DCD/DCB

MAR 1 5 1991

Mallinckrodt, Inc.
Diagnostic Imaging Services
ATTN: Jack Martin, RPh.
Facility Manager
1827 Belt Way Drive
St. Louis, MO 63114

License No. 24-04206-08MD
Docket No. 030-18546

Gentleme

This refe to the routine safety inspection conducted by Evelyn R. Matson, Mark Mit..ell and Michael Kurth, of this office on February 14, 1991 of activities authorized by License No. 24-04206-08MD and to the discussion of our findings with you by telephone on February 22, 1991.

This inspection was an examination of activities conducted under your license as they relate to radiation safety and to compliance with the Commission's rules and regulations and with the conditions of your license. The inspection consisted of a selective examination of procedures and representative records, observations, independent measurements, and interviews with personnel.

The inspection included a review of an allegation received by the NRC Region III on December 13, 1990. The details concerning this allegation are contained in the enclosure to this letter. (AMS No. RIII-90-A-0136).

During this review two apparent violations were identified related to the allegation regarding your failure to: (1) prepare radiopharmaceuticals in accordance with manufacturer's package inserts and (2) after August 1990, to obtain a written directive before deviating from the package insert instructions. These two apparent violations are described in the enclosure to this letter. As you are aware, the NRC is currently reviewing the applicability of these regulations as they relate to radiopharmaceutical preparation and use. Therefore, a final decision regarding enforcement will be withheld at this time pending the outcome of our review into this matter. No response regarding this matter is required at this time.

In addition to the above areas, the inspectors examined actions described in your letter dated March 12, 1990, regarding violations found during our January 24 and 25, 1990, inspection. We have no further questions regarding these matters.

The inspection also identified an apparent violation regarding the failure to maintain an air exhaust flow rate of 125 cfm in accordance with specifications in the license. Since this violation was identified by your staff shortly prior to this inspection and the inspection showed that corrective actions are planned, we have exercised our discretion as allowed by the NRC Enforcement Policy and will not issue a violation. This discretion policy is specified in 10 CFR Part 2, Appendix C, Section V.G. and its criteria appears to have been met.

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MAR 1 5 1991

In accordance with 10 CFR 2.790 of the Commission's regulations, a copy of this letter and the enclosure allegation report will be placed in the NRC Public Document Room.

We will gladly discuss any questions you have concerning this inspection.

Sincerely,

John A. Grobe, Chief
Nuclear Materials Safety Branch

Enclosure: Allegation Report AMS
No. RIII-90-A-0136

cc w/enclosure:
D. Funk, RIII
J. Glenn, NMSS
DCD/DCB (RIDS)

RIII	RIII	RIII	RIII
Matson/ms	Caniano	Pederson	Grobe
03/14/91	03/15/91	03/ /91	03/18/91

Allegation Report (AMS No. RIII-90-A-0136)

ALLEGATION

On December 13, 1990, the NRC Region III office received an allegation by telephone that the licensee did not appear to be complying with the interim regulation 10 CFR 35.200. Specifically, the alleger stated that the licensee was deviating from the Mo-99/Tc-99m generator package insert which states that bulk Tc-99m has an expiration time of 12 hours. The alleger stated the licensee was distributing bulk technetium-99m to customers with a 24 hour expiration time and had never obtained the required documentation described in the interim regulation which would justify the deviation.

APPLICABLE REGULATIONS

Commercial nuclear pharmacies are licensed pursuant to 10 CFR Part 30. Mallinckrodt, Inc., Diagnostic Imaging Services is required by License Condition No. 19 (which is similar to 35.200 (b)) to elute generators and process radioactive material with reagent kits in accordance with instructions furnished by the manufacturer on the label attached to or in the leaflet or brochure that accompanies the generator or reagent kit. The brochure that accompanies the licensee's generators states that the expiration time of the Sodium Pertechnetate Tc-99m solution is not later than 12 hours after time of elution. The Mo99/Tc99m brochure is enclosed as Attachment A.

