LICENSE AMENDMENT

Byproduct Material License
No. 48-18805-02
Issued February 22, 1984
Expires February 28, 1989

Expansion of Authorized Uses to Include Human
Use of Byproduct Material

for

United States Nuclear Regulatory Commission
Materials Licensing Section
Region III Office
799 Roosevelt Road
Glen Ellyn, Illinois 60137

by

Hazleton Laboratories America, Inc.
Chemical & BioMedical Sciences Division
3301 Kinsman Boulevard
Madison, Wisconsin 53704

December 11, 1984

FOREWARD

The Medical Department at Hazleton Laboratories America, Inc. (HLA) in Madison, Wisconsin has 18 years of experience in clinical trials. With the addition of a 5,800 sq ft Human Clinical Research Facility in January 1984, HLA-Wisconsin has made a commitment to offer our clients a comprehensive package of clinical research services. This amendment will make possible an expansion of our capabilities to include bioavailability and pharmacokinetic studies using IND-approved radiopharmaceuticals.

In conjunction with a Food and Drug Administration (FDA) regulated Institutional Review Board (IRB), the HLA Radiation Safety Committee (RSC) will review all proposed uses to assure compliance with the protection of human subjects as required by FDA (21 CFR 312A) and NRC (10 CFR 35) regulations. The Radiation Safety Officer (RSO) will work closely with the physicians, nursing staff, and auxillary staff to assure that all conditions of this license are properly met.

Larry M. Kneeland

Larry M. Kneeland
Radiation Safety Officer
December 10, 1984

Items 1, 2, 3, 4, 5, 6, and 7

No changes or additions.

Amendment to Item 8

Items 8A, 8B, 8C, and 8D: No changes.

Item 8E: Add the following.

For possession and use of a radioactive drug administered to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry; but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial).

The radioactive drug for the uses cited above (as defined in 21 CFR 310.3(n) and 21 CFR 361.1) must be generally recognized as safe and effective for administration to human subjects. A "Notice of Claimed Investigational Exemption for a New Drug" (IND) as defined in 21 CFR 312, Subpart A, must have been accepted by the Food and Drug Administration prior to initiation of a project using this drug.

Items 9, 10, 11, and 12

No changes or additions.

Amendment to Item 13

Addition.

A.11. Clinical Research Facility (CRF).

The CRF is located on the first floor of the south building. It is physically isolated from the remainder of the building and has its own outside entrance. The facility, which occupies 5,800 sq ft, has the following features (letters refer to locations on the floor plan):

A. A reception area near the entrance.

B. A general purpose office for client's use while a study is in progress.

C. Offices for the Director, Physicians, and other staff.

D. An examination room for performing physical examinations on volunteer subjects.

E. A clinical laboratory for processing biological samples.

F. Three sample collection rooms and a special procedures room (electrocardiography, gastric intubation, etc.).

G. A multi-purpose room with dining room/kitchen facilities.

H. Twenty-five rooms to individually house volunteer subjects; each room equipped with a bed, desk, chair, and storage.

I. Two bathrooms for use by volunteer subjects, plus a bathroom in the office area for staff and visitors.

When a project involving a radioactive drug is in progress, dose administration and sample collection (e.g. blood drawing) will take place in the Sample Collection room designated No. 14. Collected radioactive biological samples will be stored in a refrigerator in the laboratory (E). The sink in the laboratory is appropriate for disposal of small amounts of radioactive waste, and a solid radiowaste container will be provided. All areas and storage/waste containers shall be clearly marked with proper warning signs.

All standard operating procedures given in the license application apply to the CRF. Any changes in use must be approved by the HLA Radiation Safety Committee.

The Medical Department's full time professional and technical staff includes:

- The Director, an MD with more than 17 years of experience in clinical research
- A Ph.D. in exercise physiology
- Three on-call MD's
- One Registered Nurse trained in the use of radiolabeled compounds
- Two part-time Registered Nurses
- Ten on-call Registered Nurses
- One Medical Technician

Hazleton's Medical Department has experience in performing:

- Phase I, II, III, and IV of drug testing.
- Bioavailability/bioequivalency studies.
- Assessment of product efficacy.
- Substantiation of advertising claims.
- Photosensitivity (SPF)/phototoxicity.
- IV fluid tolerance studies.
- Protein efficiency and other nutritional and/or dietary studies in humans.
- Exercise physiology studies.

