ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

BRIEFING BOOK

November 8-9, 2000

U.S. Nuclear Regulatory Commission
Rockville, MD

DF03

ACMUI Briefing Book
November 8-9, 2000

1. Agenda
2. ACMUI Charter
3. Federal Register Notice
4. Minutes: October 20, 1999, ACMUI meeting
5. NRC Medical Policy Statement
6. Part 35: Status and Implementation
7. Initiatives: Risk-informed and Performance-based
8. Board Certification
9. Intravascular Brachytherapy
10. New Technology
11. Charter: Mallinckrodt Lessons Learned
12. Charter: NRC/Agreement State Working Group on Event Reporting
13. Update: Other Rulemaking Activities
14. ACMUI Self-evaluation Criteria

ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

November 8 - 9, 2000

U.S. Nuclear Regulatory Commission
Two White Flint Building - T2B3
Rockville, Maryland

AGENDA

November 8, 2000

8:00 am - 8:30 am	Annual Ethics Briefing (closed session) — John Szabo, Office of General Counsel
8:30 am - 9:00 am	Personnel/Administrative Issues (closed session)— Robin Avent, Joyce Riner
9:00 am - 9:15 am	Opening Remarks and Award of Appreciation Certificate to Louis Wagner, ACMUI Medical Physicist — Donald Cool, Director, Division of Industrial and Medical Nuclear Safety
9:15 am - 9:45 am	Status of Part 35 Rulemaking — Catherine Haney, Tom Young
9:45 am - 10:00 am	*BREAK*
10:00 am - 10:30 am	Implementation of Part 35 — Roberto Torres
10:30 am - 11:00 pm	Status update on NRC's new process to recognize certification boards - Sam Jones
11:00 am - 11:30 am	NRC Initiatives: Risk-informed — Lawrence Kokajko
11:30 am - 12:00 am	NRC Initiatives: Performance-based — Jim Smith
12:00 pm - 1:00 pm	*LUNCH*
1:00 pm - 3:00 pm	Intrasvascular Brachytherapy — Robert Ayres
3:00 pm - 3:15 pm	*BREAK*
3:15 pm - 4:45 pm	New Technology — Diane Case
4:45 pm - 5:00 pm	Open Discussion
5:00 pm	*ADJOURN*

ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

November 8 - 9, 2000

U.S. Nuclear Regulatory Commission
Two White Flint Building - T2B3
Rockville, Maryland

AGENDA

November 9, 2000

8:30 am - 9:15 am	NRC Lessons Learned: Mallinckrodt Exposure Events — Cynthia Pederson
9:15 am - 10:00 am	NRC/Agreement State Working Group on Event Reporting — Kevin Ramsey
10:00 am - 10:15 am	*BREAK*
10:15am - 10:45 am	Update on other rulemaking activities
10:45 am - 11:00 am	Self-evaluation Criteria for ACMUI — Betty Ann Torres
11:00 am - 11:45 pm	Open Discussion: next meeting dates, agenda topics, etc.
11:45 am - 12:00 pm	Summary of Meeting — Dr. Manuel Cerqueira
12:00 pm	*ADJOURN*

UNITED STATES NUCLEAR REGULATORY COMMISSION
CHARTER FOR THE ADVISORY COMMITTEE ON MEDICAL USES OF ISOTOPES
(Pursuant to Section 9 of Public Law 92-463)

1. **Committee's Official Designation**:

   Advisory Committee on the Medical Uses of Isotopes

2. **Committee's objectives, scope of activities and duties are as follows**:

   The Committee provides advice, as requested by the Director, Division of Industrial and Medical Nuclear Safety, Office of Nuclear Material Safety and Safeguards, on policy and technical issues that arise in regulating the medical use of byproduct material for diagnosis and therapy. The appointed Chairman of the Committee will conduct all meetings and will prepare minutes summarizing the deliberations of each meeting. The minutes will include the Committee's recommendations for future actions. Subcommittees may be convened to address specific problems when it is not necessary for the full Committee to be present.

3. **Time period (duration of this Committee)**:

   From April 4, 2000, to April 4, 2002

4. **Official to whom this Committee reports**:

   Donald A. Cool, Director
   Division of Industrial and Medical Nuclear Safety
   Office of Nuclear Material Safety and Safeguards
   U.S. Nuclear Regulatory Commission
   Washington, DC 20555

5. **Agency responsible for providing necessary support to this Committee**:

   U.S. Nuclear Regulatory Commission

6. **The duties of the Committee are set forth in Item 2 above**.

7. **Estimated annual direct cost of this Committee**:

   a. $161,000.00 (includes travel, per diem, and compensation)

   b. Total staff-year of support: 1.5 FTE

8. **Estimated number of meetings per year:**

Three meetings per year except when active rulemaking is conducted, then five meetings per year.

9. **The Committee's termination date.**

April 4, 2002

10. **Filing date:**

April 3, 2000

Andrew L. Bates
Advisory Committee Management Officer
Office of the Secretary of the Commission

[Federal Register: September 25, 2000 (Volume 65, Number 186)]
[Notices]
[Page 57628-57629]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr25se00-93]

NUCLEAR REGULATORY COMMISSION

Advisory Committee on the Medical Uses of Isotopes: Meeting Notice

AGENCY: U.S. Nuclear Regulatory Commission.

ACTION: Notice of meeting.

SUMMARY: The U.S. Nuclear Advisory Commission (NRC) will convene a meeting of the Advisory Committee on the Medical Uses of Isotopes (ACMUI) on November 8-9, 2000. The meeting will take place at the address provided below. Topics of discussion will include: (1) The status of the rulemaking of 10 CFR part 35, ''Medical Use of Byproduct Material''; (2) the implementation plan for Part 35; and (3) issues concerning intravascular brachytherapy. An update of other rulemaking activities will be provided. The ACMUI will also discuss: (1) The criteria for ACMUI self-evaluation; (2) NRC's Strategic Plan; and (3) the planning, budget, and performance measures process. All sessions of the meeting will be open to the public, with the exception of the first session, which will be closed to provide required Annual Ethics Training for ACMUI committee members and to discuss information that, if released for public view, would constitute a clearly unwarranted invasion of personal privacy.

DATES: The November 8, 2000, meeting will be held from 9 a.m. to 5 p.m., to accommodate Annual Ethics Training for members from 8 to 9 a.m. The November 9, 2000, meeting will be held from 8 a.m. to 12 p.m.

ADDRESSES: U.S. Nuclear Regulatory Commission, Two White Flint North Auditorium, 11545 Rockville Pike, Rockville, MD 20852-2738.

FOR FURTHER INFORMATION, CONTACT: Betty Ann Torres, telephone (301) 415-0191, e-mail bat@nrc.gov, of the Office of Nuclear Material Safety and Safeguards, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001.

Conduct of the Meeting

Manuel D. Cerqueira, M.D., will chair the meeting. Dr. Cerqueira will conduct the meeting in a manner that will facilitate the orderly conduct of business. The following procedures apply to public participation in the meeting:

1. Persons who wish to provide a written statement should submit reproducible copy to Betty Ann Torres (address previously listed), by November 1, 2000. Statements must

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pertain to the topics on the agenda for the meeting.

2. Questions from members of the public will be permitted, during the meeting, at the discretion of the Chairman.

3. The transcript and written comments will be available for inspection, and copying, for a fee, at the NRC Public Document Room,

11555 Rockville Pike, Rockville, MD 20852-27382, telephone (800) 397-4209, on or about December 6, 2000. Minutes of the meeting will be available on or about January 8, 2000.

4. Seating for the public will be on a first-come, first-served basis.

This meeting will be held in accordance with the Atomic Energy Act of 1954, as amended (primarily Section 161a); the Federal Advisory Committee Act (5 U.S.C. App); and the Commission's regulations in Title 10, U.S. Code of Federal Regulations, Part 7.

Dated: September 19, 2000.
Andrew L. Bates,
Advisory Committee Management Officer.
[FR Doc. **00-24577 Filed** 9-22-**00**; 8:45 am]
BILLING CODE 7590-01-P

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

December 17, 1999

MEMORANDUM TO: Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety
Office of Nuclear Material Safety
and Safeguards

FROM: Manuel D. Cerqueira, M.D., Chairman
Advisory Committee on the
Medical Uses of Isotopes

SUBJECT: CERTIFICATION OF THE MINUTES OF THE OCTOBER 20, 1999 MEETING OF THE ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

I hereby certify that, to the best of my knowledge and belief, the attached minutes for the meeting of the Advisory Committee on the Medical Uses of Isotopes (ACMUI) held on October 20, 1999, are an accurate record of the proceedings for that meeting.

Manuel D. Cerqueira, M.D., Chairman

12/17/99
Date

Attachment: Minutes - ACMUI mtg.
October 20, 1999

FINAL: December 15, 1999

SUMMARY MINUTES
ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

October 20, 1999

The Advisory Committee on the Medical Uses of Isotopes (ACMUI) held a meeting in Rockville, Maryland on October 20, 1999. A briefing book was provided to the ACMUI members and is available through the Public Document Room.

ACMUI members present at the meeting were:

Manuel Cerqueira, M.D., Acting Chair, representing nuclear cardiology and nuclear medicine
Nikita Hobson, representing patients' rights
Ruth McBurney, M.S., CHP, representing the states' interests
Louis K. Wagner, Ph.D., representing medical physics

Invited guests present at the meeting were:

Dennis P. Swanson, M.S., B.C.N.P, representing nuclear pharmacy

Nuclear Regulatory Commission staff present at the meeting were:

Cathy Haney, Acting Branch Chief, Rulemaking and Guidance Branch (RGB), Division of Industrial and Medical Nuclear Safety (IMNS), NMSS and Chair of the Part 35 Working Group
Donald Cool, Ph.D., Director, IMNS, NMSS

Part 35 Working Group Members present at the meeting were:

Diane Flack, RGB, IMNS
Penny Lanzisera, Region I
Barry Siegel, M.D., medical consultant to the Part 35 Working Group

OPENING REMARKS

Ms. Cathy Haney, Designated Federal Official for the Committee, opened the meeting at 2:00 p.m. with general comments on the meeting agenda and the function of the ACMUI. Ms. Haney noted that the meeting was announced in the Federal Register on October 5, 1999. She stated that any ACMUI member who becomes aware of a potential conflict of interest during the course of the meeting should state it for the record and recuse themselves from that particular aspect of the discussion. She also stated that she had reviewed the Committee members' financial and

employment interests, and had not identified any conflict of interest with the items to be discussed during the meeting.

Donald A. Cool, Ph.D., made opening remarks to the Committee. Dr. Cool said that the agenda of the meeting was focused on preparing for the ACMUI's briefing of the Commission on the revision of Part 35 the next day. He noted that the briefing is a public opportunity for the Commission to hear from the staff and the ACMUI about the revision of Part 35, and any particular issues that the advisory committee might want to bring to their attention. Dr. Cool also noted that earlier that day the Commission was briefed by the Organization of Agreement States (OAS). The OAS briefing included a presentation by Dave Walter, Chair of the Conference of Radiation Control Program Directors, Inc., SR-6 Committee that is developing the Suggested State Regulations for medical licensees. Dr. Cool reported that Mr. Walter's presentation highlighted several issues where the recommendations of the SR-6 Committee are not the same as those of the Part 35 Working Group.

SELF EVALUATION OF THE ACMUI

Ms. Haney provided background on the process and need for self-evaluation of the NRC's advisory committees. In 1998 the Commission requested that all the advisory committees develop self-evaluation criteria. The other advisory committees have already provided their self-evaluations to the Commission, but the ACMUI has had to delay their self-evaluation because of the Committee's extensive involvement with the revision of Part 35.

The committee discussed responses to the following self-evaluation criteria:

1. Does the staff and the ACMUI interact in such a manner as to satisfactorily address issues before the Commission?
2. Do the Committee members clearly define issues for staff and provide timely, useful objective information to the staff when requested?
3. Does the Committee provide critical review and oversight of issues?
4. Does the Committee provide expertise/advice which is not available from within the agency?
5. Does the Committee meet frequently enough to address issues in a timely manner? Are any changes needed to the meeting frequency?
6. Do Committee members bring issues from all elements of the medical community to the attention of NRC staff?
7. Does the Committee facilitate/foster communication between the public/medical community and NRC?
8. Does the Committee consider current resource constraints of the NRC when recommending new or enhanced regulatory programs?
9. Does the Committee make effective use of subcommittees to assist the staff on specific tasks or projects?
10. Does the scope and size of the Committee meet the current needs of NRC?

Draft responses to the above questions were developed and are to be provided to all the ACMUI members for review and comment prior to being finalized and forwarded to the Commission.

During the discussion of the criteria, Dr. Wagner noted that the selection process for ACMUI members results in a long lead time between when a position is vacated and filled. He feels that if the positions were filled more promptly, the ACMUI would be more effective and efficient. Ms. Haney noted that the process is underway to fill the currently vacant positions. She also noted that there is always the option of inviting someone to participate in the committee's meetings if expertise is needed in a specific area. She said that she would note this concern in the self-evaluation that would be forwarded to the Commission.

DISCUSSION OF STAFF'S VIEWGRAPHS FOR THE OCTOBER 21 COMMISSION BRIEFING

Ms. Haney went over the staff's viewgraphs (see Attachment 1) for the Commission briefing to assist the ACMUI members in preparing their own presentation. She said that her presentation would focus on key issues where the Commission either had concerns or specific questions, or where the stakeholders had concerns that needed to be brought to the attention of the Commission. She noted where the staff's recommendations had changed since the last Commission briefing in March 1999, e.g., the training and experience requirements no longer include an examination. She also noted where the draft final requirements were different from the Suggested State Regulations being developed by the SR-6 Committee.

DISCUSSION OF ACMUI'S PRESENTATION AT THE OCTOBER 21 COMMISSION BRIEFING

Dr. Cergueira opened the discussion of the ACMUI's presentation for the Part 35 Commission briefing the next day. The ACMUI had previously developed their viewgraphs, so the discussion focused on the actual presentation that would accompany the viewgraphs (see Attachment 2).

Radiation Safety Committee (RSC). ACMUI endorsed the requirement for an RSC for two or more different types of uses under Subparts E, F, and H or two or more types of units under Subpart H. Dr. Cerqueira noted that the requirement would allow the single use physician to act as his own radiation safety officer (RSO). Dr. Wagner reported that it is administratively much easier for physicists and radiation safety individuals to justify the establishment of a committee when there is a regulatory requirement. Therefore, the requirement for an RSC is important when you have higher-risk situations.

