



HAZLETON LABORATORIES AMERICA, INC.

3301 KINSMAN BLVD. • P.O. BOX 7545 • MADISON, WI 53707 • (608) 241-4471 • TLX 703956 HAZRAL MDS UD

April 18, 1985

Mr. Michael McCann
Materials Licensing Section
U. S. Nuclear Regulatory Commission
Region III
799 Roosevelt Road
Glen Ellyn, IL 60137

Re: Byproduct Material License No. 48-11805-02

Dear Mr. McCann:

Enclosed is the response to your requests for more information pertinent to amending our license to include human use and to the change in RSO. We would like to specify approval for licensing of materials in Groups I, II and III as defined in 10 CFR 35. Dr. Albert Alter who is licensed by the American Board of Radiology and is currently working at Jackson Clinics in Madison has agreed to participate in our studies involving human use of radiopharmaceuticals. Dr. Alter will take the place of Dr. Wilson who will no longer be involved with these studies.

Included in this response is a copy of the floor plan for our clinic as requested, an update list of members of the Radiation Safety Committee, and letters confirming support of Dr. Bosch as RSO from Dr. Roy Dagnall (Corporate Vice President and General Manager) and from Mr. Robert Daun, Director of the group that Dr. Bosch works in.

This information should satisfy the requests you made during our phone conversation February 27, 1985.

Sincerely,

Anne L. Bosch

Anne Bosch, Ph.D.
Radiation Safety Officer

AB:gbh
Enclosures

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REG3 LIC30
48-11805-02 PDR

Amendment to Test Radiopharmaceuticals in Human Subjects

Question No. 1, Radiopharmaceutical Storage and Preparation:

- 1a) All radiopharmaceuticals are separated from other incoming packages and promptly delivered to the RSO who will notify the Medical Director. The package will be stored in Room 315 (Attachment A & B) until such time as the study is to be initiated.

The package is inspected for proper identification and for evidence of breakage or leakage. The contents of the package are logged into a book along with date of receipt, nature of material, amount of activity, and the name of the supplier. Each time an aliquot is removed, the quantity and the date removed are recorded.

Prior to study initiation the radiopharmaceutical will be transported from Room 315 to the Clinical Research Facility where it will be held in either the Laboratory or the designated Blood Collection Room (Attachment C). On completion of the administration, the radiopharmaceutical will be returned to Room 315 for storage until it is either returned to the supplier or disposed of in accordance with NRC regulations.

All areas where the radiopharmaceutical is used will be properly posted as described in the amendment.

All biological specimens collected as a result of the study will be held in a locked and properly posted refrigerator until analyzed.

- 1b) No preparation of radiopharmaceuticals will be performed by Hazleton Laboratories America, Inc. (HLA). All materials received will have been prepared in accordance with the GMPs and will have a "Notice of Claimed Investigational Exemption for a New Drug" (IND) already accepted by FDA prior to their testing.

Exposure to personnel working in the area will be kept as low as reasonably achievable by storage of radiolabelled material in Room 315 where a refrigerator, hood and lead shields are available for use.

HLA will keep on file a record of the supplier's NRC license number prior to a study's approval.

Question No. 2, Equipment Description and Calibration Procedures:

The equipment and calibration procedures to be used are the same as have been described in the original license application with the following additions:

Tri-Carb Liquid Scintillation System

Manufacturer: Packard

Model: 4640

Calibration Frequency: Daily, as used. The 4640 is checked using the following standards:

| | <u>Radionuclide</u> | |
|--------------------|---------------------|------------------|
| | <u>Tritium</u> | <u>Carbon-14</u> |
| Chemical Form | Toluene | Toluene |
| Activity (dpm) | 267,600 | 102,300 |
| Assay Date | 11/4/83 | 1/19/71 |
| Packard Serial No. | 130 | 185 |

Auto-Gamma Counting System

Manufacturer: Packard

Model: 5780

Calibration Frequency: Daily, as used.

HPLC Radioactivity Monitor

Manufacturer: Berthold

Model: LB 504

Question No. 3, Radiopharmaceutical Testing:

Prior to administration each radiopharmaceutical will be tested to ensure its specific activity. These data will be maintained in the study records.

