Form AEC-313
(2-73)
10 CFR 30

UNITED STATES ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE

Form approved
Budget Bureau No. 38-R0027

INSTRUCTIONS.—Complete Items 1 through 16 if this is an initial application or an application for renewal of a license. Information contained in previous applications filed with the Commission with respect to Items 8 through 15 may be incorporated by reference provided *references are clear and specific*. Use supplemental sheets where necessary. Item 16 must be completed on all applications. Mail two copies to: U.S. Atomic Energy Commission, Washington, D.C., 20545, Attention: Materials Branch, Directorate of Licensing. Upon approval of this application, the applicant will receive an AEC Byproduct Material License. An AEC Byproduct Material License is issued in accordance with the general requirements contained in Title 10, Code of Federal Regulations, Part 30, and the Licensee is subject to Title 10, Code of Federal Regulations, Part 20, and the license fee provisions of Title 10, Code of Federal Regulations, Part 170. The license fee category should be stated in Item 16 and the appropriate fee enclosed. (See Note in Instruction Sheet).

1 (a) NAME AND STREET ADDRESS OF APPLICANT *(Institution, firm, hospital person, etc. Include ZIP Code and telephone number.)*

Department of the Army
Fitzsimons Army Medical Center and U.S. Army Medical Research and Nutrition Laboratory
Denver, Colorado 80240

(b) STREET ADDRESS(ES) AT WHICH BYPRODUCT MATERIAL WILL BE USED *(If different from 1(a). Include ZIP Code.)*

Department of the Army
Fitzsimons Army Medical Center and U.S. Army Medical Research and Nutrition Laboratory
Denver, Colorado 80240

2 DEPARTMENT TO USE BYPRODUCT MATERIAL

Department of Radiology
Nuclear Medicine Service

3 PREVIOUS LICENSE NUMBER(S). *(If this is an application for renewal of a license, please indicate and give number.)*

Amendment to Existing License No. 05-00046-13 (30 Apr 74)

4 INDIVIDUAL USER(S). *(Name and title of individual(s) who will use or directly supervise use of byproduct material. Give training and experience in Items 8 and 9.)*

See Application dated
12 March 1973 (Control No. 35871)

5 RADIATION PROTECTION OFFICER. *(Name of person designated as radiation protection officer if other than individual user. Attach resume of his training and experience as in Items 8 and 9.)*

See Application dated 12 March 1973
(Control No. 35871)

6 (a) BYPRODUCT MATERIAL. *(Elements and mass number of each.)*

Tc-99m

(b) CHEMICAL AND/OR PHYSICAL FORM AND MAXIMUM NUMBER OF MILLICURIES OF EACH CHEMICAL AND/OR PHYSICAL FORM THAT YOU WILL POSSESS AT ANY ONE TIME. *(If sealed source(s), also state name of manufacturer, model number, number of sources and maximum activity per source.)*

Tc-99m - Disodium Etidronate - 100 mCi, prepared by use of Osteoscan Kit, Proctor and Gamble, Professional Services Division, Ivorydale Technical Center, Cincinnati, Ohio 45217

Tc-99m Sodium Pertechnetate obtained as eluate from presently authorized E.R. Squibb and Sons Generator Model 08871 (See para 6 of existing AEC License 05-00040-13.

7 DESCRIBE PURPOSE FOR WHICH BYPRODUCT MATERIAL WILL BE USED. *(If byproduct material is for "human use," supplement A (Form AEC 313a) must be completed in lieu of this item. If byproduct material is in the form of a sealed source, include the make and model number of the storage container and/or device in which the source will be stored and/or used.)*

Human use - Tc-99m Disodium Etidronate - Bone imaging

See Supplement A (Form AEC - 313a)

45457

(Continued on reverse side)

TRAINING AND EXPERIENCE OF EACH INDIVIDUAL NAMED IN ITEM 4 (Use supplemental sheets if necessary)