Training and Experience. The ACMUI endorsed the alternative pathway for training and experience and the 80 hour requirement for physicians who only use I-131. Dr. Siegel noted that even if the Commission approves the training and experience requirements in the draft final rule, in the near future they will have to establish training and experience requirements for intravascular brachytherapy and other emerging technologies.

Medical Event. It was noted that the ACMUI had endorsed the dose thresholds for medical events at their March 1999 meeting. Ms. Haney pointed out that two of the biggest issues associated with medical events were patient intervention and wrong treatment site, both of which the ACMUI had previously determined were adequately addressed in the draft revised rule.

Reporting Threshold for Reporting Exposure to an Embryo/Fetus/Nursing Child. Dr. Wagner pointed out the importance of recognizing that an exposure to an embryo/fetus as a result of medical exposure of the mother has to be evaluated with the full recognition that a woman who

is sick happens to be pregnant. The sick woman and the embryo/fetus can not be treated independently. He further said that this situation can not be compared to exposure of an embryo of a working mother or to exposure of a member of the general public. In addition, he pointed out that it is important that the threshold is appropriate for all stages of pregnancy. Ms. Haney said that it would be helpful if the ACMUI provided the Commission with information on how this reporting requirement would impact medical care. ACMUI members then discussed the impact on medical care, including standards of practice for pregnancy testing, the financial impact of pregnancy testing, unduly alarming pregnant women by notifying them of low exposures to an embryo or fetus, patient-physician confidence, increased regulatory burden, and the relationship of the threshold for reporting to safety considerations. Ms. Haney noted that after this requirement was final in Part 35, NRC would consider whether a similar requirement should be in Part 20 or Parts 30, 40, and 70.

Notification Following a Medical Event or Exposure of an Embryo/Fetus or Nursing Child. Ms. Haney said that the issue for discussion is what assurance does NRC need in order to assure that a patient is informed following a medical event or exposure of an embryo/fetus or nursing child. Page 28 of the staff's viewgraphs for the Commission briefing provide alternative rule text for § 35.3045 that requires the licensee to notify both the referring physician and the individual, but does not require the licensee to provide a written report to the individual. Instead, the licensee would be required to certify that they had notified the referring physician and individual. This alternative text was not included in the draft final rule, but was provided to the Commission in response to the SRM for the March 1999 briefing on Part 35.

Ms. Hobson questioned the purpose of notifying a patient if there is no possibility that harm was done to them. In particular, if you are a cancer patient and are already fighting for your life, there is no reason to put an additional burden on the patient if no harm was done as a result of the misadministration. Unless there is scientific documentation that the misadministration or medical event is going to cause harm, she said that the act of notifying the patient is harmful because it increases the stress level, raises all kinds of other worries, and erodes the patient-physician relationship. The patient becomes less confident that the medical community can take care of their illness. However, she said that she does not have a problem with notifying NRC.

While the ACMUI does not support any regulation requiring notification of physicians and patients, since this is redundant with existing standards of care, the Committee did prefer the alternative rule text provided by staff over the existing requirements. Dr. Wagner moved that the Committee agree with the alternative rule text with regard to notification, with a change in the phraseology in (d)(vii) to indicate that the licensee certifies that they have complied with paragraph (e), i.e., both the referring physician and the individual have been notified. Ms. Hobson seconded the motion. Prior to voting, Ms. Hobson made a final comment that patient notification is not a good idea. However, she would reluctantly support the alternative rule text, rather than the current rule, if a notification requirement is included in the revised rule. The Committee unanimously approved the motion.

Implementation Issues. Ms. Haney updated the Committee on the status of the guidance document being developed along with the Part 35 rulemaking. She pointed out that the guidance document would not be used to implement "de facto" regulations. The benefit of the NUREG would be to provide model procedures for licensees that are less sophisticated than some of the larger licensees, while also providing flexibility for licensees to use different types of procedures. She also clarified the difference between "should" and "shall." "Should" means that

it is a good practice, but there is no regulatory requirement to do it. "Shall" means that there is a regulatory requirement to do something.

Dr. Wagner voiced concern that a mind-set change would be needed to be able to adequately enforce the new regulations because of their lack of prescriptiveness. He indicated that the Committee really had to reinforce to the Commission that it was going to be a challenge for NRC staff to just look at the licensee's performance, and just base their findings on performance and not on the details in the licensee's own procedures about how to do things. He also noted that ACMUI subcommittees would be useful in the development of revised inspection procedures. Ms. Haney then updated the Committee on the proposed pilot program for performance-based inspections in the medical area. Under the draft proposed inspection program, inspectors would not routinely look at licensees' procedures. Inspectors would only ask to see procedures if a major outcome, such as a misadministration or medical event, had occurred. She also indicated that the draft proposed inspection program will need Commission approval prior to implementation.

Dr. Cerqueira adjourned the meeting at 5:00 p.m.

NRC NEWS

U.S. NUCLEAR REGULATORY COMMISSION

Office of Public Affairs **Telephone: 301/415-8200**

Washington, DC 20555-001 **E-mail: opa@nrc.gov**

Web Site: http://www.nrc.gov/OPA

No. 00-115 July 26, 2000

NRC REVISES POLICY STATEMENT ON MEDICAL USES OF CERTAIN RADIOACTIVE MATERIALS

The Nuclear Regulatory Commission has revised its 1979 policy statement on the medical uses of NRC-regulated radioactive material to put greater emphasis on higher risk procedures, and correspondingly less emphasis on procedures posing lower risk to the patient, workers and the public.

The policy statement affirms the Commission's determination to continue its role in regulating the use of certain radioactive material in medicine with the goal of providing adequate radiation protection for workers, the public, and patients. The policy statement focuses the Commission's direction on radiation safety issues and furthers the objective of utilizing industry and professional standards that define acceptable levels of radiation safety.

The policy statement and amended regulations on the medical use of certain radioactive material, which will be announced separately, result from the NRC's detailed examination of its medical use program during the last several years.

One purpose of NRC regulation of the medical use of certain radioactive material is to reduce unnecessary radiation exposure to patients, workers, and the public. The focus of NRC regulation to protect the patient's health and safety is primarily to ensure that the physician's directions are followed as they pertain to the administration of radiation or of NRC-regulated radioactive material, rather than to non-radiation aspects of the administration. Although the Commission recognizes that physicians have primary responsibility for the protection of their patients, NRC also has a necessary role in the radiation safety of patients. NRC regulations are based on the assumption that properly trained and adequately informed physicians will make decisions that are in the best interest of their patients.

NRC established a working group of agency staff and state organization representatives to develop the revised policy statement. The group held a series of workshops and meetings over a two-year period. To ensure that a wide variety of interests were represented, invited workshop participants included physicians, radiopharmacists, medical physicists, radiation safety officers, educators, patients rights advocates, nurses, medical technologists, hospital administrators, representatives of state and federal governments, and radiopharmaceutical manufacturers. The revised policy statement takes into account written comments on the statement as proposed in the Federal Register, and those obtained during the workshops and meetings.

The revised medical policy contains the following statements:

"(1) NRC will continue to regulate the uses of radionuclides in medicine as necessary to provide for the radiation safety of workers and the general public." Retention of this portion of the previous policy statement affirms the Commission determination that it will continue its role of regulating the use of certain radioactive material in medicine, with the goal of providing radiation safety for workers, the public, and patients.

"(2) NRC will not intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public." This sentence is based on the third statement of the previous medical policy statement. It substitutes the phrase "will not intrude" for the previous "will minimize intrusion."

"(3) NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions." This statement makes clear that the focus of NRC regulation is primarily on ensuring that physician's directions, as they pertain to the administration of radiation or of NRC-regulated radioactive material, are followed. It also reflects the Commission's strategy of decreasing oversight of those uses of certain nuclear materials that pose the lowest radiological risks and strengthens emphasis on those posing higher risks.

"(4) NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety." The revision incorporates NRC's intention to consider industry and professional standards in developing regulations and guidance for the medical use program.

The policy statement will be published shortly in the Federal Register, and will be available at the agency's Public Document Room in Washington, D.C., telephone 202-634-3273.

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[NRC Home Page | News and Information | E-mail]

<PRE>
[Federal Register: August 3, 2000 (Volume 65, Number 150)]
[Rules and Regulations]
[Page 47654-47660]
From the **Federal Register** Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr03au00-2]

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NUCLEAR REGULATORY COMMISSION
10 CFR CH. I
Medical Use of Byproduct Material; Policy Statement, Revision

AGENCY: Nuclear Regulatory Commission.

ACTION: Final policy statement; revision.

SUMMARY: The Nuclear Regulatory Commission (NRC) is revising its 1979 policy statement on the medical use of byproduct material. These revisions are one component of the Commission's overall program for revising its regulatory framework for medical use, including its regulations that govern the medical use of byproduct material. The overall goals of this program are to focus NRC regulation of medical use on those medical procedures that pose the highest risk and to structure its regulations to be risk-informed and more performance-based, consistent with NRC's ``Strategic Plan for Fiscal Year 1997-Fiscal Year 2002.'' The policy informs NRC licensees, other Federal and State agencies, and the public of the Commission's general intentions in regulating the medical use of byproduct material.

EFFECTIVE DATE: August 3, 2000.

FOR FURTHER INFORMATION CONTACT: Thomas Young, Office of Nuclear Material Safety and Safeguards, Nuclear Regulatory Commission, Washington, DC 20555-0001, telephone (301) 415-5795, E-Mail: tfy@nrc.gov or Marjorie U. Rothschild, Office of the General Counsel, Nuclear Regulatory Commission, Washington, DC, 20555-0001, telephone (301) 415-1633, E-Mail: mur@nrc.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In 1979, the NRC published a policy statement, ``Regulation of the Medical Uses of Radioisotopes,'' (44 FR 8242, February 9, 1979) in which it informed NRC licensees, other Federal and State agencies, and the public of the Commission's general intention in regulating the medical use of byproduct material. Specifically,

1. The NRC will continue to regulate the medical uses of radioisotopes as necessary to provide for the radiation safety of workers and the general public.

2. The NRC will regulate the radiation safety of patients where justified by the risk to patients and where voluntary standards, or compliance with these standards, are inadequate.

3. The NRC will minimize intrusion into medical judgments affecting patients and into other areas traditionally considered to be a part of the practice of medicine.

NRC activities in the medical area, such as promulgation of regulations and development of regulatory guidance, as well as cooperative relationships with other Federal agencies, have been guided by this policy.

On August 6, 1997 (62 FR 42219-42220), NRC published a document in the **Federal Register**, ``Medical Use of Byproduct Material: Issues and Request for Public Input,'' describing NRC's detailed, four-year examination of the issues surrounding its medical use program. This process started with a 1993 internal senior management review; continued with a 1996 independent external review by the National Academy of Sciences' (NAS) Institute of Medicine (IOM); and culminated in NRC's Strategic

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Assessment and Rebaselining Project (SA). Since that **Federal Register** document was issued, NRC conducted an exhaustive and public review of the medical use program. Specifically, in 1997 and 1998, NRC's current and future role in regulating the medical use of byproduct material was discussed at meetings of the Advisory Committee on Medical Uses of Radioisotopes \1\ (ACMUI) and the Organization of Agreement States (OAS), and with various professional societies and government agencies. During this period, the NRC staff also presented four alternative proposed revised versions of the 1979 Medical Policy Statement (MPS) to participants at NRC sponsored workshops and public meetings. These workshops and public meetings also included discussions on the major areas that were being considered for revision in 10 CFR Part 35, ``Medical Use of Byproduct Material.''

\1\ The ACMUI advises the Commission on regulating and licensing uses of radionuclides in medicine.

On August 13, 1998 (63 FR 43580), a proposed revision to the MPS was published in the **Federal Register** for a 90 day public comment period. This comment period was later extended 30 days, to December 16, 1998, (63 FR 64829; November 23, 1998) to allow additional time for public, stakeholder, and State comments. In addition, to allow for wide participation in the process, NRC discussed the proposed revision of the MPS with interested individuals and organizations at 3 public meetings during the comment period (San Francisco, California, on August 19 and 20, 1998; Kansas City, Missouri, on September 16 and 17, 1998; and Rockville, Maryland, on October 21 and 22, 1998).

NRC received 42 specific comments on the proposed MPS from various organizations and individuals. These comments were extracted from the transcripts of the 3 public meetings and the 10 written comment letters submitted in response to the **Federal Register** document. Additional details about the comments are provided in Section IV, ``Discussion of Public Comments.'' These comments were similar to the comments that were discussed in the August 13, 1998 (63 FR 43582-43583), **Federal Register**. Based on NRC's consideration of all the

comments, no changes to the proposed MPS are being made. (See the final statements that appear in Section II, below.)

II. Statement of General Policy

This NRC policy statement informs NRC licensees, other Federal and State agencies, and the public of the Commission's general intentions regarding the regulation of the medical use of byproduct material. The current revision of 10 CFR part 35 is based on this statement of NRC policy. The Commission expects that future NRC rulemaking activities in the medical area and future NRC involvement with other Federal and State agencies will follow this statement of policy. This NRC policy promotes a more risk-informed approach to regulation of byproduct material.

The following is the final Medical Use Policy Statement to guide NRC's future regulation of the medical use of byproduct material.

1. NRC will continue to regulate the uses of radionuclides in medicine as necessary to provide for the radiation safety of workers and the general public.
2. NRC will not intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public.
3. NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions.
4. NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety.

III. Rationale

NRC's principal statutory authority for regulating medical use of byproduct material is at sections 81, 161, 182, and 183 of the Atomic Energy Act of 1954, as amended (AEA). See 42 U.S.C. 2111, 2201, 2232, and 2233. Section 81 of the Act prohibits, without NRC authorization, the manufacture, production, transfer, receipt in interstate commerce, acquisition, ownership, possession, import, and export of byproduct material (42 U.S.C. 2111). Specifically, section 81 of the AEA provides in pertinent part that:

> The Commission shall not permit the distribution of any byproduct material to any licensee, and shall recall or order the recall of any distributed material from any licensee, who is not equipped to observe or who fails to observe such safety standards to protect health as may be established by the Commission or who uses such material in violation of law or regulation of the Commission or in a manner other than as disclosed in the application therefor or approved by the Commission. Id. (emphasis added).

