G31

Bristol-Myers Squibb Company
Pharmaceutical Group Technical Operations
One Squibb Drive P.O. Box 191 New Brunswick, NJ 08903-0191
908 519-2000

MS16
Q-6

August 19, 1998

Dr. John Kinneman
U.S. Nuclear Regulatory Commission
Region I
475 Allendale Road
King of Prussia, PA 19406-1415

DOCKET NO.: 030-05222
CONTROL NO.: 124288
LICENSE NO.: 29-00139-02

Dear Dr. Kinneman:

Enclosed please find two (2) copies of your request for additional information dated July 20, 1998 regarding our license renewal application.

If you have any additional questions, please contact me at 732-519-2451.

Sincerely,

Daniel K. Balkunow

Daniel K. Balkunow
Radiation Safety Officer

DKB:bl

Enclosures (2)

DKBWRCRESP.WPD

cc: T. Primm
S. Voigt
C. Woodard
RSC*

*Circulation only

~~OFFICIAL RECORD COPY~~ ML 10

124288
AUG 20 1998

E/25

RESPONSE TO NRC REQUEST FOR ADDITIONAL INFORMATION - LICENSE #29-00139-02

Question #1:

The following questions are in regard to the present addresses where licensed material will be used or stored.

a. Since the submission of your application for renewal of License No. 29-00139-02, three amendments have been issued. These are amendments No. 91, 92 and 93. Amendment No. 91 removed the ConvaTec site in Skillman, New Jersey from the license. Amendment No. 92 added the Pennington, New Jersey site to the license. Amendment No. 93 added the Hamilton, New Jersey site. To be consistent with the current authorized locations of use, please revise and resubmit Item #2 in your application to reflect the deletion of the ConvaTec site and the addition of the two new locations.

b. Please revise and resubmit Item #5 and Item #6 in your application to reflect the deletion of the ConvaTec site in Skillman, New Jersey, and add both the Pennington and Hamilton, New Jersey sites. For these sites, please specify the byproduct materials to be used, the chemical and physical form of the materials, the maximum possession limits, and the requested authorized uses.

Response:

The below information represents BMS activities as of August 5, 1998, in accordance with Amendment #94 of License #29-00139-02. This information supersedes the information submitted in the February 18, 1997 license renewal application:

Item #2: Name and Mailing Address (unchanged)

E. R. Squibb & Sons
One Squibb Drive
P.O. Box 191
New Brunswick, NJ 08903

Item #3: Addresses where licensed material will be used or possessed (modified):

A. *E. R. Squibb & Sons**
One Squibb Drive
P. O. Box 191
New Brunswick, NJ 08903-0191

B. *E. R. Squibb & Sons**
Route 206 & Provinceline Road
Lawrenceville, NJ
P. O. Box 4000
Princeton, NJ 08543-4000

C. *BMS Clinical Research Center*
Three Hamilton Health Place
Hamilton, NJ 08690

Bristol-Myers Squibb Company

Pharmaceutical Group

ATTACHMENT 3

RADIATION SAFETY PROCEDURE

BMS-PG 457

Department: Health Physics		Subject: Mission, Scope and Major Activities of the Radiation Safety Committee			
Procedure No: GRP-31	New Procedure [ ]	Reviewed - No Changes [ ]	Revised Procedure [X]	Replaces Procedure #GRP-31 of 5/13/96	Originator: S. Voigt
Reviewed By: W. L. McGarry	Approved by: Dr. J. L. Monior H. M. Abdou		Date: / /		Effective Date: 5/15/97

I. PURPOSE

The purpose of the procedure is to outline the Mission, Scope and Major Activities of the Central New Jersey Bristol-Myers Squibb Radiation Safety Committee (RSC).

II. RADIATION SAFETY COMMITTEE MISSION AND SCOPE

Mission:

To protect the radiological health and safety of employees, the public and the environment.

Scope:

The Committee's major responsibilities include the regulation of the procurement, safe use and disposal of all sources of ionizing radiation at the sites specified in licenses issued by the State of New Jersey and the Nuclear Regulatory Commission.

III. MAJOR ACTIVITIES

The major activities of the RSC include, but are not necessarily limited to the following items:

1. Establish and periodically update policy and programs that will maintain radiation doses to all employees and the general public to levels As Low As Reasonably Achievable (ALARA).
2. Approve the procurement and use of all sources of ionizing radiation materials and the users of such materials.
3. Ensure that the disposal of radioactive waste meets Federal, State, and local requirements.
4. Provide guidance, support and authorization to the Radiation Safety Officer (RSO) in the planning and daily administration of the radiation safety program.
5. Conduct periodic reviews of the radiation safety program, initiate corrective action based on the findings, verify program implementation and training/retraining of personnel involved with the use of ionizing radiation.
6. Review deviations from established procedures and unplanned events to prevent recurrences.
7. Meet quarterly, at a minimum.
8. Periodically review the member representation of the Committee,and formally approve new members. At a minimum, representatives will be the Radiation Safety Officer, a Management representative, and an Administrative member.
9. Publish the minutes of each meeting, with copies sent to the current membership roster.
10. The periodic review of this radiation safety procedure will be recorded in the Central New Jersey RSC minutes.

Bristol-Myers Squibb Company

Pharmaceutical Group

RADIATION SAFETY PROCEDURE

BMS-PG 437

Department: Health Physics		Subject: Mission, Scope and Major Activities of the Radiation Safety Committee			
Procedure No: GRP-31	New Procedure [ ]	Reviewed - No Changes [ ]	Revised Procedure [X]	Replaces Procedure #GRP-31 of 5/13/96	Originator: S. Voigt
Reviewed By: W. L. McGarry	Approved by: Dr. J. L. Moniot 5/13/97 H. M. Abdou 5/16/97		Date: / /		Effective Date: / /

HISTORY PAGE

1. New procedure.
2. Eliminated "II. Scope"; revised "Radiation Safety Committee Mission and Scope" by removing "listed in Section II above" in the Scope section; added #10 under "Major Activities", describing the recording of the committee review process. Revised 3/28/96.
3. Titles changed to replace R. Endries with W. L. McGarry, and L. T. DiFazio with H. M. Abdou. Revised 4/7/97.

Executive Memorandum

Bristol-Myers Squibb Company

Pharmaceutical Group

ATTACHMENT 4

To: Distribution

Date: March 24, 1994

From: L. T. DiFazio

C.C.:

Subject: **RADIATION SAFETY COMMITTEE**

The Radiation Safety Committee, presently chaired by Mrs. Susan Voigt, is responsible for establishing Company policy and auditing all Company activities as they relate to the safe use of radiation and radioactive materials at our New Jersey NRC licensed facilities.

I have charged this Committee to uphold the highest standards of safety at Bristol-Myers Squibb. The principles governing their deliberations and decisions are: 1) maintaining employee health and safety; 2) preserving sound environmental controls; and 3) assuring compliance with all governmental regulations.

The Radiation Safety Committee has the authority to approve all uses of radioactive materials and disapprove their use when a potential unsafe condition exists or could exist.

The Health Physics Office, headed by Mr. Dan Balkunow, will carry out the policies of the Radiation Safety Committee and handle all administrative and technical aspects of radiation safety.

Current Radiation Safety Committee members are listed below. I trust you will give the members of this Committee and the Health Physics Office your full cooperation.

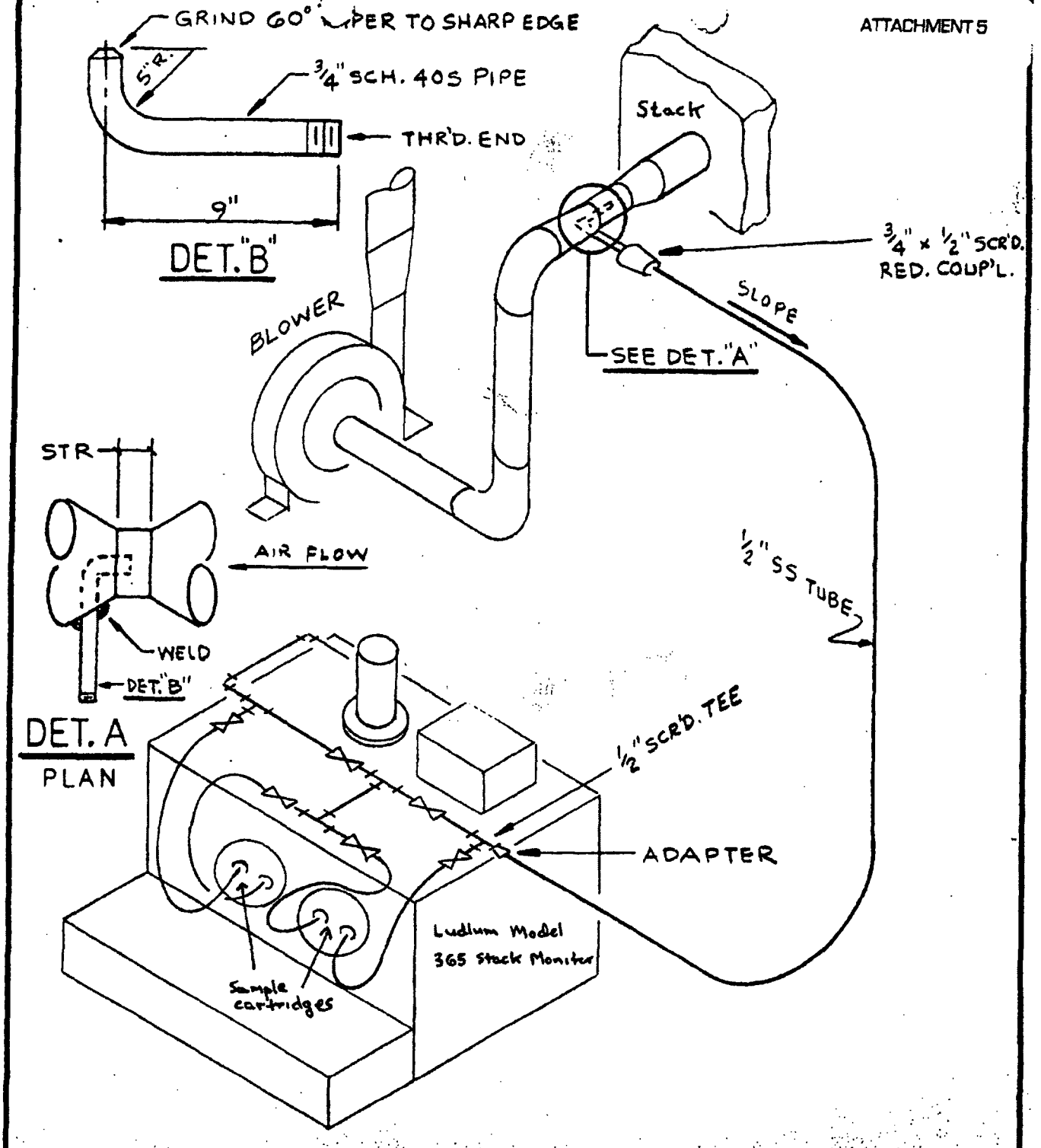
L. T. DiFazio
Chairman, Pharmaceutical Group
Environmental Health and
Safety Committee
President, Technical Operations

Radiation Safety Committee:

D. Balkunow	J. Rinehart
H. Bartlett	H. Strauss
R. Endries	C. Tuday
J. Frankowski	S. Voigt
G. Nicholl	F. Yost

2112

ATTACHMENT 5



DR.: R.G.	E. R. SQUIBB & SONS, INC. NEW BRUNSWICK, N. J.		
DATE: 9-27-88			C. A. R.
SCALE: NTS			P. N.: 124-196
CH.	MODIFICATION TO STACK SAMPLING SYS.		D. M.
APPD.			DRAWING NUMBER
APPD.	NO. / REVISIONS / DATE / BY / APPD		
APPD.			SK 9907
APPD.			

R.S. KNAPP CO.