8. TYPE OF TRAINING	WHERE TRAINED	DURATION OF TRAINING	ON THE JOB (Circle answer)	FORMAL COURSE (Circle answer)
a. Principles and practices of radiation protection	See application dated 12 March 1974 (Control No. 35871)		Yes No	Yes No
b. Radioactivity measurement standardization and monitoring techniques and instruments			Yes No	Yes No
c. Mathematics and calculations basic to the use and measurement of radioactivity			Yes No	Yes No
d. Biological effects of radiation			Yes No	Yes No

9. EXPERIENCE WITH RADIATION. (Actual use of radioisotopes or equivalent experience.)

ISOTOPE	MAXIMUM AMOUNT	WHERE EXPERIENCE WAS GAINED	DURATION OF EXPERIENCE	TYPE OF USE
See application dated 12 March 1973 (Control No. 35871)				

10. RADIATION DETECTION INSTRUMENTS. (Use supplemental sheets if necessary.)

TYPE OF INSTRUMENTS (Include make and model number of each)	NUMBER AVAILABLE	RADIATION DETECTED	SENSITIVITY RANGE (mr/hr)	WINDOW THICKNESS (mg/cm²)	USE (Monitoring, surveying, measuring)
See application dated 12 March 1973 (Control No. 35871) and application dated 25 June 1968.					

11. METHOD, FREQUENCY, AND STANDARDS USED IN CALIBRATING INSTRUMENTS LISTED ABOVE

See application dated 12 March 1973 (Control No. 35871) and application dated 25 June 1968.

12. FILM BADGES, DOSIMETERS, AND BIO-ASSAY PROCEDURES USED. (For film badges, specify method of calibrating and processing, or name of supplier.)

See application dated 12 March 1973 (Control No. 35871) and application dated 25 June 1968.

INFORMATION TO BE SUBMITTED ON ADDITIONAL SHEETS IN DUPLICATE

13. FACILITIES AND EQUIPMENT. Describe laboratory facilities and remote handling equipment, storage containers, shielding, fume hoods, etc. Explanatory sketch of facility is attached. (Circle answer) Yes No

See application dated 12 March 1973 (Control No. 35871) and application dated 25 June 1968.)

14. RADIATION PROTECTION PROGRAM. Describe the radiation protection program including control measures. If application covers sealed sources, submit leak testing procedures where applicable, name, training, and experience of person to perform leak tests, and arrangements for performing initial radiation survey, servicing, maintenance and repair of the source.

See application dated 12 March 1973 (Control No. 35871) and application dated 25 June 1968.)

15. WASTE DISPOSAL. If a commercial waste disposal service is employed, specify name of company. Otherwise, submit detailed description of methods which will be used for disposing of radioactive wastes and estimates of the type and amount of activity involved.

See application dated 12 March 1973 (Control No. 35871) and application dated 25 June 1968.)

CERTIFICATE (This item must be completed by applicant)

16. THE APPLICANT AND ANY OFFICIAL EXECUTING THIS CERTIFICATE ON BEHALF OF THE APPLICANT NAMED IN ITEM 1, CERTIFY THAT THIS APPLICATION IS PREPARED IN CONFORMITY WITH TITLE 10, CODE OF FEDERAL REGULATIONS, PART 30, AND THAT ALL INFORMATION CONTAINED HEREIN, INCLUDING ANY SUPPLEMENTS ATTACHED HERETO, IS TRUE AND CORRECT TO THE BEST OF OUR KNOWLEDGE AND BELIEF.

License Fee Category $ ____________

Fee Enclosed $ ____________

Date ____________

Fitzsimons Army Medical Center
Denver, Colorado 80240

Applicant named in item 1

By: H. F. Cowgill, M.D. *H F Cowgill*
Colonel, MC

Title of certifying official

WARNING.—18 U.S.C., Section 1001; Act of June 25, 1948; 62 Stat. 749; makes it a criminal offense to make a willfully false statement or representation to any department or agency of the United States as to any matter within its jurisdiction.