By virtue of section 161 of the Act, the Commission is authorized to undertake a variety of measures ``(in) the performance of its functions" (42 U.S.C. 2201). As stated in subsection b, the Commission may ``establish by rule, regulation, or order, such standards and instructions to govern the possession and use of special nuclear material, source material, and byproduct material as the Commission may deem necessary or desirable * * * to protect health or to minimize danger to life or property" (42 U.S.C. 2201(b) (emphasis added)). Similarly, section 161.i. authorizes the Commission to ``prescribe such regulations or orders as it may deem necessary" to ``(3) govern any activity authorized pursuant to this Act, including standards and restrictions governing the design, location, and operation of facilities used in the conduct of such

activities, in order to protect health and minimize danger to life or property" (42 U.S.C. 2201(I) (emphasis added)).

The Commission is bound by statute to regulate byproduct material (as well as source and special nuclear material) to ``protect health and minimize danger to life.'' This statutory standard applies to the myriad of uses of byproduct material, including not only medical use, but also, for example, radiography and irradiators. However, the Commission is not bound by the limitation in section 104.a. of the AEA, which is often mistakenly cited for the proposition that, in regulating the medical use of byproduct material, the AEA requires that the Commission ``impose the minimum amount of regulation consistent with its obligations under this Act to promote the common defense and security and to protect health and safety of the public'' (42 U.S.C. 2134(a)). This ``minimum regulation'' limitation does not apply to the medical use of byproduct material which falls within NRC's broad standard-setting authority in sections 81 and 161. Section 104.a., on its face, applies only to medical therapy licenses for ``utilization facilities'' (e.g., reactors) and ``special nuclear material.'' This ``minimum regulation'' directive does not govern the Commission's regulation of the medical use of byproduct material.

For the most part, the regulations to carry out the broad statutory scheme for byproduct materials are set forth in 10 CFR parts 30 through 39. In addition, the public and occupational dose limits in 10 CFR Part 20, ``Standards for Protection Against Radiation,'' apply whether the use of byproduct material is for medical or other purposes. However, the scope of Part 20 as stated in

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Sec. 20.1002 is that, ``[t]he limits in this part do not apply to doses due * * * to any medical administration the individual has received or due to voluntary participation in medical research programs.'' The Commission has clarified that ``the medical administration of radiation or radioactive materials to any individual, even an individual not supposed to receive a medical administration, is regulated by the NRC's provisions governing the medical use of byproduct material rather than by the dose limits in the NRC's regulations concerning standards for protection against radiation'' (``Medical Administration of Radiation and Radioactive Materials,'' 60 FR 48623; September 20, 1995). Thus, the Commission believes that ``an administration to any individual is and should be subject to the regulations in part 35'' (60 FR 48623).

The provisions of part 30, ``Rules of General Applicability to Domestic Licensing of Byproduct Material'' ``are in addition to * * * other requirements in this chapter'' (Sec. 30.2). This section requires that ``any conflict between the general requirements in part 30 and the specific requirements in another part'' are governed by those specific requirements (Sec. 30.2). The regulations in part 35 are designed ``to provide for the protection of the public health and safety'' and reflect the broad statutory standard in the AEA, discussed above (Sec. 35.1). The Commission has determined that, as a matter of policy, ``the patient * * * as well as the general public * * * are all members of the public to be protected by NRC'' (44 FR 8242, at 8244).

IV. Discussion of Public Comments

As previously noted, NRC received 42 comments on the proposed revision to the MPS, taken from 10 letters that were submitted and from the transcripts of the 3 public meetings. NRC received verbal comments on the proposed MPS (63 FR 43580; August 13, 1998) from stakeholders (e.g., physicians, medical physicists, nuclear medicine technologists, and radiation safety professionals) during the public meetings that were held in August, September, and

October 1998. Stakeholders also submitted written comments to NRC in response to that **Federal Register** document.

NRC has reviewed all comments, identified the issues raised by the commenters, and combined comments where appropriate. The following discussion includes these issues, the combined comments, and the NRC responses to these combined comments.

General Comments

Issue 1: Absent Harm, What Is the Purpose of NRC Regulation?

Comment. A commenter stated that only physicians can determine what is unnecessary radiation exposure to patients. This commenter cited the ``Rationale'' portion of the August 13, 1998 (63 FR 43584) document about the responsibility of NRC to regulate actual medical use of byproduct material from the standpoint of reducing unnecessary radiation exposures. According to the commenter, ``If the patient exposure is unnecessary and harm is done, then the physician may be guilty of malpractice (monetary awards, civil penalties, possible loss of medical license, etc.). NRC regulations won't prevent malpractice and NRC penalties are the least of the guilty physician's worries. If the patient exposure is unnecessary but no harm is done, then the physician may be still guilty of fraud (billing for unnecessary procedures). But if no harm is done, what is the purpose of NRC regulation?''

Response. The purpose of NRC regulation of the medical use of byproduct material is to reduce unnecessary radiation exposure to patients, workers, and the public. Protection of patient radiation safety is an overall goal in regulating the medical use of byproduct material. The focus of NRC regulation to protect the patient's health and safety is primarily to ensure that the authorized user physician's directions are followed as they pertain to the administration of the radiation or radionuclide, rather than to other, non-radiation related aspects of the administration. Although the Commission recognizes that physicians have primary responsibility for the protection of their patients, NRC also has a necessary role with respect to the radiation safety of patients. NRC regulations are predicated on the assumption that properly trained and adequately informed physicians will make decisions that are in the best interests of their patients. Moreover, there is nothing in the Commission's regulatory approach to medical use regulation that would in any way modify the legal rules governing malpractice suits arising out of the medical use of byproduct material.

Issue 2: Should the MPS Be Revised More Frequently?

Comment. A commenter noted that the proposed revision is an improvement over the 1979 MPS; however, the commenter recommended that the NRC review the MPS more frequently (e.g., every 10 years).

Response. How often the Commission reviews and/or revises the MPS depends on a variety of factors. These factors may be internal, such as the need for a change in the focus of NRC's regulations, or external, such as technological developments. NRC believes that a set interval to review the MPS would not provide the flexibility needed to respond to the many factors which may influence a decision to revise this policy. For example, this revision of the MPS coincides with the NRC's detailed examination of its medical use program which started in 1993 and includes issuance of the Commission's 1997 Strategic Plan (NUREG-1614, Vol. 1).

Issue 3: Is the MPS Being Revised To Justify the New Part 35?

Comment. Several commenters noted that the current MPS was adequate for effective regulation in safeguarding public health and safety in radiation protection and should not be revised, but simply understood and implemented as originally intended. Several other opinions were stated more strongly. Specifically, one commenter stated that NRC has never paid meaningful attention to the MPS because most existing provisions of Part 35 do not ``pass muster'' under the MPS, particularly as they apply to physicians conducting nuclear medicine procedures. Another commenter's opinion was that the proposed MPS was a step backward and the MPS is being revised to justify the proposed rule.

Response. The Commission agrees that the 1979 MPS was adequate. However, based on the Commission's recent review of its regulatory framework for medical use of byproduct material, these revisions are being made to emphasize a risk-informed regulatory approach. The Commission strongly disagrees with the commenters' opinions that the medical use regulations in part 35 were promulgated without considering the 1979 MPS. In point of fact, all part 35 rulemaking activities have been issued after ensuring compatibility with the 1979 MPS.

After the Commission initiated the review process in 1993, the policy and the rule were revised in parallel in order to achieve a consistent regulatory framework for medical use of byproduct material. As stated before in response to other comments and explanations of the background for this matter, the Commission's Strategic Assessment in 1997 included a decision to consider developing a more risk-informed, performance-based approach. In the process, the three-part 1979 MPS was

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revised into a four-part MPS with re-arranged statements to clarify NRC's policy.

The revised MPS was published for public comment in the **Federal Register** (63 FR 43580-43586; August 13, 1998) and was discussed at meetings with stakeholders and Agreement States. Discussions with stakeholders were meaningful and beneficial, and addressed substantive issues from the medical community (e.g., patient safety, perceived NRC intrusion into the practice of medicine, and regulatory relief for diagnostic nuclear medicine). No new issues were identified during the public comment period and NRC has not revised the MPS any further.

Issue 4: Should NRC Regulation of the Medical Use of Byproduct Material Be Based on Section 104 of the Atomic Energy Act?

Comment. A commenter disagreed with NRC's interpretation that section 104 of the AEA applies only to special nuclear material. In the commenter's opinion, NRC's medical use regulations should be based on section 104 of the AEA.

Response. NRC's principal authority for regulating medical use of byproduct material is at Sections 81, 161, 182, and 183 of the AEA. As previously discussed under Section III, ``Rationale'', NRC regulation of byproduct material is not bound by the limitation in section 104.a. of the AEA, that refers to minimal regulation of reactor facilities or special nuclear material used for medical therapy.

Comments on Statements 1, 2, 3, and 4 of the MPS

Statement 1: NRC will continue to regulate the uses of radionuclides in medicine as necessary to provide for the radiation safety of workers and the general public.

Issue 1: Should the MPS Refer to ``Radionuclides'' or to ``Byproduct Materials?''

Comment. Several commenters noted that Statement 1 made reference to uses of radionuclides in medicine. They indicated that NRC only has the statutory authority to regulate byproduct material.

Response. The Commission believes that the general term ``radionuclide'' is appropriate for a general statement of policy such as the MPS. The latter is intended to inform the public, NRC licensees, and other Federal and State agencies of the Commission's general intentions regarding the regulation of medical use. The 1979 MPS referred to ``medical uses of radioisotopes'' and the term is now being changed to ``uses of radionuclides in medicine'' (see 63 FR 43584; August 13, 1998). As rephrased, the term ``radionuclide'' is a more accurate technical statement of the scope of NRC regulation in this area.

Issue 2: Is Statement 1 Needed if Individuals Handling Radioactive Material Are Properly Trained?

Comment. According to one commenter, the goal of this statement is adequately served by assuring qualification of professionals involved in nuclear medicine. In the commenter's opinion, NRC has no evidence that these individuals do not already adequately provide for the radiation safety of workers and the public, and nuclear medicine is of low risk to workers and members of the public.

Response. The Commission agrees that one way of meeting the goal is to ensure that individuals are adequately trained in radiation safety practices and are placed in key positions within a licensee's organization to maintain radiation exposures as low as are reasonably achievable. Statement 1 sets forth this position. As previously stated, the Commission is bound by statute to regulate byproduct material (and source and special nuclear materials) to ``protect health and minimize danger to life.'' Statement 1 of the MPS continues to provide a regulatory approach to maintain an adequate level of safety. The Commission expects all medical licensees to provide radiation safety for workers and the general public.

Statement 2: NRC will not intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public.

Issue 1: Does This Statement Provide Justification for NRC To Interfere in the Treatment of Patients?

Comment. One commenter was concerned that Statement 2 continues to justify NRC interference in the treatment of patients. According to the comment, there is no supporting data that clearly demonstrates that unsealed byproduct material, when used by qualified authorized users to treat patients, has harmed workers or the public.

Response. Statement 2 does not provide justification for NRC to ``interfere'' in the medical treatment of patients. The modifications to this statement express the Commission's policy not to intrude (rather than ``minimizing'' intrusion as set forth in the 1979 MPS) into judgments affecting patients except to provide for the radiation safety of workers and the general public. Providing for the radiation safety of the public and workers is essential for the Commission to carry out its statutory mandate. When this protection involves a degree of regulation of medical judgments affecting patients, the NRC may find it necessary to intrude, to a certain extent, into medical judgments affecting patients.

For example, the release from a hospital of a patient to whom radioactive materials have been administered has long been considered a matter of regulatory concern to protect members of the public, not just a matter of medical judgment (``Criteria for the Release of Individuals Administered Radioactive Material,'' 62 FR 4120; January 29, 1997). From a medical point of view, it may be appropriate for a physician to release from a hospital a patient to whom radioactive materials have been administered. However, the patient release criteria in NRC regulations may require hospital confinement of that patient if his or her release could result in a dose to other individuals that exceeds the dose-based limit stated in 10 CFR 35.75(a).

In recent years, the Commission has moved away from a more rigid scheme of medical use regulation, which at one time, for example, restricted the uses of therapeutic and certain diagnostic radioactive drugs to the indicated procedures that had been approved by the FDA (44 FR 8242; February 9, 1979). Commission regulations no longer prohibit authorized user physicians from using diagnostic or therapeutic radioactive drugs containing byproduct material for indications or methods of administration that are not listed in the FDA-approved package insert. In addition, Commission regulations now permit medical use licensees and commercial nuclear pharmacies to depart from the manufacturer's instructions for preparing radioactive drugs using radionuclide generators and reagent kits. The recent amendment of 10 CFR 35.75, cited above, substitutes a dose-based limit for patient release (rather than an activity-based limit) that may provide medical use licensees greater flexibility in determining when patients may be released from their control.

Finally, Statement 2 of the MPS is consistent with recent Federal legislation (specifically applicable to FDA), which is to be construed so as not to ``limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.'' (There are certain exceptions to this

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mandate, which do not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.) ``Food and Drug Administration Modernization Act of 1997,'' Public Law 105-115, sec. 906, 111 Stat. 2296 (1997).

Issue 2: Is the NRC the Appropriate Body To Be Involved in Medical Judgments Affecting Patients?

Comment. According to one commenter, the NRC is not the right body to intrude into medical judgments affecting patients because NRC's experience in this area is extremely limited.

Response. As discussed above and noted in Statement 2, the Commission's policy is not to intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public.

This comment does not account for the principle that ``[t]he substantive area in which an agency is deemed to be expert is determined by statute.'' Massachusetts v. United States, 856 F.2d 378, 382 (1st Cir. 1988). See also, Commonwealth of Massachusetts v. NRC, 924 F.2d 311, 324 (D.C. Cir.), cert. denied, 112 S. Ct. 275 (1991). The AEA commits to the NRC the duty of regulating the use of radioactive byproduct materials, including radiopharmaceuticals, to protect public health and safety.

Issue 3: Should This Statement Include Reference To Providing for the Radiation Safety of Workers and the General Public?