Information demonstrating the radionuclide purity of the compound will be provided by the supplier and verified by HLA using methods specified by the supplier or equivalent techniques.

Question No. 4, Designation of Physician.

Dr. Albert Alter who is a licensed radiologist currently working at Jackson Clinics in Madison has agreed to participate in our studies involving human use of radiopharmaceuticals. He is certified by the American Board of Radiologists and is Board Eligible in Medical Physics. A complete curriculum vitae is included as Attachment D.

Amendment to Replace L. Kneeland with A. Bosch
as Hazleton's Radiation Safety Officer (RSO)

In reply to the questions you had concerning our Amendment No. 2 (RSO), please find attached letters to the U.S.N.R.C. from Dr. Roy Dagnall and Robert Daun designating Dr. Bosch's primary responsibilities as Radiation Safety Officer. Dr. Bosch was employed by Hazleton to serve as Radiation Safety Officer and Staff Scientist in the Hazleton Metabolism Department. Her primary reporting lines are to Mr. Robert Fischbeck, Chairman of the Hazleton Radiation Safety Committee and Dr. Roy Dagnall, General Manager, as concerns her RSO duties. As regards to her staff scientist duties, her immediate supervisor is Dr. James Puhl, Manager, Metabolism. Dr. Puhl's supervisor is Mr. Robert J. Daun, Director, Research Chemistry. Mr. Daun reports directly to Dr. Dagnall who, in addition to being General Manager, is a Corporate Vice President of the parent Corporation, Hazleton Laboratories Corporation.

To address the question of Dr. Bosch's previous experience in managing a "Broad Scope" Radiation Safety Program, she was directly involved in setting up and managing a radiation safety program for Drs. S. J. Gatley and J. E. Holden in the Medical Physics Department at the University of Wisconsin. This involved:

1. Training technical personnel, graduate and undergraduate students in the potential hazards and proper use of the radioisotopes that they would be exposed to: 18-F, 100 mCi; 3-H, 20 mCi; 14-C, 5 mCi; 125-I, 4 mCi; and 123-I, 12 mCi.
2. Training students to do laboratory surveys including the following:
 - a) Surveying work areas with a GM counter for gamma emitting contaminants;
 - b) Surveying work areas by wipe test and liquid scintillation counting for beta emitting contaminants;
 - c) Cleaning up areas shown to be contaminated and re-surveying to be certain it was decontaminated.
3. Providing an accurate inventory of radiochemicals;
4. Establishing storage areas for radioactive materials that minimized radiation exposure to personnel;
5. Establishing areas for the proper collection of radioactive waste materials, and setting up times for its disposal;
6. Annual calibration of GM counters.

In addition, Dr. Bosch was also the supervisor for most laboratory activities and was responsible for continuing research activities while Dr. Gatley took a six month leave of absence. The radiation safety program for this laboratory did not involve as many users as the program at Hazleton but the amount and type of isotopes used provided a much greater potential health hazard.

Dr. Bosch has routinely worked with radioactive materials for over 9 years at the University of Wisconsin. She has used radionuclides for measuring metabolic rates, radioimmunoassays, in vivo radiolabelling of metabolites, tracers for following isolation and purification of cell components such as RNA and proteins, and for synthesis of radiotracers. In the Medical Physics Department she was involved in methodology development for remote synthesis of radiolabelled (18-F) glucose analogues for use in PET (positron emission tomography) studies in humans. As part of these varied experiences using isotopes she has become well acquainted with the instrumentation commonly used for measuring radioactivity (liquid scintillation counters, gamma counters, GM counters and Na-I detectors), and with general good laboratory practices for handling and disposing of radioactive materials as required by the University of Wisconsin Radiation Safety Department.