Form AEC-313a
(2-73)
10 CFR 30
PAGE 1

UNITED STATES ATOMIC ENERGY COMMISSION

APPLICATION FOR BYPRODUCT MATERIAL LICENSE—MEDICAL

SUPPLEMENT A—HUMAN USE

Form approved.
Budget Bureau No. 38-R0080

If byproduct material is for "human use" (internal administration of byproduct material, or the radiation therefrom to human beings), complete this supplement and attach to the application for byproduct material license.

1. (a) USING PHYSICIAN'S NAME

(b) NAME AND ADDRESS OF APPLICANT (If different from 1(a). Include ZIP Code.)

Fitzsimons Army Medical Center
Denver, Colorado 80240

2. THE USING PHYSICIAN INDICATED ABOVE IS LICENSED TO DISPENSE DRUGS IN THE PRACTICE OF MEDICINE BY A STATE OR TERRITORY OF THE UNITED STATES, THE DISTRICT OF COLUMBIA, OR THE COMMONWEALTH OF PUERTO RICO. See application dated 12 March 1973 Control No. 35871 CIRCLE ANSWER	(YES)	NO
3. A STATEMENT OF USING PHYSICIAN'S CLINICAL RADIOISOTOPE EXPERIENCE (PAGE 3 OF THIS SUPPLEMENT) IS SUBMITTED IN SUPPORT OF THIS APPLICATION. IF ANSWER IS NO, USE PAGE 2 OF THIS SUPPLEMENT TO EXPLAIN OR REFER TO OTHER APPLICATION OR RELATED DOCUMENTS ON WHICH THIS INFORMATION APPEARS. See application dated 12 March 1973. Control No. 35871 CIRCLE ANSWER	YES	NO
4. A DESCRIPTION OF THE USING PHYSICIAN'S TRAINING AND EXPERIENCE IN BASIC RADIOISOTOPE HANDLING TECHNIQUES AND/OR RADIOPHARMACEUTICAL PREPARATION IS APPENDED. See application dated 12 March 1973. Control No. 35871 CIRCLE ANSWER	YES	NO

5. (a) DESCRIBE PURPOSE FOR WHICH MATERIAL WILL BE USED INCLUDING SPECIFIC CONDITIONS OR DISEASES TO BE DIAGNOSED OR TREATED (Use page 2 if necessary)

Lung imaging (See inclosure 1)

(b) CHEMICAL FORM ADMINISTERED

Tc-99m - Disodium Elidronate (See inclosure 1)

(c) DOSAGE SCHEDULE FOR EACH CONDITION TO BE DIAGNOSED OR TREATED

10-15 mCi (See Inclosure 1)

6. INVESTIGATIVE PROPOSAL FOR EXPERIMENTAL OR NON-ROUTINE USE IS APPENDED. (See Appendix F of AEC Licensing Guide for items to be submitted) N/A	CIRCLE ANSWER	YES	NO

7. IF BYPRODUCT MATERIAL WILL NOT BE OBTAINED IN PRECALIBRATED FORM FOR ORAL ADMINISTRATION OR IN PRECALIBRATED FORM FOR PARENTERAL ADMINISTRATION, DESCRIBE IDENTIFICATION, PROCESSING, AND STANDARDIZATION PROCEDURES:

Tc-99m obtained as eluate from ER Squidd and Son, Inc. Technetope II sterile generator (08871) Mo content 300 mCi Eluate assayed in Nuc. Chicago Dose Calibrator Model 6362

45457

8. THE PROPOSED USE OF BYPRODUCT MATERIAL HAS BEEN, OR WILL BE, APPROVED BY THE MEDICAL ISOTOPE COMMITTEE.	CIRCLE ANSWER	YES	NO

HOSPITAL FACILITIES FOR INDIVIDUAL PRACTICE USE ONLY

9. (a) THE APPLICANT HAS COMPLETED ARRANGEMENTS FOR A HOSPITAL TO ADMIT RADIOACTIVE PATIENTS WHEN EVER ADVISABLE.	CIRCLE ANSWER	YES	NO
(b) A COPY OF INSTRUCTIONS TO BE FURNISHED TO THE HOSPITAL AS TO RADIOLOGICAL SAFETY PRECAUTIONS TO BE TAKEN AND AVAILABLE RADIATION INSTRUMENTATION IS ATTACHED.	CIRCLE ANSWER	YES	NO