Comment. Several commenters requested that Statement 2 be revised to read, as follows, ``NRC will not intrude into medical judgments.'' They believed that the last phrase, ``* * * except as necessary to provide for the radiation safety of workers and the general public,'' should be deleted.

Response. The Commission does not agree that this statement should be revised as indicated by the commenters because providing for the radiation safety of the public and workers is essential for the Commission to carry out its statutory mandate. The final MPS explicitly states that the Commission's intention is not to intrude into medical judgments affecting patients except to provide for the radiation safety of workers and the general public. When this protection necessitates a degree of regulation of medical judgments affecting patients, the NRC may find it necessary, as previously explained, to intrude, to a certain extent, into medical judgments to protect the public and workers.

Statement 3: NRC will, when justified by the risk to patients, regulate the radiation safety of patients primarily to assure the use of radionuclides is in accordance with the physician's directions.

Issue 1: Does This Statement Conflict With Statement 2?

Comment. One commenter believed that, as written, Statement 3 conflicted with Statement 2, unless the word ``primarily'' was deleted from Statement 3. Without this change, the commenter believed NRC would intrude into medical judgments affecting patients.

Response. The Commission does not agree that, as written, Statement 3 conflicts with Statement 2. Statement 3 makes clear that the focus of NRC regulation to protect the patient's health and safety is primarily to ensure that the authorized user physician's directions are followed. Statement 2 emphasizes the intent of NRC to avoid intrusion into medical judgments affecting patients, except where necessary to provide for the radiation safety of workers and the public. NRC's goal in this aspect of medical use regulation is focused on the physician's directions as they pertain to the administration of radiation or a radionuclide, rather than to other, non-radiation-related aspects of the administration. Consistent with its statutory authority, if a situation should arise in the future that identifies an additional risk to a patient's health and safety, the Commission will consider adopting an additional limitation or control on a particular radiation or radionuclide modality, as necessary.

Issue 2: Does the Commission Have Any Useful Role in Assuring the Accurate Delivery of Byproduct Material to Patients? Should References to Patient Radiation Safety Be Deleted?

Comment. Several commenters indicated that NRC has no useful role in assuring the accurate delivery of byproduct material to patients. They believe that all references to patient radiation safety should be removed, and that NRC should simply state that it will make regulatory efforts to ensure the physician's orders are followed.

Response. The Commission has a role in assuring accurate delivery of radiation doses and dosages to patients and has rejected the notion that NRC should not regulate patient radiation safety (44 FR 8243, February 9, 1979). NRC will continue to regulate the radiation safety of patients when justified by the risk to patients, primarily to ensure that the authorized user physician's directions are followed. The Commission recognizes that physicians have primary responsibility for the protection of their patients. However, NRC's role is also necessary to ensure radiation safety of patients.

Issue 3: Does NRC Regulation of the Medical Use of Byproduct Material Duplicate FDA Regulation?

Comment. One commenter noted that any attempt by NRC to regulate the radiation safety of patients would duplicate the efforts of the FDA and state boards of pharmacy and medicine and, as such, would be an unwarranted intrusion into the practice of medicine.

Response. The Commission disagrees with this comment. NRC is responsible for regulating the actual medical use of byproduct material from the standpoint of reducing unnecessary radiation exposures to the public, patients, and occupational workers. In general, the FDA is responsible for assuring the safety, effectiveness, and proper labeling of medical products (i.e., drugs, devices, and biologics). NRC routinely relies on prior FDA approval of medical devices as an essential component of NRC's sealed source and device safety evaluations. In a ``Memorandum of Understanding'' (MOU), effective August 26, 1993, NRC and FDA coordinated existing NRC and FDA regulatory programs for these devices, drugs, and products (58 FR 47300, September 8, 1993).

NRC regulation of the medical use of byproduct material does not duplicate licensing by State boards of pharmacy and medicine of pharmacists and physicians, respectively, to practice pharmacy or medicine within their borders. NRC regulations rely on the licensure of these professionals by a State (or Territory of the U.S., the District of Columbia, or Puerto Rico) to practice their respective professions as a prerequisite to NRC authorizing them to use byproduct material in pharmacy or medicine.

Issue 4: Should NRC Regulation Be Risk-Based and, If So, Should NRC Share Such an Approach With the Medical Community?

Comment. A commenter insisted that NRC regulation should be ``risk-based'' (i.e., justified by risk analysis), and if NRC adopts such an approach, the risk analysis should be shared with the medical community.

Response. The Commission believes the regulations for use of byproduct material in medicine should be ``risk-informed'' rather than ``risk-based.'' In March 1997, the Commission directed the revision and restructuring of part 35 into a risk-informed and, where appropriate, more performance-based

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regulation. The Commission is attempting to make its medical use regulatory framework more ``risk-informed'' and agreeable with its regulatory strategy of regulating ``material uses consistent with the level of risk involved, by decreasing oversight of those materials that pose the lowest radiological risk to the public and continuing emphasis on high-risk activities.\2\'' In addition, this portion of the MPS reflects the Commission's strategy of identifying those regulations and processes that are now or can be made risk-informed.\3\

\2\ Page 11, NUREG-1614, Vol. 1, ``Strategic Plan, Fiscal Year 1997-Fiscal Year 2002''.

\3\ Id.; and SRM dated March 20, 1997, COMSECY-96-057, ``Materials/Medical Oversight (DSI 7) at 2.

The Commission's efforts to make the regulations more risk-informed are evidenced in its recent actions to revise part 35. Before initiating the rulemaking and the associated revision of the MPS, the Commission thoroughly reviewed several extensive assessments, as previously noted. In developing the overall revision of part 35 and the MPS, the Commission considered information on risk provided by members of the public and professional societies, professional medical standards of practice, and event databases maintained by NRC to determine where oversight of lower-risk activities could be decreased. The Commission also examined whether continuation, or even broadening, of the regulations governing higher-risk activities was needed. In addition, throughout the development of the proposed rule and associated MPS, NRC held public workshops with early opportunities for comment from potentially affected parties. These interactions included significant discussions on the risk associated with medical uses of byproduct material.

Although a formal risk assessment was not performed, the Commission believes that the risks associated with use of byproduct material in medicine have been adequately evaluated and considered. Based on these considerations, the revised regulatory approach is more risk-informed and more performance-based and significantly reduces regulatory burden in many areas. The Commission has retained prescriptive regulatory requirements (e.g., in part 35) only where it believes they are necessary to ensure adequate protection of workers, patients, and the public. However, there is nothing in the NRC's regulations that prohibits the medical community or other stakeholders from conducting an independent formal risk assessment of the medical use of byproduct material and forwarding its analysis and recommendations for Commission consideration.

Issue 5: Should NRC Be Involved With Prescriptions for the Medical Use of Byproduct Material?

Comment. A commenter pointed out that NRC should not be involved with prescriptions because the requirements for accurate delivery of prescriptions are covered under state medical and pharmacy law. The commenter believes that written directives are not necessary to ensure high confidence that the actual administration of radiation to the patient was intended by the authorized user.

Response. The Commission's statutory authority to regulate the medical use of byproduct material provides for NRC to have a role with respect to patient radiation safety. Statement 3 narrows the primary focus of NRC regulation of the radiation safety of patients to whether the physician's directions for the administration of byproduct material are followed. This regulatory role is in contrast to the broad regulation by a State board of pharmacy or medicine of the general practice of those disciplines within its borders.

The Commission is not using the term ``prescription'' because it might typically include aspects of the administration that are outside NRC's purview. Instead, the term ``written directive'' (as defined in part 35) is used to specify the physician's directions (i.e., the procedure to be performed and the dose or dosage). This regulatory objective is currently reflected in provisions of part 35 requiring ``high confidence'' that byproduct material will be administered as directed by an authorized user physician.

Statement 4: NRC, in developing a specific regulatory approach, will consider industry and professional standards that define acceptable approaches of achieving radiation safety.

Issue 1: How Should Industry Standards Be Used in Regulating the Medical Use of Byproduct Material?

Comment. According to several commenters, the NRC ignores professional standards and regulates as it pleases. In the commenters' opinions, NRC should accord industry and professional standards the respect they deserve. They believe that if NRC in fact endorses standards developed by private, consensus organizations, the revised MPS would be improved.

Response. The Commission believes that Statement 4 commits NRC to an approach for regulation of medical use that considers both industry and professional standards that define acceptable levels of achieving radiation safety. NRC reviewed industry and professional standards in developing and implementing part 35 and the guidance document (NUREG 1556, Volume 9). For example, some provisions in 10 CFR part 35 allow medical licensees the flexibility to use standards from nationally recognized organizations to meet the performance standards reflected in the rule.

Consideration of industry and professional standards as part of NRC's policy to achieve radiation safety in medical use of byproduct material conforms to the Commission's Strategic Plan \4\ that encourages ``industry to develop codes, standards, and guides that can be endorsed by the NRC and carried out by industry.'' The NRC's intention is to consider industry and professional standards in developing regulations and guidance for the medical use program, consistent with the concepts in the ``National Technology Transfer and Advancement Act of 1995'' (the NTTAA), Public Law 104-113, 110 Stat. 775 (1995). Section 12(d) of the NTTAA requires ``all Federal agencies and departments to use technical standards that are developed or adopted by voluntary consensus bodies * * * as a means to carry out policy objectives or activities, `except when use of such standards,' is inconsistent with applicable law or otherwise impractical.''

\4\ Page 10, NUREG-1614, Vol. 1, ``Strategic Plan, Fiscal Year 1997-Fiscal Year 2002''.

Not all ``medical industry and professional standards'' would meet the definition of ``technical standards'' in Section 12(d)(4) of the NTTAA (``performance-based or design-specific technical specifications and related management systems practices''). Nevertheless, as indicated above, in regulating medical use of byproduct material, the Commission endorses the concept in section 12 (a) of the NTTAA, of ``emphasizing, where possible, the use of standards developed by private, consensus organizations.''

Issue 2: Should NRC Consider Task Group Reports of the American Association of Physicists in Medicine (AAPM) for Developing Approaches for Achieving Radiation Safety?

Comment. A commenter pointed out that, in defining acceptable approaches for achieving radiation safety, NRC should consider the task group reports of the AAPM, which are the latest

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standards of practice for medical physicists.

Response. The Commission agrees that AAPM standards of practice for professionals involved in the use of certain byproduct material modalities and for radiation safety equipment should be considered as part of NRC's risk-informed and performance-based approaches to regulating the medical use of byproduct material. The Commission acknowledges that these and other standards of practice are often voluntary and, as such, medical professionals are not required to follow them. Therefore, where appropriate, the NRC focused part 35 on performance objectives to be achieved by licensees and is allowing licensees to select among the various

performance standards to meet the objective of the regulation. This provides a licensee significant flexibility in designing its radiation protection program.

For example, in developing the final rule for the therapeutic uses of sealed sources, the NRC consulted several AAPM Radiation Therapy Committee Reports, including: Task Group 40 (Comprehensive QA for Radiation Oncology, 1994); Task Group 56 (Code of Practice for Brachytherapy Physics, 1998); Task Group 59 (HDR Treatment Delivery Safety, 1997 Draft); and AAPM Report No. 54 (Stereotactic Radiosurgery, 1995).

In addition to the AAPM, other groups and societies set professional radiation safety and practice standards for medical use. NRC plans to review such standards for possible use in developing regulatory positions (e.g., National Council on Radiation Protection and Measurements, Health Physics Society, and Society of Nuclear Medicine).

Issue 3: Does the Existence of Professional Standards Mean That NRC Regulation Is Unnecessary?

Comment. Several commenters expressed the opinion that NRC regulations were unnecessary. They believe that NRC should not make regulations or license conditions out of industry or professional standards, because that reduces flexibility (i.e., regulations cannot evolve as quickly and easily as professional standards). In their opinion, NRC should recognize that these standards are implemented by other appropriate oversight bodies and that the existence of professional standards should signal to the NRC that regulation is unnecessary. Finally, these commenters indicated that a mechanism is needed to require the NRC to justify why an implemented industry standard is not acceptable.

Response. The Commission disagrees with the comment about professional standards necessarily replacing NRC's radiation safety requirements. Many of the professional standards are voluntary in nature, do not have the force of law, and may not meet the definition of a consensus standard under the NTTAA. As such, not all professional standards are adequate to meet the Commission's objectives for the regulation of medical use of byproduct material.

The Commission must consider industry consensus standards before a ``government-unique standard'' is promulgated. The process is described in NRC Management Directive 6.5, ``NRC Participation in the Development and Use of Consensus Standards.'' Further information on this topic is available on the NRC's web site, www.nrc.gov/reference__library/standards program/reference documents, e.g., Public Law 104-113, ``National Technology Transfer Advancement Act of 1995'' (NTTAA), OMB Circular on implementation of the NTTAA, NRC Annual Standards Reports (listings of consensus standards endorsed by NRC).

For example, NRC reviewed the technical literature to identify consensus standards and protocols that could be used or referenced in the rule and guidance document, thereby avoiding promulgation of ``government-unique standards'' when revising the MPS, 10 CFR part 35, and NUREG 1556 (Volume 9). Part 35, subparts C, F, and H, describe various performance objectives to be achieved (e.g., calibration of survey instruments, calibration of radiation sources used for manual brachytherapy and used in radiation therapy devices, and acceptance testing of treatment planning computers). A licensee may use measurements provided by the source manufacturer or by a calibration laboratory accredited by the AAPM. Alternatively, a licensee may select and implement an appropriate voluntary performance standard from a published protocol that was accepted by a nationally recognized body in order to meet the performance objectives of these regulations. This approach is consistent with the Commission's goal to develop regulations that are more performance-based. The Commission believes this approach provides significant flexibility for medical use licensees to design radiation protection programs

that, when fully implemented, maintain radiation exposures to workers, patients, and the public to levels that are as low as are reasonably achievable.

Dated at Rockville, Maryland, this 27th day of July, 2000.

For the Nuclear Regulatory Commission.
Annette L. Vietti-Cook,
Secretary of the Commission.
[FR Doc. 00-19573 Filed
8-2-00; 8:45 am]
BILLING CODE 7590-01-U

</PRE>

Part 35 Implementation Plan Summary

Presentation will briefly cover the following:

1) Proposed training to cognizant NRC personnel (headquarters, regions, Technical Training Center, others) and Agreement State personnel.