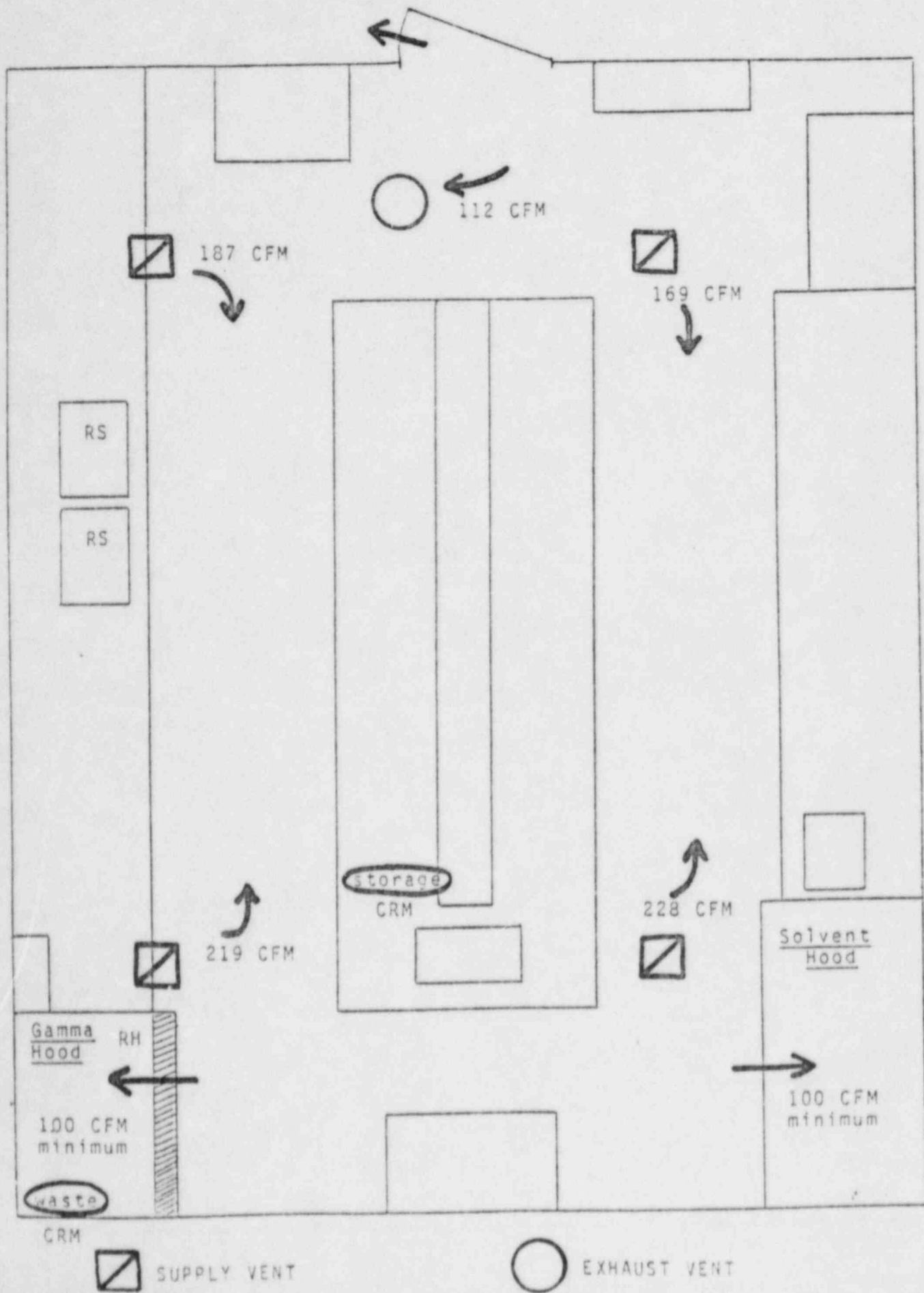
Dr. Paul DeLuca is a member of the University of Wisconsin's Radiation Safety Committee and was directly involved in the establishment of the radiation safety program for Dr. Gatley's laboratory. Dr. DeLuca is also a member of the Medical Physics Department where Dr. Bosch worked. Because of this previous contact with DeLuca in both a working situation and with regards to radiation safety, it has been convenient for Dr. Bosch to maintain contact with Dr. DeLuca. Dr. DeLuca has been an active consultant for HLA's radiation safety program and will continue to act as a consultant. He will continue to meet with Dr. Bosch and/or the radiation safety committee as often as is necessary.