On August 23, 1990, the NRC published in the Federal Register an interim rule (10 CFR 30.34) which states that each licensee eluting generators and processing radioactive material with diagnostic reagent kits may depart from the manufacturer's elution and preparation instructions provided that the licensee has a written directive made by an authorized user physician that directs a specific departure 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 instruction would obtain medical results not otherwise attainable or would reduce medical risk to particular patients because of their medical condition.

The interim rule also states that for situations not within the scope of the amended §30.34, a commercial nuclear pharmacy licensee may file an application to have its license amended to permit specific departures from the manufacturer's instruction for identified products.

INSPECTION RESULTS

During the inspection, the inspectors observed technetium-99m sodium pertechnetate solution being prepared, labelled and packaged for distribution to clients. Each of the observed preparations was labelled with an expiration time of 24 hours post elution. Licensee representatives stated that since the inception of the pharmacy's program on November 20, 1984, they have distributed technetium-99m sodium pertechnetate solution to clients with the 24 hour expiration time stated on their labels. A sample label showing this information is enclosed as Attachment B. The representatives also stated that other

Mallinckrodt nuclear pharmacies distribute the Tc-99m solution with a 24 hour expiration time specified. License Condition No. 19 (which requires radioactive material be processed in accordance with the manufacturer's instructions) has been a condition of this license since November 20, 1984. Failure to process radioactive material (technetium-99m sodium pertechnetate) from November 1984 to August 1990 in accordance with instructions furnished by the manufacturer that states the expiration time of technetium-99m sodium pertechnetate is not later than 12 hours after time of elution is an apparent violation of License Condition No. 19.

In addition, the representatives stated that since the interim rule became effective on August 23, 1990, they have not obtained written directives made by authorized user physicians that direct the departures. Failure to obtain written directives from authorized physician users when departing from the manufacturer's specified 12 hour expiration time for bulk technetium-99m from August 23, 1990 through February 14, 1991, is an apparent violation of 10 CFR 30.34.

Licensee representatives stated that all prepared reagent kits are distributed with the kit manufacturer's expiration times specified on the kit or dose labels. The inspectors observed several prepared unit doses and kits with 12 hour expiration times specified on the labels.

The facility manager and the facility RSO stated that they and Mallinckrodt, Inc. corporate managers were aware of the NRC regulation requiring medical use licensees to prepare radiopharmaceuticals in accordance with the manufacturer's instructions. However, they stated that the regulation is controversial and it is currently being challenged by the industry. They stated that the regulation infringes on their right as a pharmacy. The RSO stated that in allowing a 24 hour expiration time of bulk Tc-99m they are using their good judgement as licensed pharmacists and are operating in good faith with regard to safety. As evidence of this, the representatives provided the following information:

a. They stated that the 12 hour expiration time specified in the generator brochure was written for small users who do not have sterile preparation conditions. The Mallinckrodt Ultra-TechneKow FM technetium-99m generator brochure states that because the eluate does not contain an antimicrobial agent, it should not be used after 12 hours from the time of generator elution. The pharmacists stated that, at this facility, the Tc-99m eluate is handled using aseptic techniques in a sterile environment (i.e., a certified and inspected laminar flow sterile preparation hood) which allows it to be used safely for up to 24 hours.

b. The United States Pharmacopeia states that generally there is a 24 hour expiration time on any pharmaceutical prepared aseptically and not containing a preservative. They stated that this reference shows that the 24 hour expiration time is a traditional standard pharmacy practice.

c. In addition to the above, the RSO showed the inspectors a reference book "Practical Nuclear Pharmacy" which states that the expiration time for Tc-99m sodium pertechnetate is 24 hours after preparation. An excerpt from this manual is enclosed as Attachment C.

