NUCLEAR REGULATORY COMMISSION

[10 CFR Parts 30 and 35]

TESTING OF RADIOISOTOPE GENERATORS

AGENCY: U.S. Nuclear Regulatory Commission (NRC)

ACTION: Proposed rule.

SUMMARY: Certain NRC medical licensees are authorized to prepare radiopharmaceuticals from radioisotope generators. NRC is considering requiring licensees to test these radiopharmaceuticals for a contaminant called molybdenum-99. The proposed rule also includes maximum limits for molybdenum-99 in these radiopharmaceuticals.

DATES: Comment period expires August 6, 1979.

ADDRESSES: Written comments or suggestions for consideration in connection with the proposed amendment should be submitted to the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Docketing and Service Branch. Copies of comments received may be examined at the Commission's Public Document Room at 1717 H Street, N.W., Washington, D.C.

FOR FURTHER INFORMATION CONTACT: Edward Podolak, Office of Standards Development, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555 (Phone: 301-443-5860).

SUPPLEMENTARY INFORMATION: In diagnostic nuclear medicine, the most widely used radiopharmaceutical is technetium-99m (Tc-99m) which has a radioactive half-life of 6 hours. Many hospitals and nuclear pharmacies obtain their Tc-99m by purchasing a radionuclide generator from a radiopharmaceutical manufacturer and eluting the generator.

The radioisotope generator is a shielded device that is often called a molybdenum generator or molybdenum "cow" because molybdenum-99 (Mo-99), the parent of Tc-99m, is contained within the generator. The Mo-99 is adsorbed on an alumina column which is arranged so that sterile saline can be fed through the column to wash out, or elute, only the daughter radioisotope, Tc-99m. The parent, Mo-99, has a longer half-life than the daughter, Tc-99m, and the parent continuously decays to form the daughter radioisotope, which is eluted when needed. The generator is usually eluted, or "milked", every 24 hours and replaced with a new generator once a week because the parent, Mo-99, has decayed below useful levels.

The United States Pharmacopeia (USP) XIX, which is recognized by the Food and Drug Administration (FDA) and the pharmaceutical industry as the basic standard for drug strength, quality and purity, has upper limits for the presence of Mo-99 in Tc-99m radiopharmaceuticals. These limits apply to molybdenum generator manufacturers and the generator's labeling includes methods or references methods for quantifying the amount of Mo-99 in Tc-99m. This is usually called a molybdenum breakthrough test.

Molybdenum breakthrough testing by the generator user has always been considered a good laboratory practice or a good quality control measure. In a section describing molybdenum breakthrough testing, the Bureau of Radiological Health (FDA) "Workshop Manual on Radiopharmaceutical Quality Assurance" (July 1978) states: "Thus, it is important that testing for Mo-99 be performed routinely."

Until 1975, all NRC medical licenses authorizing generators included a license condition requiring molybdenum breakthrough testing. In 1975 this condition was dropped because of a provision in the new § 35.14 group medical licensing regulations. Section 35.14(b)(4) requires licensees to follow the generator labeling or package inserts which at that time included methods for molybdenum breakthrough testing. Over the intervening years, generator labeling has become equivocal on molybdenum breakthrough testing. Some package inserts imply that you should do it, others imply that you are doing it, and still others recommend that you do it. Thus, there are no uniform requirements in NRC licenses, regulations, or manufacturer's labeling for the performance of tests to determine the amount of Mo-99 in Tc-99m radiopharmaceuticals prior to administration to patients.

A recent joint NRC/FDA investigation revealed the possibility of greater than normal quantities of Mo-99 in Tc-99m generator eluate. The presence of molybdenum-99 serves no diagnostic purpose. It could result in a radiation dose to a critical organ of one or more rems and

if such doses occur in large populations of patients, they would be unacceptable from a public health and safety standpoint. There are several thousand generators shipped weekly with each generator accounting for up to 50 patient dosages per day. If a problem develops in the manufacture, shipping, handling or elution of these generators and this results in molybdenum breakthrough in excess of the USP XIX limits, there is a potential for the exposure of a large number of persons.

In view of this, on March 12, 1979, NRC issued an order requiring medical licensees to perform molybdenum breakthrough testing on each elution of Tc-99m from a generator and also prohibiting licensees from administering any Tc-99m radiopharmaceuticals that exceed the USP XIX limits for Mo-99 contamination. The following proposed rule contains the essentials of that order. This proposed rule does not change or modify the March 12, 1979 order to licensees requiring molybdenum breakthrough testing. However, the order will be rescinded upon publication of an effective rule.

The proposed rule (and the NRC order) covers three types of NRC medical licenses: (1) the nuclear pharmacy license, (2) the broad medical license and (3) the group medical license. The proposed rule (and the NRC order) applies only to medical licensees who actually elute the radioisotope generators and does not apply to those medical licensees who purchase prepared Tc-99m radiopharmaceuticals from a radiopharmaceutical manufacturer or nuclear pharmacy.

Basically, the proposed § 35.14(b)(4) requires the group medical licensees to perform molybdenum breakthrough tests if they use generators. The proposed § 30.34(f) requires nuclear pharmacy licensees and broad medical licensees to perform the same molybdenum breakthrough tests if they use generators.

Copies of the value/impact analysis supporting the proposed rule are available for public inspection at the Commission's Public Document Room at 1717 H Street, N.W., Washington, D.C. Single copies of the value/impact analysis may be obtained on request from Edward Podolak at the above address.

Under the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974, as amended, and section 553 of title 5 of the United States Code, notice is hereby given that adoption of the following amendments to 10 CFR Parts 30 and 35 are contemplated.

1. A new paragraph (f) is added to § 30.34 to read as follows:

§ 30.34 Terms and conditions of licenses.

* * * * *

(f) Each licensee who prepares technetium-99m radiopharmaceuticals from molybdenum-99/technetium-99m generators shall test the generator eluates for molybdenum-99 breakthrough in accordance with § 35.14(b)(4)(i) thru (iv).

2. In § 35.14, paragraph (b)(4) is revised to read as follows:

§ 35.14 Specific licenses for certain groups of medical uses of byproduct material.

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(b) Any licensee who is authorized to use byproduct material pursuant to one or more groups in §§ 35.14(a) and 35.100 is subject to the following conditions:

* * * * *

(4) For Group III, any licensee who uses generators or reagent kits shall:

(i) Elute the generator or process radioactive material with the reagent kit in accordance with instructions which are approved by the Nuclear Regulatory Commission or an Agreement State and are furnished by the manufacturer on the label attached to or in the leaflet or brochure that accompanies the generator or reagent kit;

(ii) Cause each elution or extraction from the generator to be tested to determine either the total molybdenum-99 activity, or the concentration of molybdenum-99, before administration to patients. This testing shall be conducted according to written procedures and by personnel who have been specifically trained to perform the test;

(iii) Prohibit the administration to patients of technetium-99m containing more than one microcurie of molybdenum-99 per millicurie of technetium-99m, or more than 5 microcuries of molybdenum-99 per administered dose, at the time of administration; and

(iv) Maintain for 3 years for Commission inspection records of the molybdenum-99 test conducted on each elution from the generator.

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(Secs. 81, 161, Pub. Law 83-703, 68 Stat. 935, 948 (42 U.S.C. 2111, 2201); Sec. 201. Pub. Law 93-438, 88 Stat. 1242 (42 U.S.C. 5841))

Dated at Washington, D.C. this 31st day of May, 1979.

For the Nuclear Regulatory Commission.

Samuel J. Chilk
Secretary of the Commission