In the month before Dr. Bosch actually began working for Hazleton she attended the January meeting of the Radiation Safety Committee. Following the meeting was a detailed discussion with Larry Kneeland about his specific duties, the amount and type of radioactive materials handled, time expenditures and the personnel that assisted him. She was also given a copy of the license and most of the correspondence with the NRC that had occurred since February 4, 1983. She and L. Kneeland met again on February 4, 1985 and discussed some of the particulars of the license. This discussion was followed by a tour of the facilities which included user areas, sample storage areas, waste storage areas, the incinerator, scintillation counters, shipping and receiving and where the radiation safety and inventory records were kept.

(0735G)

ATTACHMENT A

Room 315 (south)



Attachment B

Key: CRA = posted as "Caution, Radiation Area;" use of radionuclides is routine.

 CRM = posted as "Caution, Radioactive Material;" use of radionuclides is occasional.

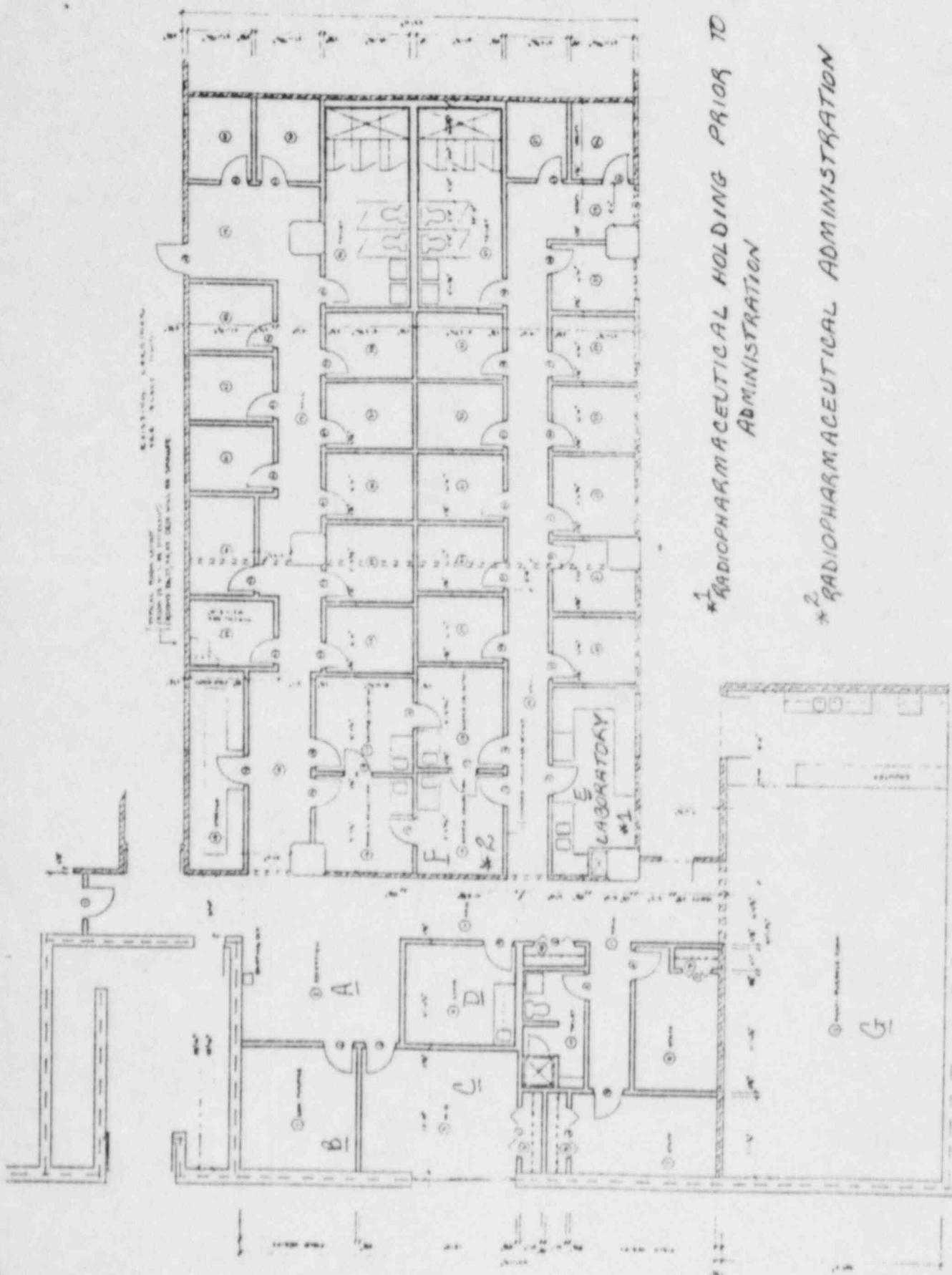
 RH = Radiation Hood - approved for the handling of volatile radioactive materials.