d. In order to demonstrate that the 12 hour expiration time is not consistent with other industry specifications, licensee representatives informed the inspectors that at least one prepared radiopharmaceutical using Tc-99m has an expiration time of 18 hours after reconstitution specified in the manufacturer's package insert. For a copy of this package brochure, refer to the enclosed Attachment D.

e. Licensee representatives also referenced the NRC Temporary Waiver Of Compliance (Effective January 15, 1991) which states that the NRC will not enforce license conditions or regulations requiring licensees authorized to possess and use molybdenum-99/technetium-99m generators and prepare reagent kits to follow manufacturer's instructions for the purpose of allowing use of generators for up to 21 days and use of technetium-99m eluant for up to 24 hours. They stated that if the NRC felt it was safe to allow a 24 hour expiration time on a temporary basis that it should be safe on a permanent basis.

SUMMARY

This inspection found evidence that substantiates the allegation that Mallinckrodt, Inc., Diagnostic Imaging Services is distributing technetium-99m sodium pertechnetate to customers with an expiration date of 24 hours post elution when the manufacturer's package insert states an expiration date of 12 hours post elution and that they have not obtained the required documentation from authorized physician users as required by the interim regulation. One apparent violation against License Condition No. 19 was identified and a second apparent violation against 10 CFR 30.34 interim regulation was identified.

Attachments:
A. Mallinckrodt Package Insert
B. Pharmaceutical Label
C. Excerpt from Practical Nuclear Pharmacy
D. Squibb Package Insert

Attachment A

R4/85

100 - 107

TECHNICAL
PRODUCT
DATA

Mallinckrodt®

DIAGNOSTIC PRODUCTS DIVISION
MALLINCKRODT, INC. • ST. LOUIS, MO. 63134

Ultra-TechneKow® FM

(Technetium Tc 99m Generator)

For the Production of
Sodium Pertechnetate Tc 99m Injection

DESCRIPTION

The **Ultra-TechneKow** FM Generator is prepared with fission-produced molybdenum-99 adsorbed onto alumina in a lead shielded column. This generator provides a closed system for the production of sterile metastable technetium-99m, which is produced by the decay of molybdenum-99. Sterile, non-pyrogenic isotonic solutions of Sodium Pertechnetate Tc 99m can be obtained conveniently by periodic aseptic elution of the generator. These solutions should be crystal clear.

The carrier-free solution may be used as is, or diluted to the proper concentration. Over the life of the generator, an elution will contain a technetium-99m yield of 70% to 86% in terms of the amount of molybdenum-99 on the generator column.

Each eluate of the generator should not contain more than the U.S.P. limit of 0.15 kilobecquerel molybdenum-99 per megabecquerel technetium-99m (0.15 microcurie Mo-99 per millicurie Tc-99m) per administered dose at the time of administration and an aluminum ion concentration of not more than 10 micrograms per milliliter of the generator eluate, both of which must be determined by the user before administration.

Since the eluate does not contain an antimicrobial agent, it should not be used after 12 hours from the time of generator elution.

Attachment A
page 1 of 2

Storage

Store generator and Sodium Pertechnetate Tc 99m solution at room temperature (15°C to 30°C).

EXPIRATION DATE

The generator should not be used after the expiration date stated on the label.

The expiration time of the Sodium Pertechnetate Tc 99m solution is not later than 12 hours after time of elution. If the eluate is used to reconstitute a kit, the radiolabeled kit should not be used after 12 hours from the time of generator elution or after the expiration time stated on the labeling for the prepared drug, whichever is earlier.

DIRECTIONS FOR USE OF THE Ultra-TechneKow FM GENERATOR

NOTE 1: Immediately upon delivery, the generator should be placed within a minimum of one inch of lead shielding in such a manner so as to minimize radiation exposure to attending personnel. The Mallinckrodt, Inc. Auxiliary Shield, Catalog #024, effects such protection.

NOTE 2: Wear waterproof gloves during the elution procedure and during subsequent reconstitution of kits with the eluate.

