NUCLEAR REGULATORY COMMISSION

10 CFR Parts 30 and 35

Testing of Radioisotope Generators

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

ACTION: Final Rule.

SUMMARY: Certain NRC medical licensees are authorized to prepare radioactive drugs from radioisotope generators. NRC is requiring licensees to test these radioactive drugs for a contaminant called molybdenum-99. NRC is also imposing maximum limits for molybdenum-99 in these radioactive drugs.

EFFECTIVE DATE: SEP 2 1980

Note - NRC has submitted this rule to the Comptroller General for review under the Federal Reports Act, as amended, 44 U.S.C. 3512. The date on which the rule becomes effective reflects inclusion of the 45-day period that the statute allows for this review (44 U.S.C. 3512(c)(2)).

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SUPPLEMENTARY INFORMATION: In diagnostic nuclear medicine, the most widely used radioactive drug 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 radioactive drug 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 solution 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. If the Mo-99 is improperly loaded on the alumina column or loaded on an alumina column that is defective (e.g., improper packing could cause "channeling" of the Mo-99), the Mo-99 will "break through" the column and contaminate the radioactive drug.

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 radioactive drugs. These limits apply to molybdenum generator manufacturers and each 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 the use of generators included a license condition requiring molybdenum breakthrough testing. A

provision in the new §35.14 group medical licensing regulations, adopted in 1975, ultimately had the effect of dropping this license condition. Section 35.14(b)(4) requires licensees to follow the generator labeling or package inserts which, in 1975, included methods for molybdenum breakthrough testing. Over the intervening years, generator labeling has become ambiguous on molybdenum breakthrough testing. Some package inserts imply that the users should do it, others imply that the users are doing it, and still others recommend that the users do it. Thus, there are no uniform requirements in NRC licenses or regulations or in connection with the generator labeling for the performance of tests to determine the amount of Mo-99 in Tc-99m radioactive drugs before administration to patients.

Following a report from an NRC medical licensee, a joint NRC/FDA investigation in March 1979 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. Therefore, the radiation exposure resulting from the administration of greater than normal amounts of Mo-99 is unnecessary radiation exposure to patients. It could result in a radiation dose to a critical organ of one or more rems. 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 that results in molybdenum breakthrough in excess of the USP XIX limits, there is a potential for unnecessary radiation exposure of patients.

In view of this, on March 12, 1979, NRC's Office of Nuclear Materials Safety and Safeguards 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 radioactive

drugs that exceed the USP XIX limits for Mo-99 contamination. On June 6, 1979, the Commission published in the Federal Register (44 FR 32394) a proposed rule that contained the essentials of that order. The March 12, 1979, order to licensees requiring molybdenum breakthrough testing remained in effect. That order is hereby rescinded by the terms of this final rule when it becomes effective.

The comment period for the proposed rule expired on August 6, 1979. Three comments were received. Two commenters favored the proposed rule. One of these commenters suggested a minor word change to clarify that the required test applies only to Mo-99/Tc-99m generators. This change was adopted in the final rule. One commenter, while agreeing that molybdenum breakthrough testing was necessary, suggested that the FDA change the generator labeling to mandate the test. The NRC believes that an NRC requirement for molybdenum breakthrough testing is more direct and effective than an FDA labeling change. FDA does not impose requirements on users of radioactive drugs through the product labeling.

The final rule covers three types of NRC medical licenses: (1) the nuclear pharmacy license, (2) the broad medical license and (3) the group medical license. Of these three types of medical licensees, the rule applies only to those who actually elute the radioisotope generators and does not apply to those who purchase prepared Tc-99m radioactive drugs from a radiopharmaceutical manufacturer or nuclear pharmacy. The manufacturer that sells prepared Tc-99m radiopharmaceuticals is covered by FDA requirements for molybdenum breakthrough testing. As noted above, nuclear pharmacies are covered by the rule.

In summary, §35.14(b)(4) requires the group medical licensees to perform molybdenum breakthrough tests if they use generators. Section 30.34(g) requires nuclear pharmacy licensees and broad medical licensees to perform the same molybdenum breakthrough tests if they use generators.

Under the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974, as amended, and sections 552 and 553 of title 5 of the United States Code, the following amendments to Title 10, Chapter I, Code of Federal Regulations, Parts 30 and 35 are published as a document subject to codification.

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

1. New paragraph (g) is added to §30.34 to read as follows:

§30.34 Terms and conditions of licenses.

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(g) Each licensee preparing 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).

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PART 35 - HUMAN USES OF BYPRODUCT MATERIAL

2. Paragraph (b)(4) in §35.14 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 authorized to use byproduct material pursuant to one or more groups in §§35.14(a) and 35.100 is subject to the following conditions:

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

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

(ii) Before administration to patients, cause each elution or extraction of technetium-99m from a molybdenum-99/technetium-99m generator to be tested to determine either the total molybdenum-99 activity or the concentration of molybdenum-99. 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 1 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, 161b, Pub. Law 83-703, 68 Stat. 935, 948 (42 U.S.C. 2111, 2201); Sec. 201 as amended, Pub. Law 93-438, 88 Stat. 1242 as amended by Pub. Law 94-79, 89 Stat. 413 (42 U.S.C. 5841))

Dated at Bethesda MD this 8th day of April 1980.

For the Nuclear Regulatory Commission

William J. Dircks
Acting Executive Director for Operations