 RS = Radiation Sink - approved for the disposing of small quantities of radioactive materials.



HAZLETON

ATTACHMENT C



*¹ RADIOPHARMACEUTICAL HOLDING PRIOR TO ADMINISTRATION

*² RADIOPHARMACEUTICAL ADMINISTRATION

Clinical Research Facility

ATTACHMENT D

CURRICULUM VITAE

NAME: Albert Jerviss Alter, Jr., M.D., M.S.

PRESENT POSITION: Radiology Consultants of Madison, S.C.
Madison, Wisconsin
1983-present
(Employed while fulltime graduate student in Medical Physics)

BIRTHPLACE AND DATE: Durham, North Carolina, July 23, 1942

CITIZENSHIP: U.S.A.

MARITAL STATUS: Married

Wife: Karen Ruth
Son: Robert Atha

EDUCATION: Phillips Exeter Academy
Exeter, New Hampshire
1960

Yale University
Trumbull College
New Haven, Connecticut
B.S., Molecular Biology
1964

Case-Western Reserve University
School of Medicine
Cleveland, Ohio
M.D.
1969

University of Wisconsin
Madison, Wisconsin
M.S. Medical Physics
1984

PROFESSIONAL EXPERIENCE/TRAINING:

Medical School

Case-Western Reserve University
School of Medicine
Cleveland, Ohio

Thesis: Electrical conductivity of bile
salts and lecithin in aqueous
solution

M.D. granted 1969

Internship

University of New Mexico Medical Center
Albuquerque, New Mexico

Type: Rotating (Surgery-Medicine-Pediatrics)
1969-1970

Service

United State Public Health Service
Santa Fe Indian Hospital

Santa Fe, New Mexico

Duty: General Medical and Tuberculosis
Control Officer

1970-1972

Residency

Royal Victoria Hospital/McGill Program
Montreal, Quebec

Diagnostic Radiology

1972-1975

CONSULTING EXPERIENCE:

Radiation Measurements Incorporated
Middleton, Wisconsin

Chest Radiology Task Group

(BRH - Centers for Radiological Physics)

LICENSURES:

Diplomate National Board of Medical Examiners,
1969

New Mexico, 1972

Ohio, 1975

Wisconsin, 1976 Number 19772

CERTIFICATION:

Diagnostic Radiology (American Board of
Radiology, 1975)

Basic Life Support (American Heart Association,
1985)

Advanced Cardiac Life Support (American Heart
Association, 1985)

PROFESSIONAL PRACTICE:

1975:

Toledo Radiologic Associates
Toledo, Ohio

1974-83:

Associate Professor of Radiology
Center for Health Sciences
Department of Radiology, Medical School
University of Wisconsin - Madison
(1/8 time appointment)

Chief, Radiology Service
William S. Middleton Memorial Veterans Hospital
Madison, WI 53705
(7/8 time Appointment)

PROFESSIONAL ASSOCIATIONS:

Radiological Society of North America, Member
American College of Radiology, Member
Canadian Association of Radiologists, Member
Wisconsin Radiological Society, Member
American Association of physicists in Medicine

RESEARCH EXPERIENCE AND TRAINING:

Post-Graduate Work: Yale University
Department of Molecular Biology
Area of Research: Bacteriophage Genetics
under Dr. Irwin Rubinstein
June 1964-January 1965

Yale University School of Medicine
Department of Ophthalmology
Area of Research: Catecholamine Levels in the
Rabbit Iris under Dr. Marvin Sears
January 1965-September 1965