Item 14

No changes or additions.

Addenda to Item 15

Add:

Appendix H

Department Operating Procedure: Use of Radiolabeled Test Materials in Human Subjects.

Appendix I:

Radiation Safety Committee Guidelines: Approving a Radioactive Drug as Safe and Effective for Administration to Human Research Subjects.

Addendum to Item 15

Appendix H

Department Operating Procedure:

Use of Radiolabeled Test Materials in Human Subjects

DEPARTMENT OPERATING PROCEDURE

DATE:
REPLACES: Original

PROCEDURE TITLE: Use of Radiolabeled Test Materials in Human Subjects

AREA OF APPLICABILITY: Hazleton Laboratories America, Inc.
Medical Department

PROCEDURE:

Receipt and Storage of Test Materials

All test materials will be received by the Radiation Safety Officer of Hazleton Laboratories America, Inc. (HLA). Whenever possible, extra test material will be supplied by the client. This extra material will be assayed by the Radiation Safety Officer to confirm its claimed activity.

The test material will then be delivered to the Medical Department and stored in the refrigerator or drug storage cabinet F in the laboratory.

All work and storage areas must have radioactive warning signs in conspicuous locations. A sink with a non-porous surface must be present in each room to permit washing of contaminated equipment and to allow personnel to clean up before leaving the room.

Administration of Radiolabeled Test Materials

All personnel working on studies involving radiolabeled test materials will have completed an appropriate training course (i.e., will have read and been tested on the contents of Section B of HLA's Radiation Safety Regulations).

All radiolabeled test materials will be administered by Dr. Dennis or a designated staff member.

All test materials will be administered in Sample Collection Room 2.

All personnel handling either these materials or biological samples generated during the study will wear full length lab coats when deemed necessary by the Radiation Safety Committee.

Collection of Biological Samples

All blood samples will be collected in Sample Collection Room 2.

Care must be taken to minimize spillage of blood. The work area should be covered with disposable plastic-backed absorbent paper.

Each tube of blood collected will be wiped and labeled with a radioactive warning label. All urine and feces samples collected during these studies will also be labeled with radioactive warning labels.

Cleaning of Rooms

All work and storage areas will be thoroughly cleaned after each use and at the completion of the study.

Wipe tests (OP-GENB 43) will be performed on designated areas and equipment (see Attachment 1) before initiation and at the completion of the study. The Radiation Safety Officer will evaluate the tests and certify the area as decontaminated.

Disposal

All refuse will be placed in a labeled yellow waste receptacle located in Sample Collection Room 2 and will be disposed of by the Radiation Safety Officer.

Shipping

All biological samples generated during these studies will be packed in an appropriate manner and shipped to the client by the Radiation Safety Officer.

Monitoring of Subjects Prior to Release

One day prior to the conclusion of each study, approximately 1 mL of urine and 1 gram of feces will be obtained from each subject to determine any remaining radioactive residues prior to their release.

APPROVED BY: _____ DATE _____
Susana Dennis, M.D.
Director, Medical Department

REVIEWED BY: _____ DATE _____
Susan Glad Anderson
Manager, Quality Assurance Unit

Addendum to Item 15

Appendix I

Radiation Safety Committee Guidelines:

Approval of Radioactive Drugs for
Administration to Human Research Subjects

The Radiation Safety Committee must approve any radioactive drug administered to human research subjects. Each of the following requirements shall be considered. It is the responsibility of the RSC to assure that each is met:

1. Radiation Dose To Subjects. To assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the criteria of 21 CFR 361.1(b)(3), the RSC shall require that:

   a. The investigator provide absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies.

   b. The amount of radioactive material to be administered be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

      (1) Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year exceed the following:

      Whole body, active blood-forming organs, eye lens, and gonads

      - Single dose - 3 rems
      - Annual and total dose commitment - 5 rems

      Other organs

      - Single dose - 5 rems
      - Annual and total dose commitment - 15 rems

      (2) For a research subject under 18 years of age at his last birthday, the radiation dose shall not exceed 10% of the above levels.

      (3) Women of childbearing potential are excluded as research subjects except when required by study protocol. When their participation on a study is required, a pregnancy test will be performed prior to study initiation.