PROCTER & GAMBLE

OSTEOSCAN

(5.9 MG DISODIUM ETIDRONATE 0.16 MG STANNOUS CHLORIDE)

SKELETAL IMAGING AGENT

DESCRIPTION

Each vial of OSTEOSCAN contains 5.9 mg disodium etidronate and 0.16 mg stannous chloride as active ingredients. Upon addition of ADDITIVE-FREE ^{99m}Tc-pertechnetate, these ingredients combine with ^{99m}Tc to form a stable soluble complex.

ACTIONS (CLINICAL PHARMACOLOGY)

When injected intravenously, ^{99m}Tc-labeled OSTEOSCAN has a specific affinity for areas of altered osteogenesis. Areas of bone which are undergoing neoplastic invasion often have an unusually high turnover rate which may be imaged with ^{99m}Tc-labeled OSTEOSCAN.

Three hours after intravenous injection of 1 ml ^{99m}Tc-labeled OSTEOSCAN, an estimated 40-50% of the injected dose has been taken up by the skeleton. At this time approximately 50% has been excreted in the urine and 6% remains in the blood. A small amount is retained by the soft tissue. The level of ^{99m}Tc-labeled OSTEOSCAN excreted in the feces is below the level detectable by routine laboratory techniques.

INDICATIONS

OSTEOSCAN is a skeletal imaging agent used to demonstrate areas of altered osteogenesis.

CONTRAINDICATIONS

None.

WARNINGS

This radiopharmaceutical should not be administered to patients who are pregnant or lactating unless the information to be gained outweighs the potential hazards.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

The ^{99m}Tc- generator should be tested routinely for molybdenum breakthrough and aluminum. If either is detected, the eluate should not be used.

PRECAUTIONS

Both prior to and following ^{99m}Tc-labeled OSTEOSCAN administration, patients should be encouraged to drink fluids. Patients should void as often as possible after the ^{99m}Tc-labeled OSTEOSCAN injection to minimize background interference from accumulation in the bladder and unnecessary exposure to radiation.

As in the use of any other radioactive material, care should be taken to insure minimum radiation exposure to the patient, consistent with proper patient management, and to insure minimum radiation exposure to occupational workers.

ADVERSE REACTIONS

None.

DOSAGE AND ADMINISTRATION

The recommended adult dose of ^{99m}Tc-labeled OSTEOSCAN is 1 ml with a total activity range of 10-15 mCi. ^{99m}Tc-labeled OSTEOSCAN should be given intravenously by slow injection over a period of 30 seconds within three (3) hours after its preparation. Optimum scanning time is 3-4 hours postinjection.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

PHYSICAL CHARACTERISTICS

Technetium-99m decays by isomeric transition with a physical half-life of 6 hours[1]. Photons that are useful for imaging studies are listed in Table I.

Table I. Principal Radiation Emission Data

Radiation	Mean %/ Disintegration	Mean Energy (keV)
M int. con. electron, γ-1	98.6	1.7
Gamma-2	88.3	140.5
K int. con. electron, γ-2	8.8	119.5
L int. con. electron, γ-2	1.1	137.7
Gamma-3	0.03	142.7
K int. con. electron, γ-3	0.96	121.7
Kα X-rays	6.5	18.4

[1]Dillman, L.T., Radionuclide Decay Schemes and Nuclear Parameters for Use in Radiation-Dose Estimation, Supplement No. 2, MIRD pamphlet No. 4, *J. Nucl. Med.*, p. 22, 1969.

The specific gamma ray constant for ^{99m}Tc is 0.72 R/mCi-hr at 1 cm. The half value layer is 4 mm of Pb.

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table II.