OFFICIAL RECORD COPY ML 10

124288

July 20, 1998

Docket No. 030-05222 License No. 29-00139-02
Control No. 124288

Thomas M. Primm
Vice President, Facilities, Engineering and Administration
E. R. Squibb & Sons
One Squibb Drive
P. O. Box 191
New Brunswick, NJ 08903-0191

Dear Mr. Primm:

This is in reference to your application dated February 18, 1997 requesting to renew Nuclear Regulatory Commission License No. 29-00139-02. In order to continue our review, we need the following additional information:

1. The following questions are in regard to the present addresses where licensed material will be used or stored.

   a. Since the submission of your application for renewal of License No. 29-00139-02, three amendments have been issued. These are amendments No. 91, 92, and 93. Amendment No. 91 removed the ConvaTec site in Skillman, New Jersey from the license. Amendment No. 92 added the Pennington, New Jersey site to the license. Amendment No. 93 added the Hamilton, New Jersey site. To be consistent with the current authorized locations of use, please revise and resubmit Item #2 in your application to reflect the deletion of the ConvaTec site and the addition of the two new locations.

   b. Please revise and resubmit Item #5 and Item #6 in your application to reflect the deletion of the ConvaTec site in Skillman, New Jersey, and add both the Pennington and Hamilton New Jersey sites. For these sites, please specify the byproduct materials to be used, the chemical and physical form of the materials, the maximum possession limits, and the requested authorized uses.

   c. We have received your letter dated June 19, 1998 in regard to the decommissioning and removal of the Princeton House facility and the other changes requested in the license, and will address these issues in a separate action.

ML10

2. The following questions are in regard to the area radiation monitoring system.

   a. Item 9 in your application discusses a "built in" area radiation monitoring system. In addition, this section states: "Each filter bank is equipped with before and after continuous tubes used to check charcoal filter efficiencies." "They are changed on a routine basis." Your application also states: "There is no definite filter change criterion." Please describe the methods you use to determine when the filters in each filter bank are changed.

   b. From various sections of the text of your submission, and your postulated emergency scenarios, it appears that you depend on area monitors, the analysis of sample tubes, the response of personnel, and fire activated systems in emergency situations.

      1. Provide a schematic diagram of all effluent pathways at each site which includes the identification of the source of the activity, the maximum typical activity at each source, the location of the sampling points in each ventilation pathway, and each contributing and final ventilation flowrates for each pathway.

      2. Please describe how your present monitoring program emulates a real-time effluent monitoring system in the timely mitigation of releases from a scenario which does not include a fire in the restricted area.

      3. Include an estimate of the time required to quantify a release, and describe the degree of correspondence you have determined between your 'built in" area radiation monitors and the present method for sampling releases.

      4. Provide the average annual Chi/Q values used for each release site, and the distance to the maximum exposed individual for each site.

3. The second paragraph in the section "Emergency Procedures" states: "The ConvaTec and Clinical Laboratory facilities have site specific procedures for emergency response." Since the ConvaTech facility was removed from the license, is the Clinical Laboratory facility the only remaining facility to have site specific emergency procedures?

4. Page 22, paragraph 6 states: "Gloves are worn while handling radioactive materials and removed before handling non-radioactive materials." Are gloves the only protective apparel used?

5. Page 22, paragraphs 12 and 13 discuss surveys and contaminated areas Paragraph 12 states: "Documentation of such surveys will not be required." "All contaminated areas are cleaned and rechecked." If these surveys are not documented, how are all contaminated areas identified so that all contaminated areas are cleaned and rechecked as stated in your application?

6. Your application does not have specific details for thyroid bioassays. Describe your bioassay program, including the type of bioassay (thyroid counts, urine counts, whole body counts, etc), the criteria and the frequency for performing bioassays, and the type of action taken when positive results are obtained. It is recommended that bioassay procedures be considered for personnel using millicurie quantities of tritiated organic compounds, iodine-131, and iodine-125 in noncontained forms.

7. Your application did not specify the instrument used in your bioassay program for determining activity in the thyroid. Please specify your instrumentation and calibration procedures, including the type of phantom you will use.

8. Specify your criteria for performing internal monitoring which may be required for certain uses of material under your license. Submit a description of procedures, including the methods and instrumentation to be used for sampling and analysis, calibration of equipment, the lower limit of detection for the method and instrumentation, and the action levels for each radionuclide.

9. Your application states: "The RSC is informed of regulatory requirements and operating procedures through routine meetings and correspondence with the Health Physics Department. At what frequency does the Radiation Safety Committee (RSC) meet?

10. Page 24, in your application, item 8, in the section entitled "Safety Evaluations of Proposed Uses and Users" requires that information on the User Form includes, among other things, whether the material will be used in human or animal studies. Please clarify this statement. License No. 29-00139-02 does not authorize use of licensed material in humans or animals. Furthermore, Research and Development, as defined in 10 CFR 30.4, states, in part, "Research and development as used in this part and parts 31 through 35 does not include the internal or external administration of byproduct material, or the radiation therefrom, to human beings."

11. Paragraph 6 on page 25 of your application discusses the use of respiratory protection equipment. Please confirm that your program conforms to 10 CFR 20, Subpart H "Respiratory Protection and Controls to Restrict Internal Exposures in Restricted Areas".

12. Provide a copy of senior management's written statement of delegation of authority to the Radiation Safety Officer. This statement should include the requisite authority to communicate with and direct your personnel regarding NRC regulations and license provisions and to enforce these requirements including the ability to terminate any unsafe operation involving the use of licensed material.

13. Confirm that management will conduct a periodic oversight of the radiation protection program, including interaction with the RSC and RSO .

14. Confirm that the Radiation Safety Committee will conduct safety evaluations of proposed users and uses.

15. Confirm that the Radiation Safety Committee will develop procedures and criteria for training and testing each category of worker.

16. Confirm that the Radiation Safety Committee will establish methods for maintaining records of safety evaluations of proposed users and uses of licensed materials.

17. Please specify the minimum representation which will be required at each Radiation Safety Committee meeting, and the quorum requirement for voting. Confirm that your list of duties and responsibilities of the Radiation Safety Officer will address the following: a) to monitor and maintain absolute and other special filter systems, b) review and determine what radiation protection consulting services may be required, c) ensure the proper receipt, delivery, opening and shipment of radioactive material, d) ensure proper radioactive material storage, e) leak testing program, f) instrument calibration program, g) isotope inventory, h) the RSO can immediately terminate unsafe activities, I) decontamination and recovery operations, and j) the records as required by 10 CFR 30.51.

18. Confirm that the RSO will meet with/ report to management and the RSC.

19. Provide a description of the duties and responsibilities of the radiation safety staff. This should include an assessment regarding staffing levels and qualifications of this support staff. The assessment should be sufficient to demonstrate that the technical staff are adequate to implement, support, and oversee your proposed radiation protection program. If current staffing is not what you consider adequate, a projected timetable when full staffing will be achieve should be included. A projection of future needs would also be useful.

20. Describe your program for training and refresher training of all persons who handle licensed material or who frequent areas where licensed material is used. This training program must include a review of emergency procedures and response criteria and include sections that are tailored to various types of radiation and ancillary workers such as authorized users, laboratory supervisors and technicians; incinerator operators, waste compactor operators, and purchasing department personnel receiving licensed material; housekeeping, nursing, security, and other ancillary personnel; and the radiation safety office staff. Confirm that you will maintain records of initial and refresher training, that include a list of topic(s) covered, the amount of time spent and the date, the instructor(s) and student(s) names. The model training program in Appendix I of Regulatory Guide 10.5, Second Proposed Revision 2 (DG-0005) may be helpful in formulating your response.

21. Provide a description of the engineered provisions for abnormal operations in which the process systems are intended to provide for the maintenance of primary confinement, protection and control conventional hazards and control of effluents in the event of abnormal occurrences

22. Provide a description of the intended performance of the alarm systems and equipment provided to prevent releases of hazardous material. Provide a description of the alarm systems intended to alert operators to releases or to otherwise mitigate the consequences of releases. Consider the range of detection of the monitors, the type of alarms, the presence of annunciators, alarm setpoints. Are engineered safety features present to preclude large releases of radioactivity in the event of an accident? Can these engineered safety features be activated both automatically and manually?

23. Provide a schematic drawing showing the location of the sample cartridge and the stack alarm detector. Paragraph #5 on page 1-8 states: "The radioactivity in the sampler is constantly measured by the stack alarm detector which will sound an alarm in the Health Physics operations area should the integrated activity representing the 24 hour effluent limit for I-131as specified in Appendix B, Table II, Column I of 10 CFR 20 be exceeded." Provide specific details about the stack alarm detector, and specify whether the alarm setpoint(s) interact with the HVAC system.

24. Condition I on page 2-2 states: "Remote monitoring detectors located in manufacturing locations would inform Health Physics operational personnel of areas with radiation levels of 50 mR/hr." Describe how these remote monitors interface with the HVAC system.

25. Item A.3. on page 2-1 describes a scenario where some of the free iodine has a potential to escape to the environment through the cave hallway area and outside door. Provide an estimate of the fraction of the release that might be released from this unmonitored pathway.

We will continue our review upon receipt of this information. Please reply in duplicate to my attention at the Region I Office and refer to Mail Control No. 124288. If you have any questions regarding this deficiency letter, please call James M. Bondick at (610) 337-6951.

In order to continue prompt review of your application, we request that you submit your response to this letter within 30 calendar days from the date of this letter.

Sincerely,

Original signed by Elizabeth Ullrich

for

John D. Kinneman, Chief
Nuclear Materials Safety Branch 2
Division of Nuclear Materials Safety

Enclosures:
10 CFR Parts 19, 20, and 30

cc:
Daniel K. Balkunow, Radiation Safety Officer

DOCUMENT NAME: G:\DNMS\DOCWORK\DEFLTR\L2900139.02 19989091

To receive a copy of this document, indicate in the box: "C" = Copy w/o attach/encl "E" = Copy w/ attach/encl "N" = No copy

OFFICE	DNMS/RI	N	DNMS/RI					
NAME	JBondick JB		JKinneman					
DATE	07/20/98		07/21/98		07/ /98		07/ /98	

OFFICIAL RECORD COPY

Bristol-Myers Squibb Company
Pharmaceutical Group Technical Operations
One Squibb Drive P.O. Box 191 New Brunswick, NJ 08903-0191
908 519-2000

97

April 24, 1997

Mr. Keith Brown
US Nuclear Regulatory Commission
Region I
475 Allendale Road
King of Prussia, PA 19406-1415

RE: LICENSE #29-00139-02
MAIL CONTROL #124288

Dear Mr. Brown:

- Currently all NRC correspondence regarding E. R. Squibb & Sons' radioactive material license is being sent to the attention of:

  Dr. Joseph P. Nirschl
  Vice President, US Manufacturing
  One Squibb Drive
  P.O. Box 191
  New Brunswick, NJ 08903-0191

  Due to recent organizational changes, all future correspondence regarding license #29-00139-02 should be sent to the attention of:

  Mr. Thomas M. Primm
  Vice President, Facilities, Engineering and Administration
  One Squibb Drive
  P.O. Box 191
  New Brunswick, NJ 08903-0191

- Currently the text of "Item 7: Individuals Responsible for Radiation Safety Program and Their Training and Experience" of E. R. Squibb & Sons' license application reads as follows:

  "Senior management...for licensed activities. This is the responsibility of the Vice President, US Manufacturing;..."

  This text should be revised to read as follows:

  "Senior management...for licensed activities. This is the responsibility of the Vice President, Facilities, Engineering and Administration;...".

124288

OFFICIAL RECORD COPY ML 10

MAY - 1 1997

The title change should also be reflected in the following section of E. R. Squibb & Sons' license application:

- Page 6, Item #7 A.

Should you have any questions or require additional information please call. I can be reached at 908-519-2451.

Sincerely,

Daniel K. Balkunow
Radiation Safety Officer

DKB:bl

DKB\RSC97.WPD

cc: J. Nirschl
T. Primm
H.P. Staff
RSC

Bristol-Myers Squibb Company
Pharmaceutical Group Technical Operations
One Squibb Drive P.O. Box 191 New Brunswick, NJ 08903-0191
908 519-2000

030-05222

April 8, 1997

Mr. Duncan White
U.S. Nuclear Regulatory Commission
Region I
475 Allendale Road
King of Prussia, PA 19406-1415

RE: LICENSE #29-00139-02 -
BRISTOL-MYERS SQUIBB RADIATION SAFETY COMMITTEE CHANGES

Dear Mr. White:

This letter is to inform you of recent changes that have occurred in the Bristol-Myers Squibb Radiation Safety Committee. The changes are:

- New Members

  Gary R. Matsueda, Ph.D. and Brian J. Gavin, Ph.D. have become members of the Radiation Safety Committee. Included for your records are copies of their résumés.