      (4) All radioactive material included in the drug either as essential material or as a significant contaminant or impurity shall be included when determining the total radiation doses and dose commitments. Radiation doses from x-ray procedures that are part of the research study (i.e., would not have occurred but for the study) shall also be included. The possibility of follow-up studies shall be considered for inclusion in the dose calculations.

(5) Numerical definitions of dose shall be based on an absorbed fraction method of radiation absorbed dose calculation, such as the system set forth by the Medical Internal Radiation dose Committee of the Society of Nuclear Medicine, or the system set forth by the International Commission on Radiological Protection.

c. The investigator provide for an acceptable method of radioassay of the radioactive drug prior to its use to assure that the dose calculations actually reflect the administered dose.

d. The radioactive drug chosen for the study has that combination of half-life, types of radiation, radiation energy, metabolism, chemical properties, etc. which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information.

e. The investigator utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.

2. Pharmacological Dosage. The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings. If the same active ingredients (exclusive of the radionuclide) are to be administered simultaneously, the total amount of active ingredients including the radionuclide shall be known not to exceed the dose limitations applicable to the separate administration of the active ingredients excluding the radionuclide. The RSC shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

3. Qualifications of Investigator. Each investigator shall be qualified by training and experience to conduct the proposed research studies.

4. Human Research Subjects. Each investigator shall select appropriate human subjects and shall obtain the review and approval of the Institutional Review Board (IRB). The investigator shall obtain the consent of the subjects or their legal representatives. The research subjects shall be at least 18 years of age (exceptions are permitted only in special situations) and legally competent.

5. Quality of Radioactive Drug. The radioactive drug used in the research study shall meet appropriate chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality, and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted. Radioactive materials for parenteral use must be prepared in sterile and pyrogen-free form.

6. Notice of Claimed Investigational Exemption for a New Drug. (IND) An IND must have been filed with the Food and Drug Administration (FDA) and have been accepted prior to conducting a research study. The IND shall contain sufficient data and information on the drug to determine the safety and effectiveness of the research study design.

7. Research Protocol. No matter how small the amount of radioactivity, no study involving administration of a radioactive drug to research subjects shall be permitted unless the RSC concludes, in its judgement, that scientific knowledge and benefit is likely to result from that study. The radiation dose shall be both sufficient and no greater than necessary to obtain valid measurement. The projected number of subjects shall be sufficient but no greater than necessary for the purpose of the study. The number of subjects shall also reflect the fact that the study is intended to obtain basic research information. The study may not be aimed at immediate therapeutic, diagnostic, or similar purposes nor to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial).

8. Adverse Reactions and Misadministrations. The investigator shall immediately report to the Radiation Safety Officer and the RSC all adverse effects associated with the use of the radioactive drug in the research study. All adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported to the FDA [21 CFR 361.1(d)(8)]. Likewise, the investigator shall immediately report to the Radiation Safety Officer and the RSC all misadministrations of the radioactive drug in the research study. Misadministration means the administration of: 1) the radioactive drug to the wrong human subject; 2) the radioactive drug by a route other than that dictated by the protocol; or 3) a dose differing from the prescribed dose by more than 50%. Records of all misadministrations shall be maintained for NRC inspection (10 CFR 35.44).

9. Approval by Institutional Review Board (IRB). The investigator shall obtain the review and approval of the IRB in addition to the RSC prior to the initiation of a research study. The IRB reviews the research protocol, in conjunction with RSC approves the initiation of the study, and continues to review any biomedical research involving human subjects in accordance with FDA regulations. The purpose of IRB review is to assure that:

   - Risks to subjects are minimized.
   - Risks to subjects are reasonable in relation to anticipated benefits.
   - Selection of subjects is equitable.
   - Informed consent is sought and documented for each subject.
   - Data collected is monitored to ensure the safety of subjects.
   - Privacy of subjects and confidentiality of data are adequately protected.

Amendment to Items 16 and 17

Add:

New members of the Radiation Safety Committee:

Michael A. Wilson, MD
Nuclear Medicine Section, Department of Radiology
University of Wisconsin Hospital and Clinics

Rosalyn Horsley, RN
Medical Department
Hazleton Laboratories America, Inc.