NOTE 3: Use a shielded syringe to withdraw patient dose or transfer Sodium Pertechnetate Tc99m into mixing vials during kit reconstitution.

Eluting the generator every 24 hours will provide optimal amounts of Sodium Pertechnetate Tc 99m. However, the generator may be eluted whenever sufficient amounts of technetium-99m have accumulated within the column.

For Example:

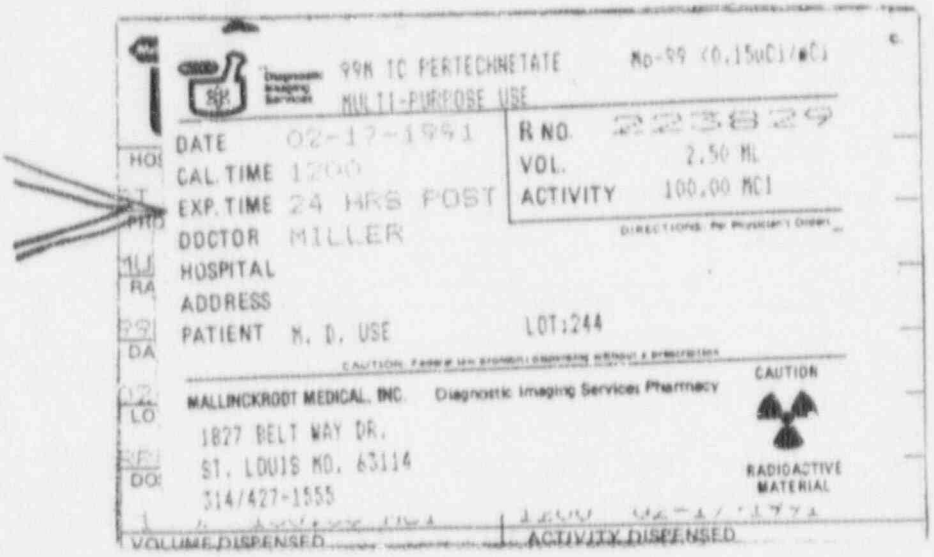
Time After First Elution (hrs)	*Approximate Yield (% of First Elution)*
1	10
2	19
3	27
4	35
5	41
6	47

First Elution

1. Remove the protective cap from the bottom of the dispenser plunger and attach the sterile Luer-Lok needle. Remove plastic needle cover.
2. Place collecting vial in the elution shield. Remove white plastic dust cover and clean rubber closure of collecting vial with antiseptic swab.

Attachment A
page 2 of 2

Attachment B



99M TC PERTECHNETATE Mo-99 (0.15uCi/uCi)
MULTI-PURPOSE USE

DATE 02-17-1991
CAL. TIME 1200
EXP. TIME 24 HRS POST
DOCTOR MILLER
HOSPITAL
ADDRESS
PATIENT M. D. USE

R NO. 223829
VOL. 2.50 ML
ACTIVITY 100.00 MCI

DIRECTIONS: Per Physician's Orders

LOT:244

CAUTION: Federal law prohibits dispensing without a prescription

MALLINCKRODT MEDICAL, INC. Diagnostic Imaging Services Pharmacy
1827 BELT WAY DR.
ST. LOUIS MO. 63114
314/427-1555

CAUTION
RADIOACTIVE MATERIAL

VOLUME DISPENSED

ACTIVITY DISPENSED

Attachment B

Attachment C

PRACTICAL NUCLEAR PHARMACY

Trent Phan, Ph.D.
Richard Wasnich, M.D.

2nd Revised Edition

Banyan Enterprises, Ltd.
Cultural Plaza
P.O. Box 27825
Honolulu, Hawaii 968[illegible]

Tc-99m SODIUM PERTECHNETATE

Tc-99m sodium pertechnetate as a sterile, pyrogen-free isotonic solution may be eluted from an alumina-column generator or extracted from a solvent extraction generator.

