutical Drugs Advisory Committee.

Sincerely yours,

Barry A Siegel, M.D.

Barry A. Siegel, M.D.

BAS:ld

cc: Norman L. McElroy
Material Licensing Branch 396-SS
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555