Sincerely,

Daniel K. Balkunow
Radiation Safety Officer

DKB:bl

Enclosures (2)

cc: B. Gavin*
G. Matsueda*
RSC*

DCB\NRC97.WPD

*Cover IOM only

~~OFFICIAL RECORD COPY~~ ML 10

124288
APR 11 1997

CURRICULUM VITAE

Brian J. Gavin

Date of Birth

Current Address

Telephone (609) 252-6388 (Bus.)

Education

(b)(6)

Ph.D., Human Genetics
Yale University
New Haven, CT

M. Phil., Human Genetics
Yale University
New Haven, CT

B.S., Biology
Muhlenberg College
Allentown, PA

Professional Experience

1997 - present

Head, Genetic Modeling
Bristol-Myers Squibb
Pharmaceutical Research Institute
Department of Cardiovascular Drug Discovery
Princeton, NJ 08543

1996 - 1997

Senior Research Investigator I
Bristol-Myers Squibb
Pharmaceutical Research Institute
Department of Cardiovascular Drug Discovery
Princeton, NJ 08543
Development of transgenic models of cardiac arrthymia

1993 - 1996

Research Investigator II
Bristol-Myers Squibb
Pharmaceutical Research Institute
Department of Oncology Drug Discovery
Princeton, NJ 08543
Development of novel transgenic mouse models of carcinogenesis

1991 - 1993	Assistant Fellow (Senior Scientist) Sandoz Research Institute Department of Receptor Mechanisms Sandoz Pharmaceuticals Corporation East Hanover, NJ 07936 *Construction and characterization of high diversity random peptide libraries expressed on the surface of bacteriophage*
1989 - 1991	Postdoctoral Research Fellow Laboratory of Dr. Andrew McMahon Roche Institute of Molecular Biology Department of Cell and Developmental Biology Nutley, NJ 07110 *Functional analysis of the Wnt-1/int-1 gene family in mouse mammary gland and fetal development.*
1984 - 1989	Thesis Research Dr. David C. Ward Yale University *Transcriptional control of the mouse parvovirus, MVM.*
1983 - 1984	Laboratory Rotations Drs. Bernard Forget and Daniel DiMaio Yale University
1980 - 1983	Laboratory Technician Dr. Debra J. Wolgemuth Columbia University *Molecular analysis of mouse gametogenesis and early development.*

Teaching Experience

Summer 1987	Co-instructor, "The Impact of Genetics on Today's Society", Albertus Magnus College, New Haven, CT
Spring 1986	Assistant Discussion Leader, "Medical Genetics" Yale University School of Medicine
1985	Teaching Assistant, Graduate Student Microcomputer, Department of Human Genetics, Yale University

Publications

1. Wolgemuth, D.J. and B.J. Gavin "Ultrastructural and Biochemical Characterization of Gene Expression in Follicular Oocytes in Neonatal and Prepubertal Rats." **In:** Development and Function of the Reproductive Organs, pp. 289-298. Byskov, A.E. and H. Peters, eds. Exerpta Medica, Amsterdam (1981).

2. Wolgemuth, D.J., Gizang-Ginsberg, E., Engelmeyer, E., Gavin, B.J. and Ponzetto, C. "Separation of Mouse Testis Cells on a Celsep Apparatus and Their Usefulness as a Source of High Molecular Weight DNA or RNA." Gamete Res., **12:** 1-10 (1985).

3. Kasher, M.S., Kumar, G., Pitluk, Z., Gavin, B.J. and Ward, D.C. "Identification and Purification of Transcription Factor Proteins Using Defined DNA Probes." **In:** Current Communications in Molecular Biology; DNA Probes - Applications in Genetic and Infectious Disease and Cancer, pp. 101-105. Lerman, L.S., ed. Cold Spring Harbor Laboratory, NY (1986).

4. Ahn, J.K., Gavin, B.J., Kumar, G. and Ward, D.C. "Transcriptional Analysis of Minute Virus of Mice P_4 Promoter Mutants." J. Virol. **63:** 5425-5439 (1989).

5. Gavin, B.J. and Ward, D.C. "Positive and Negative Regulation of the Minute Virus of Mice P_{38} Promoter." J. Virol. **64:** 2057-2063 (1990).

6. Gavin, B.J., McMahon, J.A. and McMahon, A.P. "Expression of Multiple Novel *Wnt-1/int-1*-related genes during Fetal and Adult Mouse Development." Genes & Dev. **4:** 2319-2332 (1990).

7. Christian, J.L., Gavin, B.J., McMahon, A.P. and Moon, R.T. "Isolation of cDNAs Partially Encoding Four *Xenopus Wnt-1/int-1* Related Proteins and Characterization of Their Transient Expression during Embryonic Development." Dev. Biol. **143:** 230-234 (1991).

8. Gavin, B.J. and McMahon, A.P. "Differential Regulation of the *Wnt-1/int-1* Gene Family During Pregnancy and Lactation Suggests a Role in Normal Mammary Gland Growth." Mol. Cell. Biol. **12:** 2418-2423 (1992).

9. McMahon, A.P., Gavin, B.J., Parr, B., Bradley, A. and McMahon, J. "The *Wnt*-family of Cell Signaling Molecules in Post-implantation Development of the Mouse." **In:** CIBA Foundation Symposia 165, pp. 199-218. Wiley and Sons, Chichester (1992).

10. Gavin, B.J. and McMahon, A.P. "Cloning of Developmentally Regulated Gene Families using Degenerate PCR." Methods in Enzymology **225**: 653-663 (1993).

11. Zimmerman, L., Lendahl, U., Cunningham, M., McKay, R., Parr, B., Gavin, B., Mann, J., Vassileva, G., and McMahon, A. "Independent Regulatory Elements in the Nestin Gene Direct Transgene Expression to Neural Stem Cells or Muscle Precursors." Neuron, **12**: 11-24 (1994).

12. Wong, G.T., Gavin, B.J., and McMahon, A.P. "Differential Transformation of Mammary Epithelial Cells by *Wnt* Genes." Mol. Cell. Biol. **14**: 6278-6286 (1994).

13. Gavin, B.J., Gao, J., Andahazy, M.L., Dhamija, S., Seizinger, B.R. and Kley, N. "Targeted Inactivation of the Mouse von Hippel-Lindau Disease Gene results in Mid-Gestational Embryonic Lethality". Submitted for Publication.

Patents

1. Gavin, B.J., Gao, J., Kley, N. and Seizinger, B.R. "Mice Deficient in the von Hippel-Lindau Gene". Application Submitted (1996).

CURRICULUM VITAE

Name Gary R. Matsueda

Address

Date of Birth

Place of Birth

Education

(b)(6)

B.S. Chemistry, University of California, Berkeley
Ph.D. Biochemisty, University of Hawaii, Manoa

Employment

UNIVERSITY OF COLORADO SCHOOL OF MEDICINE, Denver
1971-73 National Institutes of Health Postdoctoral Fellow
1973-76 Instructor, Department of Biochemistry,

HARVARD MEDICAL SCHOOL, Boston, Massachusetts
1976-77 Research Fellow in Medicine,
1977-80 Instructor in Pathology
1980-86 Assistant Professor of Pathology
1986-89 Associate Professor of Pathology

MASSACHUSETTS GENERAL HOSPITAL, Boston
1976-78 Research Fellow in Medicine
1978-88 Assistant in Biochemistry
1989 Associate in Biochemistry

PRINCETON UNIVERSITY, Princeton, New Jersey
1989-94 Visiting Biologist, Department of Biology

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE, Princeton, New Jersey
1989-96 Director/Sr. Res. Fellow, Macromolecular Structure
1996- Sr. Res. Fellow, Cardiovascular Drug Discovery

Memberships

American Chemical Society
American Association for the Advancement of Science
American Society for Biochemistry and Molecular Biology

Major Research Interests

Fibrinolysis and Thrombosis
Chemical synthesis of peptides
Immunochemistry

Publications

ORIGINAL REPORTS

1. Benson A, Tomoda K, Chang J, Matsueda G, Lode ET, Coon MJ, Yasunobu KT. Evolutionary and phylogenetic relationships of rubredoxin-containing microbes. *Biochem Biophys Res Commun* 1971;42:640-646.

2. Tanaka M, Haniu M, Matsueda G, Yasunobu KT, Himes RH, Akagi JM, Barnes EM, Devanathan T. The primary structure of the *Clostridium tartarivorum* ferredoxin, a heat-stable ferredoxin. *J Biol Chem* 1971;246:3953-3960.

3. Tanaka M, Haniu M, Matsueda G, Yasunobu KT, Mayhew S, Massey V. Amino- and carboxyl-terminal amino acid sequences of the *Peptostreptococcus elsdenii* and *Clostridium pasteurianum* flavodoxins. *Biochemistry* 1971;10:3041-3046.

4. Wingard M, Matsueda G, Wolfe RS. Myxobacter AL-1 protease II: Specific peptide bond cleavage on the amino side of lysine. *J Bacteriol* 1972;112:940-949.

5. Cann JR, Stewart JM, Matsueda GR. A circular dichroism study of the secondary structure of bradykinin. *Biochemistry* 1973;12:3780-3788.

6. Stewart JM, Freer RJ, Rezende L, Pena C, Matsueda GR. A pharmacological study of the angiotensin receptor and tachyphylaxis in smooth muscle. *Gen Pharmacol* 1976;7:177-183.

7. Puig MM, Gascon P, Craviso GL, Bjur RA, Matsueda G, Stewart JM, Musacchio JM. The effect of enkephalin and enkephalin analogs on the guinea-pig ileum and rat brain opiate receptor. *Arch Int Pharmacodyn Ther* 1977;226:69-80.

8. Ehrlich PH Matsueda GR, Margolies MN, Haber E. Preparation of an active Fd fragment by cyanogen bromide cleavage of an IgG heavy chain from a homogeneous rabbit antibody. *Immunochemistry* 1978;15:937-940.

9. Matsueda GR, Margolies MN. Increased efficiency in solid-phase Edman degradation of synthetic peptidyl-resins using an oxymethylphenylacetamidomethyl-linkage. *FEBS Lett* 1979;106:89-92.

10. Ehrlich PH, Matsueda GR, Haber E, Margolies MN. Isolation and characterization of an active variable domain from a homogeneous rabbit antibody light chain. *Biochemistry* 1979;18:4411-4418.

11. Matsueda GR, Haber E. The use of an internal reference amino acid for the evaluation of reactions in solid-phase peptide synthesis. *Anal Biochem* 1980;104:215-227.

12. Ehrlich PH, Matsueda GR, Margolies MN, Husain SS, Haber E. Isolation of an active heavy-chain variable domain from a homogeneous rabbit antibody by cathepsin B digestion of the aminoethylated heavy chain. *Biochemistry* 1980;19:4091-4096.

13. Matsueda GR, Haber E, Margolies MN. Quantitative solid-phase Edman degradation for the evaluation of extended solid-phase peptide synthesis. *Biochemistry* 1981;20:2471-2480.

14. Matsueda GR, Stewart JM. A p-methylbenzhydrylamine resin for improved solid-phase synthesis of peptide amides. *Peptides* 1981;2:45-50.

15. Matsueda R, Kimura T, Kaiser ET, Matsueda GR. 3-Nitro-2- pyridinesulfenyl group for protection and activation of the thiol function of cysteine. *Chem Lett* 1981;737-740.

16. Gaehde SA, Matsueda GR. Synthesis of N-tert.-butoxycarbonyl-(α-phenyl)aminomethylphenoxyacetic acid for use as a handle in solid-phase synthesis of peptide α-carboxamides. *Int J Pept Protein Res* 1981;18:451-458.

17. Katus HA, Hurrell JG, Matsueda GR, Ehrlich P, Zurawski VR Jr, Khaw BA, Haber E. Increased specificity in human cardiac-myosin radioimmunoassay utilizing two monoclonal antibodies in a double sandwich assay. *Mol Immunol* 1982;19:451-455.