Quality Control

1. pH between 4.5 and 7.5.
2. Chemical purity
   a. Eluates from alumina column generators may contain aluminum. Using an aluminum ion indicator paper, compare the pink intensity of a drop of Tc-99m pertechnetate to that produced by a drop of aluminum standard. It should contain less than 20 ug/ml for irradiated Mo-99 (1M), and less than 10 ug/ml for fission Mo-99 (FM).
   b. For liquid extraction generators, methylethylketone (MEK) content should be less than 0.1%.
3. Radionuclidic purity. Mo-99 breakthrough may be determined in a multichannel analyzer or by the simple method described in the chapter on Radionuclidic Purity. Also using the lead canister, check Mo-99 breakthrough by reading Mo-99 content in the radionuclide calibrator and relate to total Tc-99m activity. Mo-99 allowable limits are less than 0.15 uCi/mCi Tc-99m and less than 2.5 uCi/administered dose.

Since Mo-99 (T½ 67 hours) decays more slowly than Tc-99m (T½ 6 hours), it is also necessary to check if the Mo-99 content is still within permissible limits at the time of injection, by using the appropriate correction factor:

Time post-elution, hrs	0	6	12	18	24
Correction factor	1	1.9	3.5	6.6	12.5

4. Radiochemical purity. Tc-99m sodium pertechnetate (valence +7) may contain various reduced states of Tc-99m (valences +4, +5) as impurities. With ITLC-SG and 85% methanol as solvent, Tc-99m (+4) remains at the origin Rf 0, while Tc-99m (+5) moves with Rf 0.3 and Tc-99m (+7) moves with the solvent front Rf 1.0. The solution should contain 95-100% in Tc-99m (+7).
5. Expiration date: 24 hours after preparation.

Biological Behavior

1. Tc-99m pertechnetate similarly to iodide ion, an choroid plexus, and stomi thyroid trapping. A fractio accumulate in intracrani altered blood-brain barrie
2. Tc-99m pertechnetate gastric mucosa, and bloo
3. Tc-99m pertechnetate be given orally. Suggeste brain 10-20 mCi, thyroid 1 10-20 mCi.
4. Estimated absorbed ra of Tc-99m pertechnetate in 5.0, liver 0.3, testes 0.2, ov

Thyroid exposure may be (Lugol's solution) or perchl

5. In brain imaging, up orally prior to Tc-99m uptake of Tc-99m by the

Notes

1. The specific gamma r The half value layer is 0.

Shield thickness, mm lead	
Attenuation coefficient	

2. Tc-99m decay chart

Time, hrs	
% Tc-99m remaining	

Time, hrs	
% Tc-99m remaining	

3. Tc-99m sodium perte valence state, usually (+4 usually accomplished with stannous-containing kits quantity of carrier Tc-99 fraction of Tc-99m in a g

Day(s) since last elution	
% Tc-99m	

Attachment C page 2 of 2

Attachment D

SQUIBB™ Diagnostics

J3-599D

CHOLETEC®

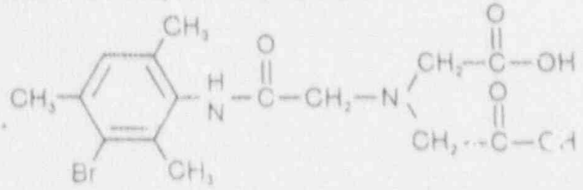
Kit for the Preparation of Technetium Tc 99m Mebrofenin

For Diagnostic Use

DESCRIPTION

Each reaction vial contains a nonradioactive, sterile, nonpyrogenic mixture of 45 mg mebrofenin, 0.54 mg (minimum) stannous fluoride dihydrate, $SnF_2 \cdot 2H_2O$ and 1.03 mg total tin, maximum (as stannous fluoride dihydrate, $SnF_2 \cdot 2H_2O$), not more than 5.2 mg methylparaben, and 0.58 mg propylparaben. The pH is adjusted with sodium hydroxide or hydrochloric acid prior to lyophilization. The contents of the vial are lyophilized and sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 4.2 to 5.7.