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

December 1, 1984

Name	RSC Position
Robert D. Fischbeck	RSC Chairman Representative of Management
Larry M. Kneeland	Radiation Safety Officer
Terry A. Aitken	Assistant Radiation Safety Officer
R. James Puhl, PhD	Representative of Chemical Sciences Division
Karen MacKenzie, PhD	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., PhD	Health Physicist Medical Physics Department University of Wisconsin-Madison
Michael A. Wilson, MD	Physician, Nuclear Medicine Department of Radiology University of Wisconsin Hospital and Clinics

September 1983

CURRICULUM VITAE

Name: Michael A. Wilson

Address: (Home) 822 Ottawa Trail
Madison, Wisconsin 53711
Tel. No.: (608) 238-5280

(Office) Section of Nuclear Medicine, Rm. D4/332
Department of Radiology
University of Wisconsin Hospital & Clinics
600 Highland Avenue
Madison, Wisconsin 53792
Tel. No.: (608) 263-8343

Birthplace and Date: Christchurch, New Zealand (9/9/43)

Citizenship: United States, Naturalized

Social Security No.: 569-33-3702

DEGREES, POSTGRADUATE EDUCATION:

1968	M.B., Ch.B.	Otago Medical School, Dunedin, New Zealand
1973	M.R.A.C.P.	Member, Royal Australasian College of Physicians (equivalent A.B.I.M.)
1975-1976	Postdoctoral Fellow (Metabolism)	Stanford University Medical Center, Stanford, California
1976	A.B.N.M.	American Board of Nuclear Medicine
1976-1977	Postdoctoral Fellow (Computers in Medicine)	Mount Sinai School of Medicine, New York, New York
1978	F.R.A.C.P.	Fellow of the Royal Australasian College of Medicine

HONORS:

1974	Roche Travel Award (Royal Australasian College of Physicians)
1975-1976	Overseas Fellowship Award (New Zealand Medical Research Council)

RESEARCH SUPPORT:

1980-1981 The study of skeletal pathophysiology using positron emission tomography. The development of Fluorine-18 bone-seeking radiopharmaceuticals, $10,000, funded by the University of Wisconsin Graduate School.

1981-1982 The development of Fluorine-18 radiopharmaceuticals, $12,000 (in conjunction with S.J. Gatley, Ph.D., University of Wisconsin Graduate School).

PROFESSIONAL AND ACADEMIC APPOINTMENTS:

1969-1971	3 years	Intern and Resident in Internal Medicine, Auckland Hospital, Auckland, New Zealand
1972-1974	3 years	Resident in Nuclear Medicine, Auckland Hospital, Auckland, New Zealand
1976-1977	1 year	Assistant, Department of Medicine, Mount Sinai School of Medicine, New York, New York
1977-1978	1 year	Coordinator, National Library of Medicine Training Program in "Computers in Medicine", $250,000 annually, NIH grant, Institute of Computer Science, Mount Sinai School of Medicine, New York, New York
1977-1978	1 year	Instructor, Department of Medicine, Mount Sinai School of Medicine, New York, New York
1978-present		Assistant Professor, Department of Radiology, Division of Biological Sciences, University of Wisconsin, Madison, Wisconsin

PUBLICATIONS:

1. Miles LEM, Raynal DM, Wilson MA: Blind man living in normal society has circadian rhythms of 24.9 hours. Science 198:421-422, 1977.

2. Wilson MA, Miles LEM: Radioimmunoassay of insulin. In Handbook on RIA (Abrahams G, ed), Marcel Dekker, pp 275-297 (1977). *Updated for new edition, 1982.*

3. Wilson MA: Multiple chemodectomas. J Nucl Med 10:904, 1979.

4. Wilson MA, Calhoun FW, Goldsmith SJ: The role of radionuclide imaging in metastatic disease. Mt Sinai J Med (NY) 47:251-254, 1980.

5. Wilson MA: Computers in medicine: Viewpoint. NZ Med J 92:17-18, 1980.

6. Wilson MA, Calhoun FW: Renal anomalies incidental to radionuclide bone scanning. Urol Radiol 2:25-28, 1980.

7. Wilson MA, Pastakia B: Biliary excretion of Technetium-99m glucoheptonate in poor renal function. Clin Nucl Med 5:448-449, 1980.