Table II. Physical Decay Chart; ^{99m}Tc, half-life 6 hours

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.779	5	.562
-4	1.587	6	.500
-3	1.414	7	.446
-2	1.260	8	.397
-1	1.122	9	.354
0*	1.000	10	.315
1	.891	11	.281
2	.794	12	.250
3	.707	18	.125
4	.630	24	.063

*Calibration time

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 15 millicuries of ^{99m}Tc-labeled OSTEOSCAN are shown in Table III. For comparison, the estimated radiation doses from a maximum dose of 4 millicuries of ^{18}F used as a bone imaging agent are also included.

Table III. Radiation Doses

Tissues	Absorbed Radiation Dose	
	^{99m}Tc-OSTEOSCAN (rads/15 mCi)	^{18}F (rads/4 mCi)
Skeleton*	0.59	0.64
Testes	0.32	0.83
Ovaries	0.33	0.85
Total Body	0.13	0.18
Bladder 4.8 hour void	8.4	
Bone Marrow	0.14	

*Local dose may be a factor of 10 or more greater.

[1]Method of Calculation: A Scheme for Absorbed-Dose Calculations for Biologically Distributed Radionuclides. Supplement No. 1, MIRD pamphlet No. 1, *J. Nucl. Med.*, p. 7, 1968.

HOW SUPPLIED

The OSTEOSCAN kit contains five (5) vials. Each vial contains 5.9 mg disodium etidronate and 0.16 mg stannous chloride as active ingredients. The contents of each vial are prepared by appropriate manufacturing procedures to be sterile and pyrogen-free.

PREPARATION FOR USE

The following aseptic procedure should be followed in the preparation of the ^{99m}Tc-labeled OSTEOSCAN skeletal imaging agent:

STEP 1.
Remove central metal disc of the OSTEOSCAN vial and swab the top of the vial with alcohol to sterilize the surface of the closure.

STEP 2.
Place the OSTEOSCAN vial in a radiation shield. In a sterile syringe, collect 5 ml of sterile pyrogen-free ^{99m}Tc-pertechnetate from an additive-free ^{99m}Tc-pertechnetate source which has been checked for molybdenum breakthrough. Check the activity of the ^{99m}Tc-pertechnetate to avoid exceeding 50-75 mCi/5 ml. If the activity exceeds this level, dilute with ADDITIVE-FREE sterile saline only such that a 5 ml portion will contain the 50-75 mCi activity.

STEP 3.
Add the ^{99m}Tc-pertechnetate to the vial. After adding the ^{99m}Tc-pertechnetate to the vial, withdraw an equivalent amount of air to equalize the pressure inside the vial to prevent spray contamination. CAUTION: DO NOT USE ^{99m}Tc-PERTECHNETATE WHICH CONTAINS AN OXIDIZING AGENT. INTRODUCTION OF AN OXIDANT MAY RESULT IN A SOLUTION UNSUITABLE FOR SKELETAL IMAGING. Commercial sources of ^{99m}Tc-pertechnetate that have been used in clinical trials with OSTEOSCAN include the New England Nuclear Technetium-99m Generator, the Mallinckrodt Technetium-99m Generator, the Squibb Hi-Con Generator, Medi-Physics Instant Technetium, and Cambridge Nuclear Instant Technetium.

STEP 4.
Shake the vial well for three (3) minutes to assure complete dissolution of the contents. Minimal exposure can be obtained by use of either an ultrasonic agitator or mechanical shaker.

STEP 5.
Record the time and date of preparation and the activity of the ^{99m}Tc-labeled OSTEOSCAN on the radiation shield label contained in the kit and affix this label to the shield.

STEP 6.
Use within three (3) hours of preparation. Discard excess material.

OSTEOSCAN (5.9 MG DISODIUM ETIDRONATE/0.16 MG STANNOUS CHLORIDE) SKELETAL IMAGING AGENT
SPECIFICATION SHEET

Product and Package

The product (pertinent data provided in attached Package Insert) is a stable dry mix. It is packed in glass vials, five per kit. Each vial contains 5.9 mg disodium etidronate and 0.16 mg stannous chloride as active ingredients. As described in the Package Insert, it is to be labeled with additive-free technetium-99m in sterile, non-pyrogenic saline solution.