18. Ridge RJ, Matsueda GR, Haber E, Matsueda R. Sulfur protection with the 3-nitro-2-pyridine sulfenyl group in solid-phase peptide synthesis. *Int J Pept Protein Res* 1982;19:490-498.

19. Matsueda GR. Deprotection of Nin-formyl tryptophan using 1,2- ethanedithiol in liquid hydrogen fluoride. Deformylation upon HF treatment of Merrifield peptidyl-resins. *Intl J Pept Protein Res* 1982;20:26-34.

20. Pacella BL Jr, Hui KY, Haber E, Matsueda GR. Induction of fibrin-specific antibodies by immunization with synthetic peptides that correspond to amino termini of thrombin cleavage sites. *Mol Immunol* 1983;20:521-527.

21. Young JD, Costello CE, Van Langenhove A, Haber E, Matsueda GR. Synthesis of a cyclic fibrin-like peptide and its analysis by fast atom bombardment mass spectrometry. *Int J Pept Protein Res* 1983;22:374-380.

22. Nussberger J, Matsueda GR, Re R, Haber E. Selectivity of angiotensin II antisera. *J Immunol Meth* 1983;56:85-96.

23. Hui KY, Haber E, Matsueda GR. Monoclonal antibodies to a synthetic fibrin-like peptide bind to human fibrin but not fibrinogen. *Science* 1983;222:1129-1132.

24. Nussberger J, Re R, Matsueda GR, Haber E. A simplified radioimmunoassay for physiologically active angiotensin peptides [(1-8) octa- and (2-8) heptapeptides]. *Horm Metab Res* 1984;16:606-610.

25. Nussberger J, Mudgett-Hunter M, Matsueda G, Haber E. A monoclonal antibody specific for the carboxy-terminus of angiotensin II. *Hybridoma* 1984;3:373-376.

26. Steiman DM, Ridge RJ, Matsueda GR. Synthesis of side chain-protected amino acid phenylthiohydantoins and their use in quantitative solid-phase Edman degradation. *Anal Biochem* 1985;145:91-95.

27. Nussberger J, Matsueda G, Re RN, Haber E. Recognition of peptide orientation: Studies with angiotensin II in the guinea-pig. *Mol Immunol* 1985;22:619-621.

28. Bode C, Matsueda GR, Hui KY, Haber E. Antibody-directed urokinase: A specific fibrinolytic agent. *Science* 1985;229:765-767.

29. Allen PM, Matsueda GR, Haber E, Unanue ER. Specificity of the T cell receptor: Two different determinants are generated by the same peptide and the I-Ak molecule. *J Immunol* 1985;135:368-373.

30. Hui KY, Haber E, Matsueda GR. Immunodetection of human fibrin using monoclonal antibody-64C5 in an extracorporeal chicken model. *Thromb Haemost* 1985;54:524-527.

31. Babbitt BP, Allen PM, Matsueda G, Haber E, Unanue ER. Binding of immunogenic peptides to Ia histocompatibility molecules. *Nature* 1985;317:359-361.

32. Bernatowicz MS, Matsueda GR. The N-hydroxysuccinimide ester of Boc-[S-(3-nitro-2-pyridinesulfenyl)]-cysteine: A heterobifunctional cross-linking agent. *Biochem Biophys Res Commun* 1985;132:1046-1050.

33. Bloch KD, Scott JA, Zisfein JB, Fallon JT, Margolies MN, Seidman CE, Matsueda GR, Homcy CJ, Graham RM, Seidman JG. Biosynthesis and secretion of proatrial natriuretic factor by cultured rat cardiocytes. *Science* 1985;230:1168-1171.

34. Fluckiger JP, Waeber B, Matsueda G, Delaloye B, Nussberger J, Brunner HR. Effect of atriopeptin III on hematocrit and volemia of nephrectomized rats. *Am J Physiol* 1986;251:H880-883.

35. Babbitt BP, Matsueda G, Haber E, Unanue ER, Allen PM. Antigenic competition at the level of peptide-Ia binding. *Proc Natl Acad Sci USA* 1986;83:4509-4513.

36. Bernatowicz MS, Matsueda R, Matsueda GR. Preparation of Boc-[S-(3-nitro-2-pyridinesulfenyl)]-cysteine and its use for unsymmetrical disulfide bond formation. *Int J Pept Protein Res* 1986;28:107-112.

37. Hui KY, Haber E, Matsueda GR. Monoclonal antibodies of predetermined specificity for fibrin: A rational approach to monoclonal antibody production. *Hybridoma* 1986;5:215-222.

38. Matsueda GR, Margolies MN. Structural basis for the species selectivity of a fibrin-specific monoclonal antibody. *Biochemistry* 1986;25:1451-1455.

39. Bernatowicz MS, Matsueda GR. Preparation of peptide-protein immunogens using N-succinimidyl bromoacetate as a heterobifunctional crosslinking reagent. *Anal Biochem* 1986;155:95-102.

40. Evin G, Carlson WD, Handschumacher M, Novotny J, Matsueda GR, Haber E, Bouhnik J, Galen FX, Menard J, Corvol P. Study of the antigenic determinants of human renin. *Hypertension* 1986;8:II72-77.

41. Zisfein JB, Matsueda GR, Fallon JT, Bloch KD, Seidman CE, Seidman JG, Homcy CJ, Graham RM. Atrial natriuretic factor: Assessment of its structure in atria

and regulation of its biosynthesis with volume depletion. *J Mol Cell Cardiol* 1986;18:917-929.

42. Waeber B, Matsueda GR, Aubert JF, Nussberger J, Brunner HR. The hemodynamic response of conscious normotensive rats to atriopeptin III: Lack of a role of the parasympathetic nervous system. *Eur J Pharmacol* 1986;125:177-184.

43. Evequoz D, Waeber B, Matsueda G, Nussberger J, Brunner HR. Differential blood pressure response to atriopeptin III and sodium nitroprusside in conscious rats with adrenal medullectomy. *Eur J Pharmacol* 1987;144:217-221.

44. Runge MS, Bode C, Matsueda GR, Haber E. Antibody-enhanced thrombolysis: Capture of tissue plasminogen activator by a bispecific antibody and direct targeting by an antifibrin-tissue plasminogen activator conjugate in vivo. *Trans Assoc Am Physicians* 1987;100:250-255.

45. Runge MS, Bode C, Matsueda GR, Haber E. Antibody-enhanced thrombolysis: Targeting of tissue plasminogen activator in vivo. *Proc Natl Acad Sci USA* 1987;84:7659-7662.

46. Allen PM, Matsueda GR, Evans RJ, Dunbar JB Jr, Marshall GR, Unanue ER. Identification of the T-cell and Ia contact residues of a T-cell antigenic epitope. *Nature* 1987;327:713-715.

47. Bode C, Runge MS, Newell JB, Matsueda GR, Haber E. Thrombolysis by a fibrin-specific antibody Fab'-urokinase conjugate. *J Mol Cell Cardiol* 1987;19:335-341.

48. Liau CS, Haber E, Matsueda GR. Evaluation of monoclonal antifibrin antibodies by their binding to human blood clots. *Thromb Haemost* 1987;57:49-54.

49. Bode C, Runge MS, Newell JB, Matsueda GR, Haber E. Characterization of an antibody-urokinase conjugate. A plasminogen activator targeted to fibrin. *J Biol Chem* 1987;262:10819-10823.

50. Schnee JM, Runge MS, Matsueda GR, Hudson NW, Seidman JG, Haber E, Quertermous T. Construction and expression of a recombinant antibody-targeted plasminogen activator. *Proc Natl Acad Sci USA* 1987;84:6904-6908.

51. Fluckiger JP, Waeber B, Nussberger J, Matsueda G, Brunner HR. Effect of indomethacin and propranolol on the blood pressure and renin response to atriopeptin III in conscious rats. *Regul Pept* 1987;17:277-284.

52. Vieira JG, Federico P, Matsueda G, Neer RM. Monoclonal antibodies to bovine parathyroid hormone: Production and characterization. *Braz J Med Biol Res* 1988;21:1005-1011.

53. Nawroth P, Handley D, Matsueda G, De Waal R, Gerlach H, Blohm D, Stern D. Tumor necrosis factor/cachectin-induced intravascular fibrin formation in meth A fibrosarcomas. *J Exp Med* 1988;168:637-647.

54. Charpie JR, Haber E, Matsueda GR. A sequence-dependent monoclonal antibody specific for single-chain urokinase. *Biochem Biophys Res Commun* 1988;152:910-915.

55. Fischman AJ, Wildey GM, Matsueda GR, Margolies MN, Zisfein JB, Homcy CJ, Graham RM. Specificity of serine proteases for cleavage sites on proatrial natriuretic factor. *Peptides* 1988;9:1275-1283.

56. Lee P, Matsueda GR, Allen PM. T cell recognition of fibrinogen. A determinant on the A α-chain does not require processing. *J Immunol* 1988;140:1063-1068.

57. Reed GL III, Matsueda GR, Haber E. Acceleration of plasma clot lysis by an antibody to α_2-antiplasmin. *Trans Assoc Am Physicians* 1988;101:250-256.

58. Runge MS, Bode C, Matsueda GR, Haber E. Conjugation to an antifibrin monoclonal antibody enhances the fibrinolytic potency of tissue plasminogen activator *in* vitro. *Biochemistry* 1988;27:1153-1157.

59. Wildey GM, Fischman AJ, Fallon JT, Matsueda GR, Zisfein JB, Preibisch G, Seipke G, Homcy CJ, Graham RM. Cellular processing of pro-atrial natriuretic factor (pro-ANF): Studies using an antiserum that selectively binds ANF-(99-126) after its cleavage from pro-ANF. *Endocrinology* 1988;123:2054-2061.

60. Allen PM, Matsueda GR, Adams S, Freeman J, Roof RW, Lambert L, Unanue ER. Enhanced immunogenicity of a T cell immunogenic peptide by modifications of its N and C termini. *Int Immunol* 1989;1:141-150.

61. Bode C, Runge MS, Branscomb EE, Newell JB, Matsueda GR, Haber E. Antibody-directed fibrinolysis. An antibody specific for both fibrin and tissue plasminogen activator. *J Biol Chem* 1989;264:944-948.

62. Branscomb EE, Runge MS, Savard CE, Adams KM, Matsueda GR, Haber E. Bispecific monoclonal antibodies produced by somatic cell fusion increase the potency of tissue plasminogen activator. *Thromb Haemost* 1990;64:260-266.

63. Charpie JR, Runge MS, Matsueda GR, Haber E. A bispecific antibody enhances the fibrinolytic potency of single-chain urokinase. *Biochemistry* 1990;29:6374-6378.

64. Runge MS, Bode C, Savard CE, Matsueda GR, Haber E. Antibody-directed fibrinolysis: A bispecific $(Fab')_2$ that binds to fibrin and tissue plasminogen activator. *Bioconjug Chem* 1990;1:274-277.

65. Reed GL III, Matsueda GR, Haber E. Inhibition of clot-bound α_2-antiplasmin enhances in vivo thrombolysis. *Circulation* 1990;82:164-168.

66. Reed GL III, Matsueda GR, Haber E. Synergistic fibrinolysis: Combined effects of plasminogen activators and an antibody that inhibits α_2-antiplasmin. *Proc Natl Acad Sci USA* 1990;87:1114-1118.

67. D'Souza SE, Ginsberg MH, Matsueda GR, Plow EF. A discrete sequence in a platelet integrin is involved in ligand recognition. *Nature* 1991;350:66-68.

68. Kanke M, Matsueda GR, Strauss HW, Yasuda T, Liau CS, Khaw BA. Localization and visualization of pulmonary emboli with radiolabeled fibrin-specific monoclonal antibody. *J Nucl Med* 1991;32:1254-1260.

69. Shiba E, Lindon JN, Kushner L, Matsueda GR, Hawiger J, Kloczewiak M, Kudryk B, Salzman EW. Antibody-detectable changes in fibrinogen adsorption affecting platelet activation on polymer surfaces. *Am J Physiol* 1991;260:C965-974.

70. Lukacova D, Matsueda GR, Haber E, Reed GL. Inhibition of factor XIII activation by an anti-peptide monoclonal antibody. *Biochemistry* 1991;30:10164-10170.