University of Wisconsin
Department of Medical Physics
Currently in Ph.D program

PRESENTATION OF PAPERS

1. "Assessment of retroperitoneal hemorrhage by CT", Wisconsin Urological Society 51st Annual Meeting, April 29, 1978, Madison, Wisconsin
2. "CT of retroperitoneum postnephrectomy", 64th Annual Meeting Radiological Society of North America, November 30, 1978, Chicago, Illinois
3. "Computerized tomography of the retroperitoneum following nephrectomy", 59th Annual Meeting of Wisconsin Urological Society, April 3, 1981, Milwaukee, Wisconsin
4. "Transthoracic needle biopsy - comparison of aspiration cytology and tissue-core histology", 68th Annual Meeting of Radiological Society of North America, November 29, 1982, Chicago, Illinois
5. "Radiologic assessment of the undescended testis", Alter AJ and Uehling DT, Wisconsin Urological Society, April 30, 1983, Milwaukee, Wisconsin
6. "Effect of experience and training on detection of pulmonary nodules", Perception and detection in Medical Imaging, Park City, Utah, Oct. 6-7, 1983

INVITED SUBMISSIONS TO PROCEEDINGS OF SYMPOSIA

1. "Portable Chest Radiography", Optimization of Chest Radiography Proceedings of Symposium: 202-206 (HHS Publication (FDA) 80-8124)
2. "CT - Clinical Perspective" in Medical Physics of CT and Ultrasound: Tissue Imaging and Characterization. Gary Fullerton and James Zagzebski eds. For American Association of Physicists in Medicine, American Institute of Physics, New York, 1980, pp. 94-124.

INVITED REVIEW ARTICLES

1. "Percutaneous Nephropylostomy" Seminars in Ultrasound 2:61-70, March 1981

EDITOR OF PROCEEDINGS

1. Optimization of Chest Radiography, HHS Publication (FDA) 80-8124

CONFERENCE ORGANIZATION AND PLANNING

| | |
|------------------------------|--|
| April 28 - 30, 1977 | Computed Tomography, Ultrasound and Nuclear Medicine |
| September, 1976 - June, 1978 | Radiology Department Research, 1 hour monthly |
| July, 1977 - July 1978 | Computerized Tomography (Dane County) 2 hours monthly |
| October 17 - 19, 1979 | Advances in Genitourinary Radiology Conference, Oconomowoc, WI |
| April 30 - May 2, 1979 | Optimization of Chest Radiography, Madison, WI |

HOSPITAL SERVICE:

Patient Care and Procedures Committee
University of Wisconsin Hospitals
July 1, 1976 to June 30, 1979

Clinical Executive Board (ex officio)
William S. Middleton Memorial Veterans Hospital
July 1, 1979 to December 31, 1983

Radiation Safety Committee (ex officio)
William S. Middleton Memorial Veterans Hospital
July 1, 1979 to December 31, 1983

Radioactive Drug Research Committee
William S. Middleton Memorial Veterans Hospital
January 1, 1980 to December 31, 1983

UNIVERSITY SERVICE:

Faculty Senate
University of Wisconsin - Madison
May 1977 to June 1979

STATE SERVICE:

Radiology and Pathology Laboratory Services
Subcommittee
Wisconsin Health Policy Council
1979

Chairman, Committee on Radiation Safety
and Legislation
Wisconsin Radiological Society
1985

NATIONAL SERVICE:

Consultant to Chest Radiography Task Group of
Centers for Radiological Physics

CORPORATE SERVICE:

Board of Directors, Radiation Measurement
Incorporated
Middleton, Wisconsin

STAFF APPOINTMENTS AND CLINICAL RESPONSIBILITIES

Assistant Professor of Radiology
Department of Radiology, Medical School
University of Wisconsin - Madison
Full-time from January 1, 1976 to June 30, 1979

Chief, Section of Genitourinary Radiology
University of Wisconsin Hospitals
From July 1, 1976 to September 30, 1979

Chief, Section of Whole Body Computed
Tomography
University of Wisconsin Hospitals
From April 1, 1977 to June 30, 1979

Chief, Radiology Service
William S. Middleton Memorial Veterans Hospital
Madison, WI
From July 1, 1979 to December 31, 1983

Active Medical Staff
Methodist Hospital
Madison, WI
From January 2, 1984 to present