2) Public outreach

3) Temporary instructions

4) Revision of Inspection Manual Chapters and Procedures

5) Revision of NRC's Nuclear Materials Event Database and NMSS Incident Events Tracking System

IN RESPONSE, PLEASE
REFER TO: M001023

October 23, 2000

MEMORANDUM FOR: William D. Travers
Executive Director for Operations

FROM: Annette Vietti-Cook, Secretary /RA/

SUBJECT: STAFF REQUIREMENTS - AFFIRMATION SESSION, 3:00 P.M., MONDAY, OCTOBER 23, 2000, COMMISSIONERS' CONFERENCE ROOM, ONE WHITE FLINT NORTH, ROCKVILLE, MARYLAND (OPEN TO PUBLIC ATTENDANCE)

I. SECY-00-0118 - Final Rules - 10 CFR Part 35, "Medical Use of Byproduct Material" and 10 CFR Part 20, "Standards for Protection Against Radiation"

The Commission[1] approved a final rule which revises 10 CFR Part 35 to make it more risk-informed and performance-based, and to codify requirements for certain therapeutic devices. Also, 10 CFR Part 20 is being revised in response to a Petition for Rulemaking from the University of Cincinnati to allow a licensee the discretion to permit visitors to a hospitalized radiation patient to receive up to 5 millisievert (0.5 rem) in a year from exposure to the hospitalized radiation patient.

Following incorporation of the changes in the attachment and submittal to OMB, the Federal Register notice should be reviewed by the Rules Review and Directives Branch in the Office of Administration and forwarded to the Office of the Secretary for signature and publication.
(EDO) (SECY Suspense: 2/25/01)

The Commission approved the staff decision not to submit an inspection plan with the final rulemaking, pending completion of the Medical Pilot Inspection Program that was approved by the Commission in the SRM for SECY-00-0001. However, the staff should, within 6 months of the completion of the pilot, report back to the Commission on the findings from the pilot and indicate how insights gained will be utilized.

The Commission disapproves staff's recommendation to develop a rulemaking plan, with options, for revising Parts 20 or 35 to add a requirement for a licensee to report events in which an individual receives an exposure in excess of 5 mSv (0.5 rem) from an individual released

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[1] Section 201 of the Energy Reorganization Act, 42 U.S.C. Section 5841, provides that action of the Commission shall be determined by a "majority vote of the members present." Commissioner Diaz was not present when this item was affirmed. Accordingly the formal vote of the Commission was 4-0 in favor of the decision. Commissioner Diaz, however, had previously indicated that he would approve this paper and had he been present he would have affirmed his prior vote.

under § 35.75. Instead, staff should develop for Commission consideration a proposed revision to Part 35 that will require a licensee to notify NRC no later than the next calendar day after it becomes aware that an individual received or is estimated to have received a dose exceeding 50 mSv (5 rem) from a patient released under § 35.75. In addition, the rule should require the licensee to submit a written report within 15 days after discovery of the event. The proposed rule should also include a requirement for the licensee to provide identified exposed individual(s) with a copy of the report submitted to the Commission. This reporting and notification threshold would be consistent with the reporting and notification requirements in § 35.3047. The proposed rule should be provided to the Commission within 7 months of the date of the SRM.

This rulemaking would encompass a patient release that was not in compliance with § 35.75, as well as a release that was in compliance, i.e., it would address instances in which the licensee either:

(1) believes the basis of the release may have been incorrect or the release instructions may have been inadequate, OR

(2) learns, through voluntary means, that the patient did not follow the physician's instructions;

AND

An individual received or is estimated to have received a dose in excess of 50 mSv (5 rem).

The Statement of Consideration for the proposed rule should clearly indicate the Commission is not modifying its previous position that the NRC does not intend to enforce a patient's compliance with the licensee's instructions nor is it the licensee's responsibility to ensure compliance by patients once they leave the licensee's facility (Federal Register, Volume 62, Number 19, pages 4120-4133, January 29, 1997).

Attachment: Changes to the Attachments to SECY-00-0118

cc: Chairman Meserve
Commissioner Dicus
Commissioner Diaz
Commissioner McGaffigan
Commissioner Merrifield
OGC
CIO
CFO
OCAA
OCA
OIG
OPA
Office Directors, Regions, ACRS, ACNW, ASLBP (via E-Mail)

PDR - Advance

Attachment

Changes to the Attachments to SECY-00-0118

Changes to Attachment 6: Draft *Federal Register* Notice for Part 35

1. The alternative rule text for 10 CFR 35.3045 and 35.3047 (Attachment 8 to SECY-00-0118) should be incorporated into the final Federal Register notice for Part 35 (Attachment 6 to SECY-00-0118)

2. The statements of consideration and all supporting documents for the rule should be revised to reflect the Commission's approval of the alternative rule text for §§ 35.3045 and 35.3047 and removal of §§ 35.2045 and 35.2047.

3. In § 20.1301(c), "Dose limits for individual members of the public," for consistency with the rest of Part 20, and in line with the final NRC Metrification Policy, the SI units should consistently be in parentheses.

4. Page 1, line 12: add "more" before "risk-informed"; Perform a global search and make the same change throughout the document.

5. Page 6, line 5, regarding "Thirty-one States": verify the number of Agreement States at the time of publication - Oklahoma may have become an Agreement State

6. Page 7, line 9: add an "s" to "Use"; line 20: change "notice" to "Notice"

7. Page 8, line 5: add "; 63 FR 43580" after "(63 FR 43516"; line 6: change "proposed rule" to "document"

8. Page 8, line 6: add "at the request of stakeholders" after "November 23, 1998)"

9. Page 10, line 16: insert FR cite and date of publication of MPS

10. Page 18, line 13: add "decades of licensing and inspection experience, the States' perspectives," after "such as"; line 17: add "formal" before "risk analysis"

11. Page 23, line 10: change "subtracting" to "diverting"

12. Page 33, second paragraph: update the status of the Medical Pilot Inspection prior to publication

13. Page 35, last three lines: update prior to publication

14. Page 41, line 13: add "that we should require that" before "individuals" and delete "must."; line 14: add "we believe that we should require that" before "they" and delete

"must"

15. Page 45, lines 5 and 12: delete the first "e" in "judgement" and "judgements"; perform a global search and make the same change throughout the document

16. Page 48, line 17: change "is" to "are"

17. Page 52, line 6: add "to FDA-approved uses of byproduct material" after "... should not be limited"

18. Page 62, line 18: replace "hassles visiting another specialist" with "need to visit additional specialists"

19. Page 68, line 18: add "the" after "determine"

20. Page 72, line 5: replace "this section" with "§§ 35.490 and 35.690"

21. Page 115, delete lines 8 and 9 in their entirety; line 12: add "35.3067" to list of rule sections.

22. Page 123, line 16: change "(e)" to "(d)"

23. Page 129, replace lines 1 through 8 with the following:

"conditions of a specific license issued by the Commission or an Agreement State. This license would require the licensee to comply with all provisions of Part 35. Section 35.49 has been modified to state that a licensee may use sealed sources or devices for medical use which are noncommercially transferred from a Part 35 licensee, i.e., if two licensees are authorized to possess sealed sources for medical use, they may transfer the sources from one to the other."

24. Page 135, line 8: replace "This section was proposed" with "Paragraph (d) was added"; line 10: replace "This section" with "Paragraph (d)(1)"

25. Page 145, line 11: delete "and"

26. Page 156, lines 12/13: Revise to state "... proposed wording was not clear *when applied to minor (ministerial) changes to the licensee's radiation protection program*, we revised the rule ...."

27. Page 165, line 8: change "23360" to "34104"; line 9: change "May 21, 1991" to "July 25, 1991"

28. Page 170, line 3: add "prescribed" before "dose"

29. Page 171, line 7: add "potential" after "based on the"

30. Page 180, Comment paragraph, revise line 4 as follows: "... is used, cesium-137 (Cs-137) ...brachytherapy"

31. Page 181, line 3: change "Cesium-137" to "Cs-137"

32. Page 192, line 9: change "(G)" to "(F)"

33. Page 196: delete the last line

34. Page 197, line 8: change "Aus" to "AUs"

35. Page 209, line 4: add a space after "1.11"; line 7: add a space after "1.11"; line 19: add "kilobecquerel" before "kBq" and put "kBq" in parentheses; line 20: change "0.555" to "0.56" in two places. The staff should perform a global search and make the change to line 20 in other places, as needed.

36. Page 209, line 19: add "(final rule paragraph (c))" after "paragraph (b)"; line 20: add "(final rule paragraph (d))" after "paragraph (c)"

37. Page 211, line 7: add a space after "3.7"

38. Page 221: *Mobile Medical Service* -- The Response to Issue 2 on page 221 of the FRN regarding mobile medical service needs to be revised. Specifically, the last sentence is unclear and could be interpreted to mean that byproduct material could be delivered to the client's address, if the material is secured against unauthorized removal, regardless of whether the client is an NRC or Agreement State licensee. Such an interpretation is not consistent with the preceding 3 sentences in the Response, the discussion on page 449 of the FRN or the proposed final 35.80(b). The staff should review the statements of consideration and the rule text to ensure that they consistently reflect the staff's position on whether, and under what conditions, byproduct material could be delivered directly to a client that is not a licensee.

39. Page 231, line 5: add "cobalt-57" before "Co-57" and put "Co-57" in parentheses

40. Page 233: insert the Section 35.190 material (from pages 236-7) here -- it was out of order; label issues "1" and "2"

41. Page 234, line 11: add "(Mo-99)" after "molybdenum-99"; line 16: change "molybdenum-99" to "Mo-99"

42. Page 235, lines 3/4: change "molybdenum-99" to "Mo-99"; line 5: change "kilobecquerel" to "kBq" and change "molybdenum-99" to "Mo-99" and change "megabecquerel" to "MBq" and change "technetium-99m" to "Tc-99m"; line 6: change "molybdenum-99" to "Mo-99" and change "technetium-99m" to "Tc-99m"; line 7: add an "s" to "page"

43. Pages 247 and 248, Issue 3, Response: Revise the first sentence of the response to state " ... individual is likely to exceed 5 mSv (0.5 rem)." Delete the remainder of the paragraph. Revise the first sentence in the second paragraph of the response to state "... for other reasons because compliance with § 35.75 ensures that the maximally exposed ...."

44. Page 249, line 8: delete "iodine" and the parentheses around "I-131"

45. Page 251, lines 1 and 11: delete "other"

46. Page 252, line 9: Insert an introductory sentence explaining that the comment pertained to all sources used under § 35.400.

47. Page 252, line 10: revise this sentence to match the regulations: "using a system or source traceable to NIST and published protocols accepted by nationally recognized bodies or by a calibration laboratory accredited by AAPM.

48. Page 261, line 5, after "... in a year.": Revise to add reference to the new provision for visitors (§ 20.1301).

49. Page 264, lines 4/5: delete "and" and add "and NIST" after "ACMP"

50. Page 267, line 14: change the parentheses to brackets, add "palladium-103" before "Pd-103" and put "Pd-103" in parentheses

51. Page 272, line 4: add "(Sr-90)" after "strontium-90"; line 5: change "strontium-90" to "Sr-90"

52. Page 272, line 4: change "improperly decaying the" to "improperly calculating the decay of sealed"

53. Page 273, lines 11, 15, 16, and 19: change "strontium-90" to "Sr-90"

54. Page 273, line 18: change "had decayed the" to "had calculated the decay of the"

55. Page 274, lines 2 and 9: change "strontium-90" to "Sr-90"

56. Page 278, lines 11/12: revise this sentence to match the regulations: "using a system or source traceable to NIST and published protocols accepted by nationally recognized bodies or by a calibration laboratory accredited by AAPM.

57. Page 293, line 15: add "gamma stereotactic radiosurgery" after "all patient"

58. Page 297, line 7: add the titles (or a footnote with the titles) for the three example documents

59. Page 301, line 6: add "(Ir-192)" after "iridium-192"; lines 12 and 13: change "iridium-192" to "Ir-192"

60. Page 304, line 3: add "in the final rule" after "However,"; line 6: delete "in the final rule"

61. Page 306, line 15: add the title for NUREG/CR-6276

62. Page 318, line 11: add "<www.nrc.gov>" after "Internet site"

63. Page 326, lines 1/2/3: delete the first sentence of the response; line 5: add additional sentence "In order for new or revised requirements to be codified in Part 35, a public rulemaking process under the Administrative Procedure Act must be followed including the development of a cost-benefit analysis made available for public comment."

64. Page 331, line 17: Insert the following at the beginning of this comment: "A comment received stated that the patient's privacy and confidentiality are "ignored" with NRC recordkeeping...."

65. Page 339, line 9: add a space after "30"

66. Page 351, line 13: add "(3.3 feet)" after "1 meter"

67. Page 355, line 4: change "radiation surveys of patients and human research subjects" to "surveys after source implant and removal"

68. Page 360, last line: change "35.2636" to "35.2635"

69. Page 362, Section 35.2643: Delete the second and third sentences under Issue 1, Response.

70. Page 363, Section 35.2647: Delete the second and third sentences under Issue 1, Response.

71. Page 387: Delete the second, third, and fifth sentences in the first paragraph. Revise the fourth sentence to state "The occurrence of such *an unintended dose* does not ...."

72. Page 397 (see also pages 405 and 407), line 15: revise to place "D (H&S)" in quotes.

73. Page 416, line 14: change "diplomats" to "diplomates"; perform a global search and make the same change throughout the document

74. Page 422, line 13: add "as described in § 35.1000, i.e., applications" after "... byproduct material"; line 16: add "(1)" after "(d)" and add "additional" before "information"; line 18: add the following additional sentences at the end of the paragraph "This additional submittal will provide NRC with information on the radiation safety aspects of the specific medical use of the material. Applicants for uses under § 35.1000 must also submit the information required by paragraphs (b) and (c) of this section.