The structure of mebrofenin(2,2'-[[2-[(3-Bromo-2,4,6-trimethylphenyl)-amino]-2-oxoethyl]imino] bisacetic acid) is shown below:



When sterile, pyrogen-free sodium pertechnetate Tc 99m injection is added to the vial, the diagnostic agent Technetium Tc 99m Mebrofenin is formed for administration by intravenous injection.

PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] The principal photon that is useful for detection and imaging studies is listed in Table 1.

TABLE 1

Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

[1]Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC-11026, (1981) p. 108.

External Radiation

The specific gamma ray constant for Tc 99m is 0.78 R/hour-millicurie at 1 cm. The first half value layer is 0.017 cm of lead (Pb). A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about

J3-599D

Attachment D page 1 of 2

of pharmacokinetic modeling to the radiation dosimetry of hepatobiliary agents. In Third International Radiopharmaceutical Dosimetry Symposium, FDA No. 81-8166, U.S. Department of Health and Human Services, Public Health Service, FDA, Bureau of Radiological Health, Rockville, MD, (1981) pp. 318-332.

(2) Values for S: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

* Bilirubin < 1.5 mg/dL
Calculations assume that 98% of the injected activity is taken up by the liver; activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.

** Bilirubin > 10 mg/dL (mean 21.8 mg/dL)
Calculations assume that 66% of the injected activity is taken up by the liver; activity not removed in the urine in 24 hours is excreted in the intestines and no enterohepatic circulation of activity.

HOW SUPPLIED

Choletec (Kit for the Preparation of Technetium Tc 99m Mebrofenin) is supplied in kits of 10 reaction vials. Each vial contains a sterile, nonpyrogenic lyophilized mixture of 45 mg mebrofenin, 0.54 mg (minimum) stannous fluoride dihydrate, $SnF_2 \cdot 2H_2O$ and 1.03 mg total tin, maximum (as stannous fluoride dihydrate, $SnF_2 \cdot 2H_2O$), not more than 5.2 mg methylparaben, and 0.58 mg propylparaben. The pH has been adjusted with hydrochloric acid or sodium hydroxide prior to lyophilization. The lyophilized vial contents are sealed under nitrogen at the time of manufacture. The pH of the reconstituted product is 4.2 to 5.7.

Kit Contents

10 sterile multidose reaction vials.
20 pressure-sensitive labels for Technetium Tc 99m Mebrofenin.
1 package insert.

Preparation

Preparation of Technetium Tc 99m Mebrofenin is done by the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure.
2. Place reaction vial in an appropriate lead shield.
3. Swab the rubber closure of the reaction vial with a germicide.
4. Inject 1 to 5 mL sterile additive free sodium pertechnetate Tc 99m injection containing up to 370u MBq (100 mCi) Tc 99m into the reaction vial. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution. NOTE: If sodium pertechnetate Tc 99m injection must be diluted for use with Choletec (Kit for the Preparation of Technetium Tc 99m Mebrofenin), only preservative free Sodium Chloride Injection USP should be used.
5. Secure the lead shield cover. Swirl the vial gently to mix contents and let stand for 15 minutes.
6. Record the date and time of preparation on pressure-sensitive label.
7. Affix pressure-sensitive label to shield.
8. Examine vial contents. If the solution is not clear and free of particulate matter and discoloration on visual inspection, it should not be used.
9. Measure the radioactivity by a suitable calibration system and record on the shield label prior to patient administration.
10. Withdraw material with a sterile lead shielded syringe for use within 18 hours of preparation.

Storage

Store the kit as supplied at 15-30° C prior to and following reconstitution. Use within 18 hours of reconstitution.

The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material identified in §35.200 of 10 CFR Part 35, to persons who hold an equivalent license issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

Squibb Diagnostics
Princeton, NJ 08543