ARTICLES IN REFEREED JOURNALS

1. Sears M, Mizuno K, Cintron C, Alter A, and Sherk T: Changes in outflow facility and content of norepinephrine in iris and ciliary processes of albino rabbits after cervical ganglionectomy. Investigative Ophthalmology 5:312-318, 1966.
2. Mueller CF, Morehead R, Alter AJ, Michener W: Pneumatosis intestinalis in collagen disorders. AJR 115:300-305, 1972.
3. Alter AJ and Farrer PA: The perihepatic halo in liver scintiangiographic perfusion studies: a sign of ascites. J Nucl Med 15:396-398, 1974.
4. Alter AJ, Crummy AB, Benson RC: Nephrostomy tube replacement using a steerable catheter. J Urology 119:332, 1978.
5. Alter AJ, Peterson DT, and Plautz AC: Nonradiopaque calculus demonstrated by CT. J Urology 122:699-700, October 1979.
6. Alter AJ, Uehling DT, Zwiebel WJ: CT of retroperitoneum postnephrectomy. Radiology 133:663-668, December 1979.
7. Yandow D, Wojtowycz M, Alter A, and Crummy AB: Detection of retroperitoneal hemorrhage after translumbar aortography by computerized tomography. Angiology 31:655-659, October 1980.
8. Alter AJ, Zimmerman S, and Kirachaiwanich C: Computerized tomographic assessment of retroperitoneal hemorrhage after percutaneous renal biopsy. Arch Internal Med 140:1323-1326, October 1980.
9. Lange TA and Alter AJ: Evaluation of complex acetabular fractures by computed tomography. J Comput Assist Tomogr 4:849-852, December 1980.
10. Gentry LR, Gould HR, Alter AJ, Wegenke JD and Atwell DT: Hemorrhagic angiomyolipoma: Demonstrated by computed tomography, J Comput Assist Tomogr 5(6):861-865, December 1981.
11. Keene JS, Golez TH, Lilleas F, Alter AJ, and Sackett JF: Diagnosis of vertebral fractures - a comparison of conventional radiography, conventional tomography and computed axial tomography. J Bone Joint Surg 64-A(4):586-595, April 1982.
12. Gould HR, Benjamin S, Alter AJ, Crummy AB, and Atwell DT: Retroperitoneal varices simulating masses. Gastrointest Radiol 7:335-339, November 1982.
13. Alter AJ, Kargas GA, Kargas SA, Cameron JR, and McDermott JC: The influence of ambient and viewbox light upon visual detection of low-contrast targets in a radiograph. Invest Radiol 17(4):402-406, July/August 1982.
14. Rao BK, Lange TA, Hafez GR, and Alter AJ: Extension of recurrent rectal carcinoma through sciatic foramen: diagnosis by computed tomography. Comput Radiol 6:193-197, October 1982.

ARTICLES IN REFEREED JOURNALS (Continued)

15. Uehling DT, Alter AJ. Current diagnostic modalities for undescended tests. Wisc Med J 1984;83(3):20-22.
16. Wegenke JD, Malek GH, Alter A, Olson J. Acute lobular nephronia. Urology (submitted for publication).

Radiation Safety Committee
Hazleton Laboratories America, Inc.
Chemical and BioMedical Sciences Division
3301 Kinsman Boulevard
Madison, Wisconsin 53704

April 16, 1985

| <u>Name</u> | <u>RSC Position</u> |
|-----------------------------|---|
| Robert D. Fischbeck | RSC Chairman Representative of Management |
| Robert J. Daun | Vice Chairman Representative of Management |
| Anne L. Bosch, Ph.D. | Radiation Safety Officer |
| Terry A. Aitken | Assistant Radiation Safety Officer |
| R. James Puhl, Ph.D. | Representative of Chemical Sciences Division |
| Karen MacKenzie, Ph.D. | Representative of Life Sciences Division (Laboratory Animals) |
| R. Michael Bodden | Representative of Life Sciences Division (Domestic Livestock) |
| Susan Glad Anderson | Representative of the Quality Assurance Unit |
| Rosalyn Horsley, RN | Representative of Nursing Staff |
| Paul DeLuca, Jr., Ph.D. | Health Physicist Medical Physics Department University of Wisconsin-Madison |
| Albert J. Alter, M.D., M.S. | Physician, Radiology Consultants of Madison, S.C. Madison, Wisconsin |