75. Page 423: Combine the last two paragraphs on page 423.

76. Page 427, line 10: add "the current" after "... we do not believe that"

77. Page 430, line 11: change "tied" to "limited"

78. Page 431, line 21: change "not clearly understood" to "subject to misinterpretation"

79. Page 433, line 19: add "for certain procedures" after "rule"

80. Page 440, line 8: add "or by" before "a decay correction"; line 10: delete the semicolon

81. Page 442, line 5: add "or by" before "a decay correction"; line 7: delete the semicolon; line 15: add "by" before "combination"

82. Page 443, lines 16 and 19: add a space after "1.11"

83. Page 446, line 19: delete "a" and add an "s" to "directive" and change "was" to "were"; line 20: change "in an area(s)" to "areas"

84. Page 450, second paragraph, last two sentences: combine as follows and move up to be the third sentence in the new paragraph: "This change provides licensees with greater flexibility in handling radioactive waste and codifies current licensing practice."

85. Page 451, line 14: add "associated with administrations of unsealed byproduct material" after "... levels of risks"

86. Page 452, line 19: add "for use in research" after "(e.g., radiochemicals)"; line 20: add "accepted by FDA" after "IND protocol" and delete "for use in research"

87. Page 453, line 13: add a comma and "Program-Specific Guidance About Medical Use Licenses" after "NUREG-1556, Vol. 9"

88. Page 455, line 8/9: add a space between these lines; line 10: add "for use in research" after "(e.g., radiochemicals)"; line 11: add "accepted by FDA" after "IND protocol" and delete "for use in research"

89. For publication purposes, ADM should ensure that the use of abbreviations and symbols are used consistently through Section V and are consistent with the rules of the *Office of the Federal Register*.

90. Page 461, line 2: change "instruction and training" to "safety instruction"; line 11: add "that" before "patients" and add "would" before "receive"

91. Page 461, lines 4/5: change "in accordance with" to "under"

92. Page 466, line 1: change "in accordance with" to "under"

93. Page 467, last line: add a space after "and"

94. Staff should do a global review of the citations to the AAPM documents (including title, if referencing a new AAPM document) to make sure that they are complete and consistently presented in the FRN and acronyms are used whenever possible.

95. Page 476, line 2: add "at least" before "annual instruction"; line 3: replace "device" with "unit" and add "at least" before "annual practice."

96. Page 480, line 1: delete second "the current"

97. Page 480, line 14: replace "monthly" with "once in each calendar month"

98. Page 518, last line and top of page 519: update to provide status of publication of the revised MPS; page 519, line 1: change "addresses" to "addressed"

99. Page 537, lines 10 and 11: Revise to state ". . . visitors to an individual who cannot be released under § 35.75, to . . ." This change should be reflected in other appropriate sections in the statements of consideration and in the supporting documentation for the rule.

100. Page 548, line 22: change "several medical disciplines are practiced" to "more than one medical discipline is practiced". This change should be reflected in other appropriate sections in the statements of consideration and in the supporting documentation for the rule.

101. Page 585, lines 18 and 19: Change "cannot be released in accordance with" to "cannot be released under".

102. Page 586, lines 14/15: change "that cannot be released in accordance with" to "who cannot be released under"

103. Page 594, line 17: revise to read " ... human research subjects who are receiving brachytherapy and cannot be released under § 35.75." The change from using the term "implant therapy" to "brachytherapy" should be reflected in other appropriate sections in the statements of consideration and in the supporting documentation for the rule.

104. Page 595, line 12: Revise to state "... human research subject who is receiving brachytherapy and cannot be released under § 35.75 ...."

Changes to Attachment 9: Assessment of Federal Regulations and Policies on Family

1. Page 1, line 22: change "mSV" to "mSv"; line 27: replace "eight" with "$8.7" and delete "dollars"

2. Page 1, line 26: add "and Agreement States" after "NRC"

Changes to Attachment 10: Draft Final *Federal Register* Notice for Enforcement Policy

1. Page 1, line 14: change "or" to "of"

2. Page 2, line 10: add ", email rwb1@nrc.gov" after "(301) 415-2741"

3. Page 2, line 15: hyphenate "risk informed" and "performance based"; line 17: change "will" to "would"

4. Page 3, lines 1/2: delete the first full sentence; line 4: replace "It was" with "The terms "written directive" and "misadministration" were"

5. Page 4, line 2: delete the comma after "medical events" and replace "such as" with "(e.g.,"; line 4: add ")" after "follow procedures"

Changes to Attachment 11: Letter to University of Cincinnati

1. Page 1, line 10: change "milliSievert" to "millisievert"

2. Page 2: combine third, fourth and fifth full paragraphs into a single paragraph

3. Page 2, line 16: delete "the" before "request" and add "(2)" after "request" and delete "(2)" after petition; line 31: change "of" to "in" and delete "("; line 33: delete ")"; line 34: add a period after "radiation patients" and capitalize "however"; line 36: add "in the petition to require licensees to instruct visitors about radiation safety" after "(4)"

Changes to Attachment 12: Draft Final Regulatory Analysis

1. Use numbers rather than words for radiological units to be consistent with the rest of the documents. (i.e., use "5 mSv", not "five mSv", see page 1-3 for some specific examples)

2. Page 5-39, lines 16 and 22: change "0.555" to "0.56"; line 31: add a space between "to" and "151"

3. Page 6-5, second to last line: add "revising" before "10 CFR Part 35"

Changes to Attachment 13: Draft Final Environmental Assessment

1. Page 2, line 35: add a space before "mSv" (2 places)

2. Page 3, line 30: add a space before "mSv"

3. Page 4, line 12: add a space before "mSv"

4. Page 5, line 21: add a space before "mSv"; line 24: add "and Measurements" after "National Council on Radiation Protection"

Development of a Risk-Informed Regulatory Framework for the Office of Nuclear Material Safety and Safeguards

In the past the Office of Nuclear Material Safety and Safeguards (NMSS) has used risk information in making regulatory decisions on a case by case basis. Due to the varied nature of the activities in these two arenas, a single approach, such as Probabilistic Risk Assessment, is not possible. In Secy-99-100, "Framework for Risk-informed Regulation in the Office of Nuclear Material Safety and Safeguards," dated March 31, 1999, the U.S. Nuclear Regulatory Commission staff proposed a framework for risk-informed regulation in NMSS. In a Staff Requirements Memorandum, dated June 28, 1999, the Commission approved the staff's proposal. As a first step toward developing a framework, the staff proposed establishing a systematic method to identify and prioritize the candidate regulatory applications that are amenable to expanded use of risk assessment information. This step will be accomplished by applying screening criteria to regulatory application areas as a means to identify the candidate regulatory applications. To be a candidate for expanded use of risk information in NMSS, the regulatory application areas must meet the screening criteria.

As part of the staff's effort to use an enhanced public participatory process in developing the framework, the staff held a public workshop in Washington, DC, on April 25-26, 2000. The staff published draft screening criteria in the Federal Register (65 FR 14323, March 16, 2000) announcing the workshop. The purpose of the first part of the workshop was to solicit public comment on the draft screening criteria and their

applications. The purpose of the second part of the workshop was solicit public input for the process of developing safety goals for nuclear material applications. A consensus among the workshop participants was that case studies and iterative investigations would be useful in order to (1) test the draft screening criteria, (2) show how the application of risk information has affected or could affect a particular area of the regulatory process, and (3) develop safety goal parameters and a first draft of safety goals for each area.

The NMSS staff decided to pursue case studies with the following purposes: (1) to illustrate what has been done and what could be done in NMSS to alter the regulatory approach in a risk-informed manner, and (2) to establish a framework for using a risk-informed approach in NMSS by testing the draft screening criteria, and determining the feasibility of safety goals. Once the screening criteria have been tested using a spectrum of case studies, the criteria can be modified as appropriate, placed in final form, and established as part of the framework for prioritizing the use of risk information in NMSS regulatory applications.

Performance-based Initiatives

To increase reliance on performance-based regulatory approaches, the Commission directed the staff to develop high-level guidelines. These guidelines can be applied to regulatory requirements to identify and assess the use of performance results instead of prescriptive criteria to assure safe performance.

The staff has developed and tested high-level guidelines to identify and assess the viability of performance-based activities. The guidelines are intended to promote development of performance-based activities throughout the agency. In general, a performance-based regulatory approach focuses on results as the primary basis for regulatory decision-making and as such allows licensee flexibility in meeting a regulatory requirement. This in turn, can result in a more efficient and effective regulatory response.

Internal and external stakeholders have commented on the guidelines and their comments have been addressed in the development of the guidelines. Specifically, the staff has addressed concerns among some stakeholders that application of the guidelines would focus only on reductions in regulatory burden and that prevention of accidents would lose emphasis. These high level guidelines were provided to the Commission in the information paper, SECY 00-0191, on September 1, 2000.

The performance-based approach would be applied in conjunction with the agency's defense-in-depth principles as articulated in the Commission's White Paper, "Risk-Informed and Performance-Based Regulation," SRM to SECY-98-144 (White Paper). As such, it has the potential of enhancing safety.

Based on the testing conducted so far, the guidelines can be used to effectively focus the effort to make regulatory activities more performance-based by:

(A) Identifying the components of the regulatory framework which can be made more performance-based;

(B) Selecting or formulating performance parameters and associated performance criteria appropriate to the regulatory issue being addressed.

The staff plans trial applications of the guidelines on a broad range of regulatory activities. Once satisfactory testing is completed, the staff intends to incorporate the guidelines into internal NRC procedures and also pursue wider acceptance of the guidelines by involving stakeholders.

These high level guidelines were provided to the Commission in the information paper, SECY 00-0191, on September 1, 2000.

POLICY ISSUE
INFORMATION

September 1, 2000 SECY-00-0191

FOR: The Commissioners

FROM: William D. Travers
Executive Director for Operations

SUBJECT: HIGH-LEVEL GUIDELINES FOR PERFORMANCE-BASED ACTIVITIES

PURPOSE:

This paper is to inform the Commission of the development of the high-level guidelines consistent with the direction in the Staff Requirements Memorandum (SRM) to SECY-99-176, "Plans for Pursuing Performance-Based Initiatives." The guidelines, their relationship to the risk-informed program, and the results of test applications of the guidelines are provided. These guidelines can be applied to regulatory activities to identify and assess the use of performance-based regulatory approaches instead of prescriptive criteria to assure safe performance, and as such, should help to increase reliance on performance-based regulatory approaches throughout the agency.

SUMMARY:

The staff has developed and tested high-level guidelines (Attachment 1) to identify and assess the viability of making elements of the regulatory framework performance-based. The guidelines are intended to promote the use of a performance-based regulatory framework throughout the agency. In general, a performance-based regulatory approach focuses on results as the primary basis for regulatory decision-making and as such allows licensee flexibility in meeting a regulatory requirement. This in turn, can result in a more efficient and effective regulatory process.

Internal and external stakeholders have commented on the guidelines and their comments have been addressed in the development of the guidelines. Specifically, the staff has addressed concerns among some stakeholders that a performance-based regulatory framework would focus only on reductions in regulatory burden and that public health and safety would lose

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emphasis. The staff notes that a performance-based approach is intended to focus the regulatory framework on desired outcomes and would be applied in conjunction with the agency's defense-in-depth principles as articulated in the Commission's White Paper, "Risk-Informed and Performance-Based Regulation," SRM to SECY-98-144 (White Paper).

Based on feasibility testing of the guidelines, the staff concludes that they can be used to effectively focus the regulatory framework to be more performance-based by:

(A) Identifying the elements of the regulatory framework which can be made more performance-based. Note, the regulatory framework may include the regulation and its supporting regulatory guides, standard review plans, technical specifications, NUREGs, and inspection guidance.

(B) Selecting or formulating performance parameters and associated performance criteria appropriate to the regulatory issue being addressed. For example, they facilitate identifying the level (i.e., component, train, system) at which performance criteria should be set.

Having established the feasibility of the guidelines, the staff plans to develop implementing guidance to incorporate the guidelines into internal NRC procedures, and to apply the guidelines to future regulatory initiatives, including those that are identified through risk-informed activities.

BACKGROUND:

In the SRM to SECY-99-176, issued on September 13, 1999, the Commission directed the staff to develop high-level guidelines to identify and assess the viability of candidate performance-based activities. The staff published a set of proposed guidelines in the Federal Register on January 24, 2000. The Commission was provided with a copy of the guidelines for information prior to the Federal Register publication.

In the SRM to SECY-99-176 the Commission directed that:

(A) The guidelines should be developed with input from stakeholders and the program offices.

(B) The guidelines should include discussion on how risk information might assist in the development of performance-based initiatives.

(C) The guidelines should be provided to the Commission for information.

(D) The staff should periodically update the Commission on its plans and progress in identifying and developing performance-based initiatives.

DISCUSSION:

The staff has used definitions from the White Paper for terminology such as "deterministic analyses," "risk insights," and "performance-based approach" in developing the guidelines.

Consistent with the NRC's Strategic Plan and the White Paper, the guidelines are to be applied across the full spectrum of materials, processes, and facilities regulated by the NRC.

Program Office and Stakeholder Input

In response to the SRM, the staff took the following actions:

The staff established a Performance-Based Regulation Working Group (PBRWG) to ensure broad NRC program office participation in the development of the guidelines. The PBRWG has representation from RES, NRR, NMSS, and regional representation through Region III. The PBRWG was instrumental in developing consensus among the offices on this initiative. Once these guidelines are incorporated into internal NRC procedures, the PBRWG will cease to exist and line management will assume responsibility for applying the guidelines.

A facilitated workshop was held on March 1, 2000 with a number of internal and external stakeholders representing the reactor, materials, and waste areas. This workshop solicited comments on an initial draft of the proposed guidelines and on a set of specific questions which were posed in two Federal Register Notices. Revised guidelines were published on May 9, 2000, and an on-line workshop was held on June 8, 2000. Comments were received at the workshops and in response to the Federal Register Notices, and the guidelines contained herein have been modified in response to public comments. The majority of the comments were supportive of the guidelines and staff efforts to make NRC regulatory requirements more performance-based. The staff's response to all comments appears in Attachment 2.

In addition, the staff briefed the Advisory Committee on Reactor Safeguards (ACRS) and the Advisory Committee on Nuclear Waste (ACNW). The Advisory Committee on Medical Uses of Isotopes (ACMUI) was provided briefing material.