71. Reed, G. L., Matsueda, G. R., & Haber, E. (1991). Fibrin-fibrin and alpha 2-antiplasmin-fibrin cross-linking by platelet factor XIII increases the resistance of platelet clots to fibrinolysis. Trans Assoc Am Physicians.

72. Shiba, E., Lindon, J. N., Kushner, L., Matsueda, G. R., Hawiger, J., Kloczewiak, M., Kudryk, B., & Salzman, E. W. (1991). Antibody-detectable changes in fibrinogen adsorption affecting platelet activation on polymer surfaces. Am J Physiol, 260(5 Pt 1), 74.

73. Chen, F., Haber, E., & Matsueda, G. R. (1992). Availability of the B beta(15-21) epitope on cross-linked human fibrin and its plasmic degradation products. Thromb Haemost, 67(3), 335-40.

74. Valenzuela, R., Shainoff, J. R., DiBello, P. M., Urbanic, D. A., Anderson, J. M., Matsueda, G. R., & Kudryk, B. J. (1992). Immunoelectrophoretic and immunohistochemical characterizations of fibrinogen derivatives in atherosclerotic aortic intimas and vascular prosthesis pseudo-intimas. Am J Pathol, 141(4), 861-80.

75. Gron, B., Bennick, A., Filion, M. C., Matsueda, G. R., Nieuwenhuizen, W., & Brosstad, F. (1992). Soluble, cross-linked fibrin(ogen) hybrid oligomers do not stimulate t-PA conversion of plasminogen. Thromb Res, 66(2-3), 231-8.

76. Groen, B., Filion, M. C., Bennick, A., Nieuwenhuizen, W., Matsueda, G. R., & Brosstad, F. (1992). Early cross-linked fibrin in human plasma contains .alpha.-polymers with intact fibrinopeptide A. Blood Coagulation Fibrinolysis, 3(6), 731-6.

77. Haber, E., Bode, C., Matsueda, G. R., Reed, G. L., & Runge, M. S. (1992). Antibody targeting as a thrombolytic strategy. Ann. N. Y. Acad. Sci., 667, 365-81.

78. Reed, G. L., Matsueda, G. R., & Haber, E. (1992). Platelet factor XIII increases the fibrinolytic resistance of platelet-rich clots by accelerating the crosslinking of alpha 2-antiplasmin to fibrin. Thromb Haemost, 68(3), 315-20.

79. Blumenstein, M., Matsueda, G. R., Timmons, S., & Hawiger, J. (1992). A beta-turn is present in the 392-411 segment of the human fibrinogen gamma-chain. Effects of structural changes in this segment on affinity to antibody 4A5. Biochemistry, 31(44), 10692-8.

80. Bernatowicz, M. S., Wu, Y., & Matsueda, G. R. (1992). 1H-Pyrazole-1-carboxamidine hydrochloride an attractive reagent for guanylation of amines and its application to peptide synthesis. J. Org. Chem., 57(8), 2497-502.

81. Ju, S. T., Nonogaki, T., Bernatowicz, M. S., & Matsueda, G. R. (1993). The B cell immune response to an idiotype-inducing peptide epitope can be inhibited by immunodominance of a neighboring epitope. J Immunol, 150(7), 2641-7.

82. Loike, J. D., Silverstein, R., Cao, L., Solomon, L., Weitz, J., Haber, E., Matsueda, G. R., Bernatowicz, M. S., & Silverstein, S. C. (1993). Activated platelets form protected zones of adhesion on fibrinogen and fibronectin-coated surfaces. J Cell Biol, 121(4), 945-55.

83. Ball, E. L., Dunlop, K., & Matsueda, G. R. (1993). Selection of monoclonal antibodies that bind and inhibit tissue-type plasminogen activator. Hybridoma, 12(3), 317-26.

84. Bernatowicz, M. S., & Matsueda, G. R. (1993). An improved synthesis of NG-allyl-(L)-arginine. Synth. Commun., 23(5), 657-6.

86. Chao, H. G., Bernatowicz, M. S., Klimas, C. E., & Matsueda, G. R. (1993). N,N-Diisopropyl-bis(2-(trimethylsilyl)ethyl)phosphoramidite. An attractive phosphitylating agent compatible with the Fmoc/tert-butyl strategy for the synthesis of phosphotyrosine containing peptides. Tetrahedron Lett, 34(21), 3377-80.

87. Chao, H. G., Bernatowicz, M. S., & Matsueda, G. R. (1993). Preparation and use of the 4-(1-(N-(9-fluorenylmethyloxycarbonyl)amino)-2-(trimethylsilyl)ethyl)ph enoxyacetic acid linkage agent for solid-phase synthesis of C-terminal peptide amides: Improved yields of tryptophan-containing peptides. J. Org. Chem., 58(9), 2640-4.

88. Gartner, T. K., Amrani, D. L., Derrick, J. M., Kirschbaum, N. E., Matsueda, G. R., & Taylor, D. B. (1993). Characterization of adhesion of "resting" and stimulated platelets to fibrinogen and its fragments. Thromb. Res., 71(1), 47-60.

89. Song, Y., S. M. Taubenfeld, D. Sheng and G. R. Matsueda (1994). Characterization of a monoclonal antibody directed against the carboxyl-terminus of human factor XIII. An epitope exposed upon denaturation and conserved across species lines. Thromb Haemost 71(1): 62-7.

90. Song, Y. C., D. Sheng, S. M. Taubenfeld and G. R. Matsueda (1994). A microtiter assay for factor XIII using fibrinogen and biotinylcadaverine as substrates. Anal Biochem 223(1): 88-92.

91. Love, T. W., T. Quertermous, M. S. Runge, K. D. Michelson, G. R. Matsueda and E. Haber (1994). Attachment of an antifibrin antibody to the amino terminus of tissue-type plasminogen activator impairs stimulation by fibrin. Fibrinolysis 8(5): 326-32.

92. Yang, W. P., J. Goldstein, R. Procyk, G. R. Matsueda and S. Y. Shaw (1994). Design and evaluation of a thrombin-activable plasminogen activator. Biochemistry 33(8): 12.

93. Micanovic, R., R. Procyk, W. Lin and G. R. Matsueda (1994). Role of histidine 373 in the catalytic activity of coagulation factor XIII. J. Biol. Chem. 269(12): 9190-4.

94. Chao, H. G., M. S. Bernatowicz, P. D. Reiss and G. R. Matsueda (1994). Synthesis and Application of Bis-Silylethyl-Derived Phosphate-Protected Fmoc-Phosphotyrosine Derivatives for Peptide Synthesis. J. Org. Chem. 59(22): 6687-91.

95. Fairman, R., H. G. Chao, L. Mueller, T. B. Lavoie, L. Shen, J. Novotny and G. R. Matsueda (1995). Characterization of a new four-chain coiled-coil: influence of chain length on stability. Protein Sci 4(8): 1457-69.

96. Chao, H. G., B. Leiting, P. D. Reiss, A. L. Burkhardt, C. E. Klimas, J. B. Bolen and G. R. Matsueda (1995). Synthesis and Application of Fmoc-O-(Bis(dimethylamino)phosphono)tyrosine, a Versatile Protected Phosphotyrosine Equivalent. J. Org. Chem. 60(24): 7710-11.

97. Taubenfeld, S. M., Y. Song, D. Sheng, E. L. Ball and G. R. Matsueda (1995). A monoclonal antibody against a peptide sequence of fibrinogen gamma chain acts as an inhibitor of factor XIII-mediated crosslinking of human fibrin. Thromb Haemost 74(3): 923-7.

98. Robertson, J. G., M. S. Bernatowicz, A. M. Dhalla, B. B. Muhoberac, J. Yanchunas, G. R. Matsueda and J. J. Villafranca (1995). Inhibition of bovine brain nitric oxide synthase by .alpha.-amino and .alpha.-carboxyl derivatives of NG-allyl-L-arginine. Bioorg. Chem. 23(2): 144-51.

99. Rowley, R. B., A. L. Burkhardt, H. G. Chao, G. R. Matsueda and J. B. Bolen (1995). Syk protein-tyrosine kinase is regulated by tyrosine-phosphorylated Ig.alpha./Ig.beta. immunoreceptor tyrosine activation motif binding and autophosphorylation. J. Biol. Chem. 270(19): 11590-4.

100. Brown, L. F., S. M. Olbricht, B. Berse, R. W. Jackman, G. Matsueda, K. A. Tognazzi, E. J. Manseau, H. F. Dvorak and d. W. L. Van (1995). Overexpression of vascular permeability factor (VPF/VEGF) and its endothelial cell receptors in delayed hypersensitivity skin reactions. J Immunol 154(6): 2801-7.

101. Fairman, R., H. G. Chao, T. B. Lavoie, J. J. Villafranca, G. R. Matsueda and J. Novotny (1996). Design of heterotetrameric coiled coils: evidence for increased stabilization by Glu(-)-Lys(+) ion pair interactions. Biochemistry 35(9): 2824-9.

102. Seiler, S. M., M. Peluso, J. G. Tuttle, K. Pryor, C. Klimas, G. R. Matsueda and M. S. Bernatowicz (1996). Thrombin receptor activation by thrombin and receptor-derived peptides in platelet and CHRF-288 cell membranes: receptor-stimulated GTPase and evaluation of agonists and partial agonists. Mol Pharmacol 49(1): 190-7.

103. Goldstein, J., G. R. Matsueda and S. Y. Shaw (1996). A chimeric streptokinase with unexpected fibrinolytic selectivity. Thromb. Haemostasis 76(3): 429-438.

REVIEWS

1. Jackson RL, Matsueda GR. Myxobacter AL-1 protease. In: Perlmann GE, Lorand L, eds. *Methods in Enzymology. Vol. 19.* New York: Academic Press, 1970:591-598.

2. Stewart JM, Matsueda GR. Some problems in solid-phase peptide synthesis. In: Meienhofer J, ed. *Chemistry and Biology of Peptides. Proceedings of the Third American Peptide Symposium.* Ann Arbor, MI: Ann Arbor Science Publishers, 1972:221-224.

3. Stewart JM, Matsueda GR. New urethane protecting groups: The optically active 1-arylethoxycarbonyl group. In: Walter R, Meienhofer J, eds. *Peptides: Chemistry, Structure and Biology. Proceedings of the Fourth American Peptide Symposium.* Ann Arbor, MI: Ann Arbor Science Publishers, 1975:333-339.

4. Stewart JM, Pena C, Matsueda GR, Harris K. Some improvements in the solid phase synthesis of large peptides. In: Loffet A, ed. *Peptides 1976. Proceedings of the Fourteenth European Peptide Symposium.* Brussels: Editions de l'Université de Bruxelles, 1976:285-290.

5. Matsueda GR, Gaehde SA. The solid phase synthesis of peptide α-carboxamides: The synthesis of handles and their characterization by the use of internal reference amino acids. In: Gross E, Meienhofer J, eds. *Peptides: Structure and Biological Function. Proceedings of the Sixth American Peptide Symposium.* Rockford, IL: Pierce Chemical, 1979:353-356.

6. Margolies MN, Matsueda GR. Solid-phase Edman degradation as an aid in evaluation of the homogeneity of peptidyl-resin intermediates obtained from Merrifield solid-phase synthesis. In: Liu T, Schechter A, Heinrikson R, Condliffe P. *Chemical Synthesis and Sequencing of Peptides and Proteins.* New York: Elsevier/North-Holland, 1981:207-219.

7. Matsueda GR, Steiman DM, Matsueda R. 3-Nitro-2-pyridinesulfenyl-amino acids in solid-phase peptide synthesis. In: Rich D, Gross E, eds. *Peptides: Synthesis - Structure - Function. Proceedings of the Seventh American Peptide Symposium.* Rockford, IL: Pierce Chemical, 1981:205-208.

8. Ridge RJ, Matsueda GR, Haber E, Matsueda R. Sulfur protection with the novel 3-nitro-2-pyridinesulfenyl group in solid-phase peptide synthesis. In: Rich DH, Gross E, eds. *Peptides: Synthesis - Structure - Function. Proceedings of the Seventh American Peptide Symposium.* Rockford, IL: Pierce Chemical, 1981:213-216.