8. Wilson MA: Prolonged partial epilepsy: A case report. Radiology 137:550, 1980.

9. Wilson MA, Pastakia B, Polcyn RE, Gentry L: Perfusion lung scans: Letter to editor. J Nucl Med 21:1204-1205, 1980.

10. Shore RM, Wilson MA, Rao BA: Sacrococcygeal trauma. Clin Nucl Med 6:124-125, 1980.

11. Wilson MA, Pollock ML: Gastric visualization and image quality in radionuclide bone scanning. J Nucl Med 22:518, 1981.

12. Wilson MA, Kao Y, Miles L: Direct comparison of a radioimmunoassay and an immunoradiometric technique in the measurement of Human Growth Hormone. Nucl Med Communications 2:68-74, 1981.

13. Wilson MA: The effect of age on the quality of bone scans using Technetium-99m pyrophosphate. Radiology 139:703-705, 1981.

14. Wilson MA, Calhoun FW: The distribution of skeletal metastases in breast and pulmonary cancer: Concise communication. J Nucl Med 22:594-597, 1981.

15. Wilson MA, Gaines JS: Correction of respiratory motion in hepatic scintigraphy. Clin Nucl Med 6:372-374, 1981.

PUBLICATIONS (continued).

16. Wilson MA: Is radionuclide brain scanning an adequate evaluation for cerebral metastases in asymptomatic lung cancer patients? Wisc Med J 80:26-28, 1981.

17. Wilson MA, Kahn D: Scintigraphic assessment of heterotopic cardiac transplants. AJR 137:689-693, 1981.

18. Wilson MA, Calhoun FW, Gaines JS, Goldsmith SJ: Patterns of diffusely increased skeletal radiopharmaceutical uptake. Australian Radiology 25:177-180, 1981.

19. Hellman RS, Wilson MA: Discordance of sclerosing skeletal secondaries between sequential scintigraphy and radiographs. Clin Nucl Med 7:97-99, 1982.

20. Wilson MA: Improvement in information obtained with a new x-ray requisition. Radiology 146:677-679, 1983.

21. Wilson MA, Hellman RS: The detection of gastrointestinal bleeding using nuclear medicine techniques: A local experience and review. Wisc Med J 83:15-19, 1984.

22. Wilson MA, Liss LF, Studey CL. Uptake of Technetium-99m MDP in hepatic metastases. Noninvasive Medical Imaging 1:253-257, 1984.

23. Wilson MA, Liss LF: The pattern of hepatic metastases. Submitted to Clinical Nuclear Medicine 1984.

CURRICULUM VITAE: ROSALYNN A. HORSLEY

CURRENT POSITION

Title: Staff Nurse
Department: Medical
Hazleton Laboratories America, Inc.
Chemical and BioMedical Sciences Division
Madison, Wisconsin

EDUCATION

Nursing Diploma (3-Year) - Madison General Hospital School of Nursing, Madison, Wisconsin, 1966.

Attended University of Wisconsin - Platteville, Platteville, Wisconsin, 1963-1964.

LICENSE/CERTIFICATION

State of Wisconsin; Department of Regulation and Licensing; Board of Nursing - R.N., No. 46325 (Expiration Date January 31, 1986).

PROFESSIONAL EXPERIENCE

1983 - Present: Staff Nurse, Medical

As Staff Nurse, Ms. Horsley is responsible for monitoring clinical research study volunteers. She collects and processes samples including blood, urine, and feces; and monitors EKG's, blood pressure, pulse, temperature, and weight. Ms. Horsley performs physical examinations and records medical histories on the research subjects. She also schedules appointments, prepares case report forms and enters data into them, and administers medication.

1981 - 1983: Registered Nurse, Methodist Health Center, Madison, Wisconsin

Ms. Horsley worked with geriatric patients in a permanent-care facility. She performed complete medical histories and physical examinations, administered medications (oral, intramuscular, subcutaneous, rectal, intravenous, and by heparin flushes). Various treatments she performed include: changing dressings, caring for wounds and colostomies, and performing tube feedings. Ms. Horsley also performed venipunctures for laboratory work, physical assessments on permanent residents, and patient education. She assisted in preparing patient care plans.

1966 - 1981: Registered Nurse, East Madison Clinic, Madison, Wisconsin

Ms. Horsley was responsible for performing medical history and physical examinations, administering medication, scheduling appointments, and educating patients.

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