Interrelationships Among Regulatory Initiatives

Initiatives to change the regulatory framework arise from various sources such as Commission direction, operating experience, stakeholder suggestions and staff initiatives. These proposed initiatives are normally subjected to a screening process that include identification of the specific modification of the regulatory framework and an initial prioritization utilizing the NRC's performance goals to determine whether the proposed initiative should be pursued and with what priority. A determination will then be made as to whether to pursue a "Risk-Informed and Performance-Based," "Risk-Informed," "Performance-Based," or "Traditional" approach based on guidelines described in this paper and in the Risk-Informed Regulation Implementation Plan (RIRIP). The staff would use the guidelines to assess the viability (discussed below) to make this determination. When feasible, it is preferable to use a risk-informed and performance-based approach. The staff is coordinating the guidelines in both areas to assure that no inconsistencies exist between them. A separate paper on RIRIP will be presented to the Commission. Once a decision is made to pursue a performance-based approach, the staff will apply the guidelines to assess the change (as described below) to further develop the approach. If the staff finds that a performance-based approach is not feasible, then the staff will assess what other methods can be used.

Overview of Guidelines

The guidelines are structured under three main groupings:

(i) Guidelines to Assess Viability: These guidelines rely on the four attributes of a performance-based approach as discussed in the White Paper. These are: measurable or calculable parameters; objective performance criteria; flexibility; and a performance failure not resulting in an immediate safety concern. These guidelines assess whether a more performance-based approach is feasible for any given new regulatory initiative. This assessment would be applied on a case-by-case basis and would be based on an integrated consideration of the individual guidelines within this grouping. In applying the guidelines, the staff must be cognizant of circumstances when implementation of a performance-based approach, in a manner inconsistent with the intent or objective, may have a negative or unacceptable effect on safety. For example, postponing needed maintenance in order to meet an availability goal would not be an acceptable way to use flexibility. However, it would be appropriate to revise the availability goal, reflecting considerations of safety significance, and expand flexibility if a sound technical basis is demonstrated.

(ii) Guidelines to Assess Change: If a performance-based approach is deemed viable based on the guidelines in (i) above, then the regulatory activity would be evaluated against guidelines that assess whether a more performance-based approach results in opportunities for regulatory improvement (by which is meant a positive contribution to the NRC's performance goals and achieving a net societal benefit). The performance goals are: maintain safety; increase public confidence; increase effectiveness, efficiency and realism; and reduce unnecessary regulatory burden. Additional guidelines in this group include a net benefit test, the ability of the proposal to be incorporated in the regulatory framework, and the ability to accommodate new technology. This evaluation is to be based on an integrated assessment of the individual guidelines within this grouping.

(iii) Guidelines to Assure Consistency with Other Regulatory Principles: These guidelines assess consistency and coherence with overriding NRC goals and principles (e.g., the defense-in-depth principle). It only needs to be applied if the candidate activity passes the first two sets of guidelines.

Use of Risk Information Relative to Performance-Based Initiatives

Consistent with the definition of a "risk-informed, performance-based approach" provided in the White Paper, risk information will be used to assist in the development of performance-based initiatives so that the staff will accomplish the following:

- Focus attention on the most important activities;
- Establish objective criteria for evaluating performance;
- Develop measurable or calculable parameters for monitoring system and licensee performance;
- Provide flexibility to determine how to meet the established performance criteria in a way that will encourage and reward improved outcomes; and

- Focus on the results as the primary basis for regulatory decision-making.

The staff has identified risk information to be relevant with respect to performance-based initiatives in three ways:

(1) A Basis for Establishing Appropriate Level of Performance:

A performance-based approach will assist in ensuring that important systems, functions, and other elements of regulated activity provide the requisite level of performance. In effect, the high level performance-based guidelines, and specifically the viability guidelines, provide a framework to search for the appropriate performance parameter and the level of performance necessary to achieve the safety objective. For example, for a given activity, the guidelines can help determine if performance goals should be set at the component, system or function level.

(2) To Provide Metrics, Thresholds and/or Regulatory Response:

The staff is using risk considerations to select performance metrics in several contexts. The reactor oversight program uses performance indicators which rely on risk information such as reliability and availability of certain systems, trains and components. The risk significance of performance changes can be evaluated directly where performance indicators are based on risk information. Performance thresholds and appropriate regulatory responses could then be determined in a straightforward manner. The guidelines are useful to characterize the appropriate performance attributes that might be monitored using risk insights. For example, risk information can be used to set reliability and availability goals for critical safety equipment.

(3) Unavailability of Quantitative Risk Evaluation Models:

On February 11, 1999, the Commission issued the SRM to SECY-98-132 in which the staff was directed to pursue performance-based initiatives that are not amenable to probabilistic risk assessment. Although many regulated activities may not be easily related to a quantitative risk model, they should not be precluded from being made more performance-based. Therefore, the staff is planning to apply the guidelines to suitable candidates in this category. In these instances, risk information of a less quantitative or non-quantitative nature, such as that available from an integrated safety assessment, should be relied upon. In some or all of these areas, a performance-based approach may present opportunities for regulatory improvements.

Testing of the High-Level Guidelines

Application of the guidelines requires that the nature of the regulated activity and the safety issues be defined with specificity. To explore how such challenges can be met in practice, the staff selected two issues to test the guidelines. For each issue, an NRC panel was formed consisting of experts on the specific regulatory issue. The first issue is related to the ongoing effort to risk-inform 10 CFR 50.44 (Standards for Combustible Gas Control System in Light-Water-Cooled Power Reactors). Although the hypothetical regulatory change is thought to be plausible, it must be considered purely illustrative at this time while the alternatives that will be proposed for revisions to 10 CFR 50.44 are still under consideration. The second issue involves a recent change that was made to Subpart H (Respiratory Protection and Controls to Restrict Internal Exposure in Restricted Areas) of 10 CFR Part 20. In this case, the guidelines were applied retrospectively for illustrative purposes. The results of tests clearly support the

utility of the high-level guidelines. A detailed description of these tests and the results appears in Attachment 3.

On the basis of the two test cases, the staff identified two issues concerning generic application of the guidelines. First, for a given regulatory activity, it appears that, in order to maximize the performance-based potential, one must apply the guidelines to the entire regulatory framework as it relates to that activity. This is because there typically exists a hierarchy of information pertaining to a regulated activity which encompass the more general provisions of the rule language to the relatively detailed supporting documents. Thus, opportunities to make an activity more performance-based could occur anywhere along the hierarchy. Further, an assessment that fails to apply the guidelines to the full regulatory framework could result in partial or ineffectual results, where, for example, a rule is made more performance-based but remains supported by unnecessarily prescriptive regulatory guidance.

Second, in most instances, performance will not be dependent on a single parameter. Rather, the guidelines will have to be applied to a combination of performance parameters each of which contributes to attaining the performance goals. For example, the first case study in Attachment 3 uses the combination of capability, reliability, and availability to provide the basis for setting performance criteria.

PLANS FOR PERFORMANCE-BASED INITIATIVE:

The staff plans to:

- Apply the guidelines in ongoing or future approved rulemakings, as appropriate.
- Apply the guidelines to ongoing regulatory efforts under Option 3 of SECY-98-300, "Options for Risk-Informed Revisions to 10 CFR Part 50."
- Apply the guidelines to suitable candidates identified as being not appropriate to be risk-informed pursuant to the "Risk-Informed Regulation Implementation Plan" (SECY-00-0062, March 15, 2000).
- Develop a management directive to support agency-wide implementation of the guidelines in ongoing or future approved rulemakings and other regulatory activities, as appropriate (e.g., the inspection process). Supporting guidance at the office level will occur through office letters.
- Develop a communications plan to promote broader awareness of performance-based approaches on the part of external stakeholders. Wider acceptance of the guidelines should lead to efficiencies and an overall increased level of performance-based activities.
- Provide a report to the Commission on the above activities at the end of FY-2001.

RESOURCES:

For FY 2001, RES currently has 1 FTE to: (1) apply the guidelines to a candidate regulation identified as not appropriate to be risk-informed; (2) develop a management directive; and (3) develop a communication plan. Resources requirements for developing specific

performance-based changes to the regulatory framework as a result of implementing the high-level guidelines will be addressed, as appropriate, by the performing office(s). Future requirements will be addressed through the Planning, Budgeting, and Performance Management process.

COORDINATION:

The Office of the General Counsel has no legal objection to this paper. The Office of the Chief Financial Officer has reviewed this Commission Paper for resource implications and has no objection. The Office of the Chief Information Officer has reviewed this Commission Paper for information technology and information management implications and concurs in it.

/RA/

William D. Travers
Executive Director
for Operations

Attachments: 1. High-Level Guidelines for Performance-Based Activities
2. NRC Response to Public Comments
3. Process and Case Studies Applying High-Level Guidelines

High-Level Guidelines for Performance-Based Activities

The proposed guidelines to identify and assess performance-based activities are shown below. They are substantially the same as those published in the Federal Register on May 9, 2000, with modifications based on internal and external stakeholder input. These guidelines are based on the four attributes in the Commission's White Paper, "Risk-Informed and Performance-Based Regulation," SRM to SECY-98-144. The nature of the regulated activity and the safety issues for which regulatory requirements are to be developed need to be defined with specificity before the guidelines are applied. Generally, an integrated assessment from a set of guidelines will provide the basis for any conclusion.

I. Guidelines to Assess Viability

The staff will apply the following guidelines to assess whether a more performance-based approach is viable for any given new regulatory initiative. This assessment would be applied on a case-by-case basis and would be based on an integrated consideration of the individual guidelines. Risk information provides the basis for identifying systems, functions or other elements of regulated activity which should be targeted for application of these guidelines so that the appropriate performance parameters are chosen and the level of performance is set to achieve the safety objective. The assessment for viability will ensure that sufficient information (data) and analytical methods exist or can be developed. The guidelines are listed below:

A. Measurable (or calculable) parameters to monitor acceptable plant and licensee performance exist or can be developed.

   (1) Directly measured parameter related to safety objective will typically satisfy this guideline.

   (2) A calculated parameter may also be acceptable if there is a clear relationship to the safety objective.

   (3) Parameters which licensees can readily access, or are currently accessing, in real time will typically satisfy this guideline. Parameters monitored periodically to address postulated or design basis conditions may also be acceptable.

   (4) Acceptable parameters should be consistent with defense-in-depth and uncertainty considerations.

B. Objective criteria to assess performance exist or can be developed.

   (1) Objective criteria consistent with the desired outcome are established based on risk insights, deterministic analyses and/or performance history.

C. Licensee flexibility in meeting the established performance criteria exists or can be developed.

   (1) Programs and processes used to achieve the established performance criteria would be at the licensee's discretion.

(2) A consideration in incorporating flexibility to meet established performance criteria will be to encourage and reward improved outcomes provided inappropriate incentives can be avoided.

D. A framework exists or can be developed such that performance criteria, if not met, will not result in an immediate safety concern.

(1) An adequate safety margin exists.

(2) Time is available for taking corrective action to avoid the safety concern.

(3) The licensee is capable of detecting and correcting performance degradation.

II. Guidelines to Assess Performance-Based Regulatory Change

If a more performance-based approach is deemed to be viable based on the guidelines in I. Guidelines to Assess Viability above, then the consequences of adopting a more performance-based approach would be evaluated based on an integrated consideration of this second group of guidelines. This assessment would compare the start up and implementation costs of the regulatory change relative to the NRC's performance goals and other desirable outcomes. The outcomes would be considered applicable to the public, the applicant or licensee, and the NRC staff. The guidelines are listed below:

A. Maintain safety, protect the environment and the common defense and security.

(1) Safety considerations play a primary role in assessing any change arising from the use of performance-based approaches.

(2) Adequate safety margins are maintained using realistic safety analyses, including explicit consideration of uncertainties.

B. Increase public confidence.

(1) An emphasis on results and objective criteria (characteristics of a performance-based approach) can help NRC to be viewed as an independent, open, efficient, clear, and reliable regulator.

(2) A performance-based approach helps with providing the public clear and accurate information about, and a meaningful role in the regulatory programs.

(3) A performance-based approach helps explain NRC's roles and responsibilities and how public concerns are considered.

C. Increase effectiveness, efficiency and realism of the NRC activities and decision-making.

(1) An assessment would be made of the level of conservatism existing in the currently applicable regulatory requirements considering analysis methodology and the applicable assumptions. Any proposal to use realistic analysis would take into account uncertainty factors and defense-in-depth relative to the scenario under consideration.

(2) An assessment would be made of the performance criteria and the level in the performance hierarchy where they have been set. In general, performance criteria should be set at a level commensurate with the function being performed. In most cases, performance criteria would be expected to be set at the system level or higher.

D. Reduce unnecessary regulatory burden.

(1) A performance-based approach enables NRC to impose regulatory burden which is commensurate with the safety benefit, and which effectively focuses resources on safety issues.

(2) A performance-based approach will enable the costs associated with NRC activities to States, the public, applicants and licensees to be focused on areas of highest safety priority and avoid burden imposed by overly prescriptive regulatory requirements.

E. The expected result of using a performance-based approach shows an overall net benefit.

(1) A reasonable net benefit test would begin with a qualitative approach to evaluate whether there is merit in changing the existing regulatory framework. When the net benefit test is approached from the perspective of existing practices, stakeholder input may be sought.

(2) Unless imposition of a safety improvement or other societal outcome is contemplated, expending resources for a change in regulatory practice would be justified in most cases only if NRC or licensee operations benefit from such a change. The primary source of initial information and feedback regarding potential benefits to licensees would be the licensees themselves.

(3) For the limited purpose of screening potential performance-based changes, consideration of a specific result (such as net reduction in worker radiation exposure) may be sufficient for weighing the immediate implications of a proposed change.

F. The performance-based approach can be incorporated into the regulatory framework.

(1) The regulatory framework may include the regulation in the Code of Federal Regulations, the associated Regulatory Guide, NUREG, Standard Review Plan, Technical Specification, and/or inspection guidance.

(2) A feasible performance-based approach would be one which can be directed specifically at changing one, some, or all of these elements.

(3) The proponent of the change to the elements of the regulatory framework would have the responsibility to provide sufficient justification for the proposed change; all stakeholders would have the opportunity to provide feedback on the proposal, typically in a public meeting.

(4) Inspection and enforcement considerations would be addressed during the formulation of regulatory changes rather than afterwards. Such considerations could include reduced NRC scrutiny if performance so warrants.

G. The performance-based approach would accommodate new technology.

(1) The incentive to consider a performance-based approach may arise from development of new technologies as well as difficulty stemming from technological changes in finding spare components and parts.