9. Haber E, Katus HA, Hurrell JG, Matsueda GR, Ehrlich P, Zurawski VR Jr, Khaw BA. Detection and quantification of myocardial cell death: Application of monoclonal antibodies specific for cardiac myosin. *J Mol Cell Cardiol* 1982;14(Suppl 3):139-146.

10. Wang S-S, Matsueda R, Matsueda GR. Automated peptide synthesis under mild conditions. In: Shioiri T, ed. *Peptide Chemistry 1981. Proceedings of the 19th Symposium on Peptide Chemistry.* Osaka: Protein Research Foundation, 1982:37-40.

11. Matsueda R, Higashida S, Ridge RJ, Matsueda GR. 3-Nitro-2-pyridinesulfenyl(Npys) protecting group: Protection and activation of the thiol function. In: Shiolri T, ed. *Peptide Chemistry 1981. Proceedings of the 19th Symposium on Peptide Chemistry.* Osaka: Protein Research Foundation, 1982:31-36.

12. Haber E, Katus HA, Hurrell JG, Matsueda GR, Ehrlich P, Zurawski VR Jr, Khaw B-A. Detection and quantification of myocardial cell death: Application of monoclonal antibodies specific for cardiac myosin. *J Mol Cell Cardiol* 1982;14(Suppl 3):139-146.

13. Haber E, Katus HA, Hurrell JG, Matsueda GR, Ehrlich P, Zurawski VR Jr, Khaw BA. Monoclonal antibodies specific for cardiac myosin: In vivo and in vitro diagnostic tools in myocardial infarction. In: Hurrell JG, ed. *Monoclonal Hybridoma Antibodies: Techniques and Applications.* Boca Raton: CRC Uniscience, 1982:91-101.

14. Matsueda GR, Hui KY, Pacella BL Jr, Young JD, Haber E. Synthetic fibrin-like peptides used as antigens yield fibrin-specific antibodies. In: Hruby VJ, Rich DH, eds. *Peptides: Structure and Function. Proceedings of the Eighth American Peptide Symposium.* Rockford, IL: Pierce Chemical, 1983:873-876.

15. Haber E, Matsueda GR, Khaw BA. New directions in the use of radioactive antibodies and plasma proteins for in vivo diagnosis of cardiovascular disease. In: Nakamura RM, Dito WR, Tucker ES III, eds. *Clinical Laboratory Assays: New Technology and Future Directions.* New York: Masson Publishing, 1983:205-222.

16. Matsueda GR, Hui KY, Haber E. Fibrin-specific monoclonal antibodies are elicited by immunization with a synthetic fibrin-like peptide. In: Henschen A, Hessel B, McDonagh J, Saldeen T, eds. *Fibrinogen - Structural Variants and Interactions. Vol. 3.* Berlin & New York: Walter de Gruyter, 1985:43-50.

17. Bernatowicz MS, Matsueda GR, Matsueda R. Facilitated formation of unsymmetrical disulfide bonds via the S-(3-nitro-2-pyridenesulfenyl) derivative of cysteine. In: Deber CM, Hruby VJ, Kopple KD, eds. *Peptides: Structure and Function. Proceedings of the Ninth American Peptide Symposium.* Rockford, IL: Pierce Chemical, 1985:233-236.

18. Bode C, Runge MS, Matsueda GR, Haber E. Antifibrin-urokinase complex. In: Effert S, et al., eds. *Facts and Hopes in Thrombolysis in Acute Myocardial Infarction.* Darmstadt: Steinkopff-Verlag, 1986:35-42.

19. Ridge RJ, Ball EL, Matsueda GR. Chemical synthesis of peptides. In: Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE, eds. *The Heart and Cardiovascular System.* New York: Raven, 1986:203-219.

20. Haber E, Matsueda GR. Monoclonal antibodies as diagnostic and therapeutic cardiovascular agents. In: *Advances in Immunopharmacology. Proceedings of the Third International Conference on Immunopharmacology.* Oxford: Pergamon, 1986:303-307.

21. Haber E, Matsueda GR. Monoclonal antibodies to fibrin: Their use for imaging clots, and in antibody-targeted thrombolysis. In: Spry CJF, ed. *Immunology and*

Molecular Biology of Cardiovascular Diseases. Lancaster, UK: MTP Press, 1987:97-101.

22. Haber E, Runge MS, Bode C, Branscomb EE, Schnee JM, Quertermous T, Matsueda GR. Antibody-targeted plasminogen activators. In: Hubbard R, Marks V, eds. *Clinical Applications of Monoclonal Antibodies*. New York and London: Plenum, 1988:207-213.

23. Matsueda GR, Bernatowicz MS. ε-(γ-glutamyl)lysyl amide crosslink in fibrin peptides. In: Schlesinger DH, ed. *Macromolecular Sequencing and Synthesis. Selected Methods and Applications*. New York: Alan R. Liss, 1988:195-198.

24. Haber E, Runge MS, Bode C, Branscomb EE, Schnee JM, Quertermous T, Matsueda GR. Antibody-targeted fibrinolysis. In: Brew K, Ahmad F, Bialy H, Black S, Fenna RE, Puett D, Scott WA, Van Brunt J, Voellmy RW, Whelan WJ, Woessner JF, eds. *Advances in Gene Technology: Protein Engineering and Production. ICSU Short Reports Volume 8.* Oxford and Washington, DC: IRL Press, 1988:218-219.

25. Bernatowicz MS, Costello CE, Matsueda GR. Synthesis of an ε-(γ-Glu)Lys cross-linked peptide in human fibrin. In: Marshall GR, ed. *Peptides: Chemistry and Biology. Proceedings of the Tenth American Peptide Symposium*. Leiden: ESCOM Science Publishers, 1988:187-188.

26. Matsueda GR, Bernatowicz MS, Costello CE. Antibodies that bind to a protein but not its precursor: Synthesis of fibrin-unique peptides and selection of high-affinity, fibrin-specific antibodies. In: Shiba T, Sakakibara S, eds. *Peptide Chemistry 1987. Proceedings of the Japan Symposium on Peptide Chemistry*. Osaka: Protein Research Foundation, 1988:787-790.

27. Runge MS, Quertermous T, Matsueda GR, Haber E. Increasing selectivity of plasminogen activators with antibodies. *Clin Res* 1988;36:501-506.

28. Bode C, Runge M, Matsueda G, Haber E. Antikörper-vermittelte Thrombolyse. In: Schölmerich P, Mutschler E, eds. *Molekularbiologische Grundlagenforschung - therapeutische Innovationen*. Stuttgart, New York: Gustav Fischer Verlag, 1989:89-102.

29. Haber E, Quertermous T, Matsueda GR, Runge MS. Innovative approaches to plasminogen activator therapy. *Science* 1989;243:51-56.

30. Bernatowicz MS, Ball EL, Matsueda GR. Chemical synthesis of peptides. In: Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE, eds. *The Heart and Cardiovascular System*. Second edition. New York: Raven, 1991:523-542.

31. Reed GL, Matsueda GR, Haber E. Fibrin-fibrin and α_2-antiplasmin-fibrin crosslinking by platelet factor XIII increases the resistance of platelet clots to fibrinolysis. *Trans Assoc Am Physicians*, in press.

32. Blumenstein, M., Matsueda, G. R., <editor>, S. J. A. (., & Rivier, J. E. (. (1992). Correlation of conformation with antibody affinity for fibrinogen .gamma.-chain carboxyl terminal peptide segment. Pept.: Chem. Biol., Proc. Am. Pept. Symp., 12th, P237.

33. Gartner, T. K., D. L. Amrani, J. M. Derrick, N. E. Kirschbaum, G. R. Matsueda and D. B. Taylor (1994). Characterization of adhesion of resting and stimulated platelets to fibrinogen and its fragments. Ann. N. Y. Acad. Sci. 714: 303-5.

34. Chao, H. G., M. S. Bernatowicz, G. R. Matsueda, J. A. Smith, ed. (1994). SAL: a silicon-based linkage agent for Fmoc solid phase synthesis: improved yields of peptide amides containing tryptophan. Pept.: Chem., Struct. Biol., Proc. Am. Pept. Symp., 13th, P138.

35. Bernatowicz, M. S.; Matsueda, G. R. Synthesis of peptides containing p-guanidinophenylalanine. Maia, Hemani L. S (Ed) ESCOM, Leiden, Neth., Pept. 1994, Proc. Eur. Pept. Symp., 23rd, P759-760.

Patents

1. Ehrlich PH, Matsueda GR, Margolies MN, Haber E. Immunogenic fragment of rabbit immunoglobulin G antibody with high activity against specific antigens. Basic Patent US 4,355,023, 1982.

2. Haber E, Matsueda GR. Products and method for site-specific activation for targeting drugs, e.g. to tumor sites, or enhancing fibrinolysis. Basic Patent EP 187,658, 1986.

3. Matsueda GR, Haber E. Screening of fibrin-specific monoclonal antibodies by contact with immobilized cross-linked fibrin clot and screening with detectable labeling step. Basic Patent WO 8,706,263, 1987.

4. Reed GL, Matsueda G, Haber E. Treating myocardial infarction or blood clots using a hapten-binding molecule capable of preventing inhibition of plasmin and optimizing a thrombolytic agent. Basic Patent EP 336,693, 1989.

5. Khaw BA, Nicol PD, Matsueda GR. Monoclonal antibody to human ventricular myosin light chain-1, used in immunoassays to diagnose myocardial infarction or other cardiomyopathies. Basic Patent WO 9,015,993, 1991.

6. Matsueda, G. R., Haber, E., & Hui, K. Method of producing fibrin-specific monoclonal antibodies lacking fibrinogen cross-reactivity using fibrin-specific peptides, and use of the monoclonal antibodies in thrombus detection. , P12 pp. Cont. in part of U.s. Ser. No.

7. Reed, G. L., Matsueda, G. R., & Haber, E. Compositions and methods to inhibit the activation of precursor proteins, especially active Factor XIII. , P61 pp.

8. Yang, Wen-pin; Matsueda, Gary R.; Shaw, Shyh-yu. Thrombin-activatable plasminogen activator. US 5571708 A.

9. Reed, Guy L.; Matsueda, Gary R. Thrombin-activated platelet protein-2 (TAPP-2). US 5446132 A.

Question #1 con't:

D. Bristol-Myers Squibb
311 Pennington-Rocky Hill Road
Pennington, NJ 08543

**A wholly-owned subsidiary of Bristol-Myers Squibb Company*

Item #4: Contact Person (unchanged)

Mr. Daniel K. Balkunow
Radiation Safety Officer/Department Head - Health Physics
(732) 519-2451

Question #1 con't:

Items #5 and #6: ***Possession Limits for the Lawrenceville Site, Rt. 206 & Provinceline Road, Princeton, NJ 08540 (modified)***

5A. Byproduct, Source, and/or Specific Nuclear Material	5B. Chemical and/or Physical Form	5C. Max. Amount that licensee may possess at any 1 time	6. Authorized Use
Any byproduct material with Atomic Nos. 1 - 83 except Strontium 90	Any	200 millicuries per radionuclide and 6 curies total	Research and development as defined in 10 CFR 30.4
Hydrogen 3	Any	7 curies	Research and development as defined in 10 CFR 30.4; Manufacture of labelled compounds intended for human use and transfer of the compounds to individuals authorized to receive the material by the terms and conditions of a specific license issued by the USNRC or an Agreement State.
Carbon 14	Any	5 curies	Same as Hydrogen 3
Phosphorous 33	Any	1 curie	Research and development as defined in 10 CFR 30.4
Sulfur 35	Any	1 curie	Research and development as defined in 10 CFR 30.4
Molybdenum 99/ Technetium 99m	Any	50 curies	Research and development as defined in 10 CFR 30.4
Iodine 125	Any	500 millicuries	Research and development as defined in 10 CFR 30.4
Iodine 131	Any	500 millicuries	Research and development as defined in 10 CFR 30.4
Technetium 99	Any	200 millicuries	Research and development as defined in 10 CFR 30.4
Nickel 63	Plated sources in detector cells	not to exceed 15 millicuries per source and 750 millicuries total	Research and development as defined in 10 CFR 30.4

Question #1 con't:

Items #5 and #6: ***Possession Limits for the BMS Clinical Research Center, Three Hamilton Health Place, Hamilton, NJ 08690***

5A. Byproduct, Source, and/or Specific Nuclear Material	5B. Chemical and/or Physical Form	5C. Max. Amount that licensee may possess at any 1 time	6. Authorized Use
Any byproduct material with Atomic Nos. 1 - 83 except Strontium 90	Any	Not to exceed 10 millicuries per radionuclide and 1 curie total	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Hydrogen 3	Any	100 millicuries	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Carbon 14	Any	100 millicuries	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Sulfur 35	Any	300 millicuries	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Phosphorous 32	Any	100 millicuries	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Phosphorous 33	Any	200 millicuries	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Iodine 125	Any	50 millicuries	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Nickel 63	Plated sources in detector cells	Not to exceed 15 millicuries per source and 750 millicuries total	Research and development as defined in 10 CFR 30.4; Calibration of instruments.