Licensing Requirements for Usage

Each hospital, other than one with a broad license, must have an approved amendment to its byproduct material license from the Atomic Energy Commission or the appropriate State licensing body. The following information must accompany new orders: the hospital's AEC or State license number, the amendment number for use of Osteoscan, sub-items added (byproduct material, chemical and/or physical form, radioactive possession limit), name of the official approving the license amendment and the date of the amendment's approval. A copy of the amendment to the hospital's byproduct material license is requested.

Purchase Data

Product Code No.	Product Packing	Kit Size	Cost Per Kit (5 vials)	Terms
70372	5 vials to a kit	Each kit measures 8" x 5" x 2"	$ 75.00	Net 30 days. F.O.B. plant Freight is prepaid.

Shipments

Orders will be shipped via First Class Air Mail. For ordering details, see "Ordering Information" below.

In order to facilitate inventory control, a "Convenient Shipment Plan" arrangement is available as a service which allows periodic regular shipment of Osteoscan (tailored to the quantity needs of the hospital). Fluctuations in needs are handled by supplemental fill-in orders or cut-back notices as requested by the hospital.

Ordering Information/Product Questions

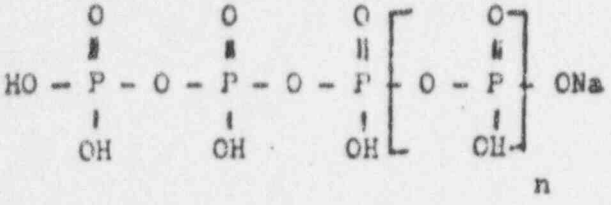
For ordering or product questions, the following guidelines are suggested:

- Regular Orders/Delivery Follow-Up or Invoicing/Service Questions
  Mail to: Procter & Gamble Distributing Co.
  Professional Services Division
  P. O. Box 1127, Kansas City, Missouri 64141
  Phone: Area Code 816-753-7224
  Prof. Serv. Div. Order Desk o
  Prof. Serv. Div. Supervisor
- Product Performance Questions
  Procter & Gamble Technical Services
  Phone: Area Code 513-977-8547
- Please always indicate Procter & Gamble Professional Services Division on orders.

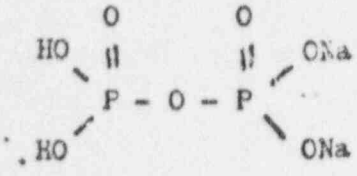
Product Shelf Life and Return Policy

There is a product expiration date noted on each kit and on each individual vial. Please rotate stock. Procter & Gamble will exchange any full kits of unused product which have exceeded the package expiration date or which have been damaged in shipment. Return over-age or damaged product to the following address:

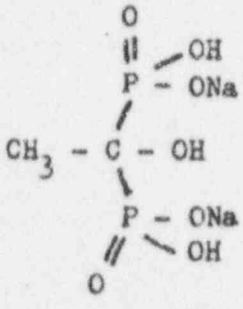
Procter & Gamble
Professional Services Division
Ivorydale Technical Center
Cincinnati, Ohio 45217



polyphosphate (mono-sodium polyphosphate)
hydrolizable, non-discrete chain length



pyrophosphate (di-sodium pyrophosphate)
hydrolizable, discrete chain length.



OSTEOSCAN

diphosphonate (disodium ethane - 1 - hydroxy - 1, 1 - diphosphonate)
non-hydrolizable, discrete chain length

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Diphosphonates as Bone Scanning Agents

October 5, 1973

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Subramanian, G.; Blair, R. J.; Kallfelz, E. A.; Thomas, F. D.; and McAfee, J. G.: 99mTc-MDP (Methylene Diphosphonate): A Superior Agent for Skeletal Imaging. J. Nucl. Med. 14, 640 (1973).

Subramanian, G.; McAfee, J. G.; Blair, R. J.; Mehter, A.; and Connor, T.: 99mTc-EHDP: A Potential Radiopharmaceutical for Skeletal Imaging. J. Nucl. Med. 13, 947-950 (1972).

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* Research which involved Osteoscan