Question #1 con't:

Items #5 and #6: ***Possession Limits for the Pennington Site,311 Pennington-Rocky Hill Road, Pennington, NJ 08543***

5A. Byproduct, Source, and/or Specific Nuclear Material	5B. Chemical and/or Physical Form	5C. Max. Amount that licensee may possess at any 1 time	6. Authorized Use
Any byproduct material with Atomic Nos. 1 - 83 except Strontium 90	Any	200 millicuries per radionuclide and 6 curies total	Research and development as defined in 10 CFR 30.4; Calibration of instruments.
Nickel 63	Plated sources in detector cells	Not to exceed 15 millicuries per source and 750 millicuries total	Research and development as defined in 10 CFR 30.4; Calibration of instruments.

Question #1 con't:

Items #5 and #6: ***Possession Limits for the New Brunswick Site (unchanged)***

5A. Byproduct, Source, and/or Specific Nuclear Material	5B. Chemical and/or Physical Form	5C. Max. Amount that licensee may possess at any 1 time	6. Authorized Use
Any byproduct material with Atomic Nos. 1-83 except Strontium 90	Any	5 Curies per radionuclide and 1000 Curies total	1. Research and development as defined in 10 CFR 30.4 2. For possession, use and processing incident to the manufacture of radiochemicals and radiopharmaceuticals 3. For storage prior to distribution of manufactured radiochemicals and radiopharmaceuticals 4. For packaging and distribution of manufactured radiochemicals and radiopharmaceuticals to persons authorized to receive the licensed material pursuant to the terms and conditions of a specific license issued by the Nuclear Regulatory Commission or an Agreement State
Iodine 131	Any	150 Curies	Same as A. above
Hydrogen 3	Any	20 Curies	Research and development as defined in 10 CFR 30.4; Manufacture of labeled compounds intended for human use and transfer of the compounds to individuals authorized to receive that material by the terms and conditions of a specific license issued by the NRC or an Agreement State.
Carbon 14	Any	20 Curies	Same as Hydrogen 3
Sulphur 35	Any	10 Curies	Research and development as defined in 10 CFR 30.4; calibration of instruments
Strontium 90	Any	2 millicuries	For interim storage of waste returned from a processor; calibration of instruments
Any byproduct material with Atomic Nos. 84-103	Any	1 millicurie	For interim storage of waste returned from a processor
Nickel 63	Plated Sources in detector cells	Not to exceed 15 millicuries per source and 750 millicuries total	Research and development as defined in 10 CFR 30.4; calibration of instruments

Question #2a:

Item 9 in your application discusses a "built in" area radiation monitoring system. In addition, this section states: "Each filter bank is equipped with before and after continuous tubes used to check charcoal filter efficiencies." "They are changed on a routine basis." Your application also states: "There is no definite filter changer criterion." Please describe the methods you use to determine when the filters in each filter bank are changed.

Response:

The "built in" area radiation monitors do not monitor the ventilation system. They measure ambient radiation levels in operational work areas. The before and after continuous air (sampling) tubes that are used to check charcoal filter efficiencies are collected routinely, typically weekly. Based upon the ratio of the before and after sample tubes, an efficiency for each filter bank is calculated. If a filter bank drops below 90% efficiency and is significantly contributing to the total stack effluent, the filters are replaced.

Question #2b:

From various sections of the text of your submission, and your postulated emergency scenarios, it appears that you depend on area monitors, the analysis of sample tubes, the response of personnel, and fire activated systems in emergency.

Response:

All emergency scenarios have been developed for New Brunswick Building 124 Manufacturing operations. It is these licensed activities that require a Radiological Contingency Plan. Therefore, the responses to Questions 2.b.1 - 2.b.4 will be specific to Building 124 Manufacturing operations.

Question #2b.1:

Provide a schematic diagram of all effluent pathways at each site which includes the identification of the source of the activity, the maximum typical activity at each source, the location of the sampling points in each ventilation pathway, and each contributing and final ventilation flowrates for each pathway.

Response:

All ventilation systems in the manufacturing area are manifolded to a single stack prior to release to the environment. Page 15, paragraph 5 of the February 18, 1997 license renewal application details the sampling of this effluent pathway. The typical flowrate through this stack is approximately 70,000 cfm, seven days a week, twenty-four hours per day. The primary contribution to the effluent is due to hot cell operations where approximately 35 Curies per week of I^{131} is processed. Each ventilation pathway is monitored by pre and post air sampling tubes as described in Question 2.a above. A schematic of the Building 124 ventilation system is attached (see Attachments 1 & 2).

Question #2b.2:

Please describe how your present monitoring program emulates a real-time effluent monitoring system in the timely mitigation of releases from a scenario which does not include a fire in the restricted area.

Response:

The radioactive material present in the effluent air stream is constantly monitored by the stack monitor detectors. When these detectors register a count rate above the alarm set point, the stack monitor is designed to trigger an alarm in the Health Physics office. This feature on the stack monitor is currently undergoing modifications to replace aging equipment. The manufacturer's service representative has been contacted and this feature is expected to be upgraded in the near future. Currently, the integrating charcoal sample cartridge is collected and analyzed each business day. Close coordination between Health Physics and manufacturing personnel have ensured that any abnormal occurrences are promptly identified and investigated before any impact on stack effluent occurs.

Question #2b.3:

Include an estimate of the time required to quantify a release, and describe the degree of correspondence you have determined between your "built in" area radiation monitors and the present method for sampling releases.

Response:

If a release is suspected, the charcoal sample cartridge on the stack monitor can be collected and analyzed within fifteen minutes. Subsequent samples could be collected on an hourly basis to continue to assess the stack effluent. Post samples from the filter banks, described in question 2.a, can be collected and analyzed within one hour to determined precisely which hot cell, glove box, or fume hood filter train is contributing to the release. The "built in" area radiation monitors measure ambient radiation levels in operational work areas. Any release in an operation area will result in an elevated radiation level in that area that will be immediately detected by these monitors. As stated previously, these "built in" monitors do not monitor the ventilation system, any correspondence to effluent releases would be qualitative, not quantitative.

Question #2b.4:

Provide the average annual Chi/Q values used for each release site, and the distance to the maximum exposed individual for each site.

Response:

Chi/Q values are not utilized to characterize site effluent. The measured stack concentrations are compared to the limits specified in 10 CFR 20 Appendix B. The effluent concentrations for the previous five years have been 5% or less of the Appendix B limit. This is well within the constraint limit of 10 CFR 20.1101(d) for air releases. If the effluent releases approached 20% of the limit, BMS will calculate the Chi/Q value for the stack release based upon a stack height of 29 meters and the distance to the maximum exposed individual of 5 meters.

Question #3:

The second paragraph in the section "Emergency Procedures" states: "The ConvaTec and Clinical Laboratory facilities have site specific procedures for emergency response." Since the ConvaTec facility was removed from the license, is the Clinical Laboratory facility the only remaining facility to have site specific emergency procedures?

Response:

The Clinical Laboratory at Princeton House has been decommissioned and re-located to Hamilton (see Question #1). Hamilton has site specific emergency procedures and is supported by the Lawrenceville site staff.

Question #4:

Page 22, paragraph 6 states: "Gloves are worn while handling radioactive materials and removed before handling non-radioactive materials." Are gloves the only protective apparel used?

Response:

Page 26, paragraph 5 of the February 18, 1997 renewal application details the protective apparel required by personnel in radiologically restricted areas. Lab coats are required for personnel that are not wearing company issued uniforms. Gloves are required when handling radioactive materials. Additional protective apparel will be used in areas as the situation warrants.

Question #5:

Page 22, paragraphs 12 and 13 discuss surveys and contaminated areas. Paragraph 12 states: "Documentation of such surveys will not be required." "All contaminated areas are cleaned and rechecked." If these surveys are not documented, how are all contaminated areas identified so that all contaminated areas are cleaned and rechecked as stated in your application?

Response:

Page 25, paragraph 3 of the February 18, 1997 renewal application outlines Health Physics contamination surveys and operation contamination surveys. Health Physics surveys are documented, appropriate area personnel are informed of any contamination identified and are responsible for decontamination. Health Physics will verify the decontamination was completed. Operational contamination surveys conducted by personnel in their own work areas, as part of proper handling techniques for radioactive materials, are not required to be documented. If an operational contamination survey identifies contaminated areas or equipment, the item is promptly decontaminated by that person or someone in their group. Personnel that handle radioactive materials are responsible for maintaining their work area free of contamination.

Question #6:

Your application does not have specific details for thyroid bioassays. Describe your bioassay program, including the type of bioassay (thyroid counts, urine counts, whole body counts, etc.), the criteria and the frequency for performing bioassays, and the type of action taken when positive results are obtained. It is recommended that bioassay procedures be considered for personnel using millicurie quantities of tritiated organic compounds, iodine-131, and iodine-125 in noncontained forms.

Response:

As stated in paragraph 1, page 26 of the February 18, 1997 license renewal application, it is not likely that any employee will exceed 10% of the ALI under anticipated licensed activities. Bioassay by evaluation of the thyroid and urine are available to employees and are performed to verify the adequacy of procedures and engineered controls. Personnel that handle millicurie quantities of unsealed volatile iodine are required to

Question #6 con't:

perform a thyroid bioassay within 72 hours of performing work. Manufacturing personnel who handle iodine typically perform a routine thyroid evaluation weekly. Urine bioassays are conducted on personnel who process ten millicuries or greater of tritium or Carbon-14 on the bench top or 100 millicuries of either isotope in a ventilated enclosure. Urine bioassays are sent to a contract laboratory for analysis (currently, Radiation Science, Inc. License #29-30310-01). Positive results that exceed 0.2% per week of the ALI are investigated with a deviation report. If an employee is expected to exceed 2.5% of the ALI in any quarter, their committed effective dose equivalent is calculated and reported in accordance with 10 CFR 20 requirements.

Question #7:

Your application did not specify the instrument used in your bioassay program for determining activity in the thyroid. Please specify your instrumentation and calibration procedures, including the type of phantom you will use.

Response:

Thyroid evaluations are currently performed utilizing a Model 8501-S2 Thyroid In-Vitro System manufactured by Specialties Electronic Company of Mount Holly, New Jersey. This instrument consists of a collimated 2×2 NaI detector that is connected to a microprocessor unit which calculates and records the thyroid activity for each participant. Each sample is typically collected for two minutes. The instrument is calibrated daily utilizing a mock iodine^{131} (Ba^{133}) standard or an I^{125} standard placed in a tissue equivalent neck phantom.

Question #8:

Specify your criteria for performing internal monitoring which may be required for certain uses of material under your license. Submit a description of procedures, including the methods and instrumentation to be used for sampling and analysis, calibration of equipment, the lower limit of detection for the method and instrumentation, and the action levels for each radionuclide.

Response:

Internal monitoring is not currently required due to the extensive use of engineered controls and administrative procedures. Bioassays are performed to verify the adequacy of procedures and engineered controls. Personnel that handle millicurie quantities of unsealed volatile iodines are required to perform a thyroid bioassay within 72 hours of performing work as described in Question #7. Manufacturing personnel who handle iodine typically perform a routine thyroid evaluation weekly. Urine bioassays are conducted on personnel who process ten millicuries or greater of tritium, Carbon^{14}, or other beta emitters on the bench top or 100 millcuries in a ventilated enclosure. Urine bioassays are collected and sent to a contract laboratory for analysis (currently, Radiation Science, Inc. License #29-30310-01). Positive results that exceed 0.2% per week of the ALI are investigated. If an employee is expected to exceed 2.5% of the ALI in any quarter, their committed effective dose equivalent is calculated and reported in accordance with 10 CFR 20 requirements on NRC Form 5. Typical lower limits of detection for each isotope are at least 0.1% of the ALI.

Question #9:

Your application states: "The RSC is informed of regulatory requirements and operating procedures through routine meetings and correspondence with the Health Physics Department." At what frequency does the Radiation Safety Committee (RSC) meet?

Response:

Page 7, item C.7 of the February 18, 1997 renewal application states that the RSC is required to meet quarterly at a minimum.

Question #10:

Page 24, in your application, item 8, in the section entitled "Safety Evaluations of Proposed Uses and Users" requires that information on the User Form includes, among other things, whether the material will be used in human or animal studies. Please clarify this statement. License No. 29-00139-02 does not authorize use of licensed material in humans or animals. Furthermore, Research and Development, as defined in 10 CFR 30.4, states, in part, "Research and development as used in this part and parts 31 through 35 does not include the internal or external administration of byproduct material, or the radiation therefrom, to human beings."

Response:

New users of radioactive material are queried regarding the use of radioactive material in humans so that this work can be identified before license material is used for activities that are beyond the scope of the license. If a users wishes to use licensed material in humans, the work is done by an outside clinical lab that possess the proper licensing.

The Commission's statement that our license does not authorize the use of licensed material in animals is incorrect. The definition of R&D in 10 CFR 30.4 does not exclude the use of animals. Further, license condition 14 of License Number 29-00139-02 implies the use of animals with licensed material.

Question #11:

Paragraph 6 on page 25 of your application discusses the use of respiratory protection equipment. Please confirm that your program conforms to 10 CFR 20, Subpart H "Respiratory Protection and Controls to Restrict Internal Exposures in Restricted Areas."

Response:

The Bristol-Myers Squibb Respirator Protection Program complies with the requirements of 10 CFR 20, Subpart H.

Question #12:

Provide a copy of senior management's written statement of delegation of authority to the Radiation Safety Officer. This statement should include the requisite authority to communicate with and direct your personnel regarding NRC regulations and license provisions and to enforce these requirements including the ability to terminate any unsafe operation involving the use of licensed material.

Response:

A copy of GRP- 31, Mission, Scope, and Major Activities of the Radiation Safety Committee and an interoffice memorandum from the President of Technical Operations, are attached for review (see Attachments 3 & 4). This material is submitted for informational purposes only and should not be considered as part of the license renewal application.

Question #13:

Confirm that management will conduct a periodic oversight of the radiation protection program, including interaction with the RSC and RSO.

Response:

Page 7, Items B.1, B.2, and B.4 of the February 18, 1997 renewal application provide the mechanism to ensure that senior management is aware of the activities of the RSC and the RSO. Senior management is copied on the RSC minutes and receives a summary briefing on licensed activities on a biennial basis.

Question #14:

Confirm that the Radiation Safety Committee will conduct safety evaluations of proposed users and uses.

Response:

Page 7, Item C.2 of the February 18, 1997 renewal application specifically states that the RSC is responsible for approving the procurement and use of all sources of licensed material. The information available for review by the committee of a new user is specified on page 24, Safety Evaluations of Proposed Uses and Users of the renewal application.

Question #15:

Confirm that the Radiation Safety Committee will develop procedures and criteria for training and testing each category of worker.

Response:

The RSC does not develop procedures and criteria for training and testing each category of worker. The RSO and staff develop these procedures and criteria for comment and approval by the RSC.

Question #16:

Confirm that the Radiation Safety Committee will establish methods for maintaining records of safety evaluations of proposed users and uses of licensed material.

Response:

The RSC is circulated on all routine audits performed by the Health Physics Supervisors. These audits verify approved users are following safety procedures and license requirements.

Question #17:

Please specify the minimum representation which will be required at each Radiation Safety Committee meeting, and the quorum requirement for voting. Confirm that your list of duties and responsibilities of the Radiation Safety Officer will address the following: a) to monitor and maintain absolute and other special filter systems, b) review and determine what radiation protection consulting services may be required, c) ensure the proper receipt, delivery, opening and shipment of radioactive material, d) ensure proper radioactive material storage, e) leak testing program, f) instrument calibration program, g) isotope inventory, h) the RSO can immediately terminate unsafe activities, I) decontamination and recovery operations, and j) the records as required by 10 CFR 30.51.

Response:

Each RSC meeting requires a simple majority for a quorum, excluding alternates. There is no minimal representation requirement for a meeting beyond the required quorum.

In addition to the qualifications and responsibilities detailed on pages 7 - 8 of the February 18, 1997 renewal application, the RSO will also address:

a. *Monitoring and maintaining absolute and other filter systems*
b. *Review and determine what radiation protection consulting services may be required*
c. *Ensure the proper receipt, delivery, and opening and shipment of radioactive materials*
d. *Ensure proper radioactive material storage*
e. *Maintain leak testing program of sealed sources*
f. *Instrument calibration program*
g. *Isotope inventory*
h. *Immediately terminate unsafe activities*
I. *Decontamination and recovery operations*
j. *Maintain records required by 10 CFR 30.51*

Question #18:

Confirm that the RSO will meet with/report to management and the RSC.

Response:

The RSO has and will continue to meet with and report to management and the RSC regarding licensed activities.

Question #19:

Provide a description of the duties and responsibilities of the radiation safety staff. This should include an assessment regarding staffing levels and qualifications of this support staff. The assessment should be sufficient to demonstrate that the technical staff are adequate to implement, support, and oversee your proposed radiation protection program. If current staffing is not what you consider adequate, a projected timetable when full staffing will be achieved should be included. A projection of future needs would also be useful.

Response:

The duties and qualifications of the Health Physics staff are described in detail on pages 7 - 11 of the February 18, 1997 renewal application. The current staff is technically qualified to implement, support and oversee the radiation protection program. Current staffing levels are adequate.

Question #20:

Describe your program for training and refresher training of all persons who handle licensed material or who frequent areas where licensed material is used. This training program must include a review of emergency procedures and response criteria and include sections that are tailored to various types of radiation and ancillary workers such as authorized users, laboratory supervisors and technicians; incinerator operators, waste compactor operators, and purchasing department personnel receiving licensed material; housekeeping, nursing, security, and other ancillary personnel; and the radiation safety office staff. Confirm that you will maintain records of initial and refresher training, that include a list of topic(s) covered, the amount of time spent and the date, the instructor(s) and student(s) names. The model training program in Appendix I of Regulatory Guide 10.5, Second Proposed Revision 2 (DG-0005) may be helpful in formulating your response.

Response:

The training program is described in detail on pages 11 - 13 of the February 18, 1997 renewal application. Specific training for various categories of personnel are tailored accordingly to align the topics covered with the departments needs. All initial and refresher training is documented.

Question #21:

Provide a description of the engineered provisions for abnormal operations in which the process systems are intended to provide for the maintenance of primary confinement, protection and control conventional hazards and control of effluents in the event of abnormal occurrences.

Response:

Primary confinement of concentrated solutions of radioactive materials is the purpose of the hot cells and their supporting engineered controls. Access to the interior of the hot cell is interlocked such that the inner door cannot be opened at the same time as the outer door. The ventilation system maintains the hot cell at a constant negative pressure compared to the room pressure. Pressure monitors are installed in each hot cell room and alarm if the hot cells loose pressurization and become positive to the room. The ventilation system is a once through system and is comprised of two parallel redundant filter trains with a fan motor. These filter banks are operated one at a time and are isolated by dampers. If a fan motor or filtration system fails, the second filter train can be manually started to maintain adequate ventilation. The ventilation is supplied with backup electrical power from an on-site generator. In the event of an abnormal occurrence, the hot cell construction and the redundant nature of the ventilation system and power supply provide sufficient confinement of hazardous materials and control of gaseous effluents. Abnormal occurrences resulting in liquid effluents are contained by the holding tank system described on page 14, paragraph 6 of the February 18, 1997 license renewal application.

Question #22:

Provide a description of the intended performance of the alarm systems and equipment provided to prevent releases of hazardous material. Provide a description of the alarm systems intended to alert operators to releases or to otherwise mitigate the consequences of releases. Consider the range of detection of the monitors, the type of alarms, the presence of annunciators, alarm setpoints. Are engineered safety features present to preclude large releases of radioactivity in the event of an accident? Can these engineered safety features be activated both automatically and manually?

Response:

The hot cell negative pressure alarms are discussed above in question #21. Ambient room radiation alarms are discussed on page 14, paragraph 8 of the February 18, 1997 license renewal application. HVAC status is monitored by a panel in the Health Physics Office. This panel indicates which fan motors are currently in operation and alarms if a fan motor fails. Fire alarm panel is also located in the corridor of the first floor of Building 124. This panel monitors the status of all smoke and heat detectors and indicates the location of any alarms. A panel in the south warehouse of Building 124 monitors and controls the holding tank liquid effluent system.

Engineered features that are in place to preclude large releases of radioactivity are summarized in Item #9 of the February 18, 1997 license renewal application. Further detail is given in Question #21 above. These redundant features are always in operation and do not need to be activated in the event of an abnormal occurrence. Specific pieces of equipment (i.e. filter trains, holding tanks) are controlled manually.

Question #23:

Provide a schematic drawing showing the location of the sample cartridge and the stack alarm detector. Paragraph #5 on page 1-8 states: "The radioactivity in the sampler is constantly measured by the stack alarm detector which will sound an alarm in the Health Physics operations area should the integrated activity representing the 24 hour effluent limit for I-131 as specified in Appendix B, Table II, Column I of 10 CFR 20 be exceeded." Provided specific details about the stack alarm detector, and specify whether the alarm setpoint(s) interact with the HVAC system.

Response:

A schematic of the sample cartridge and the stack detector is attached (see Attachment 5). The stack monitor for Building 124 is a Ludlum Model 365 Stack Monitor consisting of two detector assemblies that monitor filters accumulating particulate and gaseous effluents from the stack stream. It is located in the second floor machine room adjacent to the exterior wall. A sample is collected from the stack duct just prior to the stack duct exits the interior of the building. The alarm set points on the stack monitor do not interact with the HVAC system.

Question #24:

Condition I on page 2-2 states: "Remote monitoring detectors located in manufacturing locations would inform Health Physics operational personnel of areas with radiation levels of 50 mR/hr." Describe how these remote monitors interface with the HVAC system.

Response:

The remote monitoring detectors do not monitor the HVAC system nor do they interface with that system. They measure ambient radiation levels in operational work areas.

Question #25:

Item A.3. on page 2-1 describes a scenario where some of the free iodine has a potential to escape to the environment through the cave hallway area and outside door. Provide an estimate of the fraction of the release that might be released from this unmonitored pathway.

Response:

An 8 curie vial containing approximately 1.5 milliliters of sodium iodide is dropped in the hallway outside the hot cell. Approximately 5 curies of sodium iodide is spilled from the vial, 4.5 curies volatilizes in the fire. Approximately 4 curies of this amount is drawn into the air system in the form of smoke and free iodine. The airflow in the area is into the hot cells since they are negative to the hallway. The volatile iodine and smoke is drawn into the hot cell pass through into the ventilation system. Of the remaining 0.5 curies, 90% plates out on the surface in the form of smoke and free iodine. The remaining 0.05 curies migrates into the mechanical area between the ceiling and the second floor, down the hall into the front corridor, and up the hall towards the outside door. The majority (~ 90%) rises to the ceiling due to the heat from the fire. The remaining 45 millicuries is equally split traveling up and down the hallway, plating out as it travels. Approximately 5 millicuries may reach the first of two doors to the environment. These doors are interlocked so that they both cannot be opened at the same time. One millicurie may reach the environment by this pathway for a release fraction of 1.25×10^{-4}. A release to the environment of this type is highly unlikely since all exterior building doors, when opened, would remain negative to the environment.

ATTACHMENTS

1. Bldg. 124 Exhaust Air Flow Study Diagram - South End (D-26984)
2. Bldg. 124 Exhaust Air Flow Study Diagram - North End (D-26985)
3. GRP-31, *Mission, Scope, and Major Activities of the Radiation Safety Committee*
4. Interoffice Memorandum from the President of Technical Operations
5. Schematic of Bldg. 124 Stack Monitor