(2) Advanced proven technologies may provide more economical solutions to a regulatory issue without compromising safety, hence justifying consideration of a performance-based approach.

III. Guidelines to Assure Consistency with Other Regulatory Principles

A. A proposed change to a more performance-based approach is consistent and coherent with other overriding goals, principles and approaches involving the NRC's regulatory process.

(1) These principles are provided in the Principles of Good Regulation, the Probabilistic Risk Assessment (PRA) Policy Statement, the Regulatory Guide 1.174, "An Approach for Using PRA in Risk-Informed Decisions on Plant-Specific Changes to the Licensing Basis," and the NRC's Strategic Plan.

(2) Consistent with the high-level at which the guidance described above has been articulated, specific factors which need to be addressed in each case (such as defense-in-depth and treatment of uncertainties) would depend on the particular regulatory issues involved.

NRC Response to Public Comments:

The Federal Register Notice (FRN), 65 FR 3615 on January 24, 2000, requested comments on the proposed high-level guidelines with particular interest in a set of specific questions. Comments were provided at the March 1, 2000 workshop and in writing. The workshop was conducted as a facilitated discussion among stakeholders representing a wide variety of interests, including NRC representatives from the program offices. Revised guidelines were published in the Federal Register on May 9, 2000 (65 FR 26772), reflecting comments to that point. In addition, an on-line workshop, held on June 8, 2000, provided another opportunity for public comment. Limited comments were received as a result of this workshop.

In the January 24, 2000, FRN, the NRC specifically requested comments on a number of key questions concerning the proposed guidelines. The NRC's response to comments has been structured within the framework of the questions published in the January FRN. Comments not associated directly with any of the questions are shown under the heading "Other Comments."

The NRC's response to the comments and any indication as to how the guidelines have changed in response to the comments follows:

A. Clarity and Specificity of the Guidelines

1. Are the proposed guidelines appropriate and clear?

   Comment: Overall, favorable opinions were expressed regarding appropriateness and clarity of the guidelines. However, two commenters who were generally opposed to any shift to a more performance-based approach provided unfavorable responses. Specifically, those clearly opposed to the performance-based regulatory approach are concerned that its primary purpose is to reduce regulatory requirements and licensee burden thereby compromising the safety standard for overseeing regulated activity. Additionally, there is concern that under a performance-based approach, one would not be able to prevent accidental releases of radioactive material.

   Response: In the NRC's view, the performance-based approach has the potential of making the regulatory decisions more effective and efficient by reducing unnecessary regulatory burden, and do so without compromising overall safety. Further, the guidelines require that in order for an activity to be a viable performance-based candidate, failure to meet its performance criteria will not result in an immediate safety concern. Amplifying guidelines specify that a sufficient safety margin exists, time is available to take corrective action, and the licensee is capable of detecting and correcting performance degradation. Active consideration of all these factors can lead to superior safety standards while avoiding unnecessary regulatory burden. At the same time, the guidelines focus attention on the factors which prevent release of unsafe amounts of radioactive materials.

2. Are there additional guidelines that would improve clarity and specificity?

Comment: One comment proposed a guideline to increase safety and another comment proposed a guideline to prevent incentives to "perverse" outcomes.

Response: As discussed below, a framework and process to increase safety by adding to regulatory requirements (subject to 10 CFR 50.109, the Backfit Rule) exists and it would not be efficient to duplicate this through additional guidelines. No changes were made in the main guidelines because safety and beneficial outcomes are generally desirable goals which form parts of normal staff considerations. However, the amplifying guidelines under "Maintain Safety" have been modified to emphasize that safety considerations will play the primary role in NRC's assessments. Since the Commission addressed the matter of encouraging and rewarding improved outcomes in the White Paper (SRM to SECY-98-144, "White paper on Risk-Informed and Performance-Based Regulation)," an amplifying guideline to this effect has been added. This amplifying guideline under overall net benefit generated a comment indicating a misunderstanding that cost would be given a greater emphasis than safety. A revision has been made regarding the considerations related to a simplified net benefit test.

3. How does the "high-level" nature of the guidelines affect the clarity and specificity of the guidelines?

   Comment: The comments provided did not indicate any need to change any of the guidelines due to this factor. One commenter specifically endorsed the "high-level" approach to the guidelines, while also suggesting a graded approach incorporating a minimum acceptable risk.

   Response: The NRC interpreted "minimum acceptable risk" to mean a level of risk consistent with adequate protection considerations. The NRC agrees that a graded approach is appropriate for regulatory changes above and beyond adequate protection. The NRC maintains that the guidelines, as currently formulated, allow for this; thus, no changes were made to address this comment.

B. Implementation of the Guidelines

1. What guidelines, if any, are mandatory for an activity to qualify as a performance-based initiative?

   Comment: Commenters stated that none of the guidelines should be mandatory.

   Response: The viability guidelines must be satisfied for an activity to qualify as a performance-based initiative. In this sense, they may be considered mandatory. For example, a sufficient safety margin must exist. Also, the "Guidelines to Assure Consistency with Other Regulatory Principles" could be considered mandatory because they cover principles which the NRC would not knowingly violate.

2. What is the best way to implement these guidelines?

   Comment: An issue of considerable interest was whether a performance-based approach should be voluntary or not. Certain commenters believed that voluntary changes negatively affect the NRC's inspection and enforcement role whereas others maintained that changes must be voluntary to ensure flexibility on the part of licensees.

Response: It is anticipated that voluntary implementation will often be proposed, and where mandatory implementation is proposed, such a change would be subject to the Backfit Rule. Additionally, the NRC has decided to implement the guidelines to new initiatives. Initiatives proposed by stakeholders, such as in petitions for rulemaking, would thus be considered as potential candidates.

3. How should the Backfit Rule apply to the implementation of performance-based approaches?

   Comment: Most commenters indicated that reliance on a performance-based approach would have no bearing on whether or not the Backfit Rule applied. One commenter expressed the view that the Backfit Rule should apply to reductions in regulatory burden.

   Response: The NRC concurs that increased reliance on a performance-based approach poses no unique considerations relative to the Backfit Rule. The NRC fully expects that all new requirements, including those made performance-based, will be subject to existing NRC procedures which include backfit considerations as well as formal regulatory analysis requirements. This comment goes well beyond the scope of these guidelines as currently envisaged.

4. Should these guidelines be applied to all types of activity, e.g., should they be applied to petitions for rulemaking?

   Comment: To the extent that commenters favored application of the guidelines, they also supported application to all activities directed at improving the effectiveness of regulations. One commenter acknowledged that it may not be appropriate for some regulations, such as the Fitness for Duty Rule.

   Response: The NRC intends to apply the guidelines to all activities including responding to and resolving petitions for rulemaking. The commenter who indicated that they were not appropriate for all regulations did not provide a rationale for that position.

5. Should these guidelines only be applied to new regulatory initiatives?

   Comment: A number of commenters from industry preferred wider implementation. For example, one suggestion was to use the guidelines as a screen against existing regulations and to propose changes to the rules based on the potential for significant benefit.

   Response: NRC's current plans are to only implement the guidelines for new initiatives primarily because of NRC resource constraints. However, it should be noted that other mechanisms would continue to exist to identify potential changes to the regulatory framework.

6. Will these guidelines be effective in determining whether we can make a regulatory initiative more performance-based?

Comment: In general, to the extent that any comments were offered in this regard, the response was in the affirmative.

C. Establishment of Objective Performance Criteria

1. In moving to performance-based requirements, should the current level of conservatism be maintained or should introduction of more realism be attempted?

   Comments: Commenters expressed the view that the appropriate level of conservatism depends on the analysis methodology and the applicable assumptions. Defense-in-depth and uncertainty factors also need to be considered. One commenter stated that it should not be assumed that the level of defense-in-depth remain the same in a performance-based approach.

   Response: The NRC agrees with the commenters and amplifying guidelines have been modified or added under main guidelines associated with "Measurable (or calculable) parameters to monitor acceptable plant and licensee performance exist or can be developed" and "Increase effectiveness, efficiency and realism of the NRC activities and decision-making."

2 What level of conservatism (safety margin) needs to be built into a performance criterion to avoid facing an immediate safety concern if the criterion is not met?

   The comments and response from (C.1) above are also applicable here.

3. Recognizing that performance criteria can be set at different levels in a hierarchy (e.g., component, train, system, release, dose), on what basis is an appropriate level in the hierarchy selected for setting performance-based requirements, and what is the appropriate level of conservatism for each tier in the hierarchy?

   Comment: Oral and written comments expressed the view that performance criteria are best set at the function or system level.

   Response: Some amplifying guidelines which address this issue have been added under the main guideline of "Increase effectiveness, efficiency and realism of the NRC activities and decision-making".

4. Who would be responsible for proposing and justifying the acceptance limits and adequacy of objective criteria?

   Comment: A commenter suggested that the proponent of a change should bear the responsibility for justifying the criteria and the adequacy of acceptance limits.

   Response: The NRC agrees with the commenter. Some amplifying guidelines have been added under the main guideline of "The performance-based approach can be incorporated into the regulatory framework".

5. What are examples of performance-based objectives that are not amenable to risk analyses such as PRA or Integrated Safety Assessment?

   Comment: Examples offered were cross-cutting issues, including fitness-for-duty, safety conscious work environment and management effectiveness.

   Response: The NRC agrees with the commenter's examples and they are included in the Commission Paper.

6. In the context of risk-informed regulation, to what extent should performance criteria account for potential risk from beyond-design-basis accidents (i.e., severe accidents)?

   Comment: A commenter stated that risk-informed regulation reaches beyond design basis events by its nature.

   Response: The NRC agrees that risk-informed regulation needs to consider beyond-design-basis accidents.

D. Identification and use of measurable (or calculable) parameters

1. How and by whom are performance parameters to be determined?

   Comment: Comments were presented expressing concern that the NRC would be entirely dependent on licensees' own reports regarding performance. One commenter has stated that information collection at nuclear facilities may require changes to better measure performance. Another commenter raised concerns about licensee honesty and full disclosure.

   Response: The NRC would be responsible for setting the performance parameters with input from stakeholders. Further, the NRC would always maintain vigilance over performance observations. If information collection requirements need to be changed to implement a performance-based approach, such proposals will be addressed in the context of the specific regulatory requirement under consideration. No changes were made in the guidelines based on these comments.

2. How do you decide what a relevant performance parameter is?

   Comment: Some commenters expressed reservations with the use of performance parameters such as core damage frequency as a calculable parameter. Other comments cautioned against drawing broader conclusions (such as overall level of safety or lack thereof) from performance measures than may be justified.

   Response: As these considerations are context specific, and the merits of specific performance parameters are explicitly considered by the guidelines, no changes are proposed in the guidelines. However, on the basis of the experience gained from the limited testing of the guidelines, the scope of what is meant by "performance parameter" has been

expanded. It was found that a number of relevant parameters may be required to address the guidelines relative to a given regulatory issue.

3. How much uncertainty can be tolerated in the measurable or calculated parameters?

   Comment: Comments indicate a strong connection between consideration of uncertainty and the level of conservatism in establishing the performance parameters and acceptance criteria.

   Response: Changes made in response to (C.1) above are also applicable to this issue.

E. Pilot projects

1. Would undertaking pilot projects in the reactor, materials, and waste arenas provide beneficial experience before finalizing the guidelines?

   Comment: Some commenters stated that pilot projects would be useful, and others stated that they were not needed. One commenter suggested that it was important to learn appropriate lessons from implementation of the maintenance rule. Another commented that Option B of 10 CFR 50, Appendix J has already appropriately demonstrated the favorable results from a performance-based regulation.

   Response: The NRC plans to apply the guidelines to specific regulations as part of the implementation process and does not currently plan to conduct pilot projects. Based on testing, as reported in Attachment 3, the NRC believes the guidelines are sufficiently developed such that pilots are not needed.

2. What should be the relationship between any such pilot projects and those being implemented to risk-inform the regulations?

   Comment: Commenters generally stated that the ongoing pilot projects related to risk-informing the regulations need not be perturbed by including consideration of the guidelines, but appropriate coordination should be maintained. Any screening of regulations should be done one time as opposed to subjecting each regulation to various screenings at different times under different processes.

   Response: The NRC proposes to integrate the interfaces between performance-based and risk-informed activities so as to help ensure a more integrated approach and avoid duplication.

F. Other Comments

1. Eliminate all high-level guidelines used to evaluate opportunities for regulatory improvement (II. Guidelines to Assess Performance-Based Regulatory Change):

   Comment: One commenter at the public workshop suggested that the set of guidelines to assess performance-based regulatory improvement be eliminated.

Response: The NRC continues to believe that this set of guidelines constitutes an integral part of a structure and logic to consider explicitly the values important to any regulatory improvement program. No changes were made based on this comment.

2. Inclusion of the Advisory Committee on Medical Uses of Isotopes (ACMUI):

   Comment: One commenter at the public workshop suggested that ACMUI should be included among the advisory committees which would have an opportunity to review the high-level guidelines.

   Response: ACMUI has been included with ACRS and ACNW as committees whose feedback will be sought before the guidelines are submitted to the Commission.

3. Inclusion of perspective from the NRC regions in the work of the Performance-Based Regulations Working Group (PBRWG):

   Comment: One commenter at the public workshop suggested that a representative from the NRC regional offices should be included in the PBRWG, which will play an instrumental role in developing and applying the guidelines.

   Response: Regional representation has been added to the PBRWG.

4. Inspection and enforcement considerations:

   Comment: Comments from within and outside the NRC expressed the need for inspection and enforcement aspects to be front-end considerations. A commenter also suggested that performance above a threshold should result in reduced NRC scrutiny, as long as future departures from good performance would be detectable. Similarly, another commenter supported the notion that past performance could be used to determine the level of flexibility, thereby rewarding or penalizing licensees based on performance history.

   Response: An amplifying guideline has been added under the guideline "The performance-based approach can be incorporated into the regulatory framework" to address this comment.

5. Consideration of a significantly different regulatory paradigm:

   Comment: One commenter offered suggestions to significantly modify the regulatory framework so that any changes undertaken by the NRC would have as a pre-requisite an improvement in the level of safety.

   Response: The NRC notes that current NRC procedures fully allow for identification and implementation of safety enhancements subject to the Backfit Rule. The proposals presented would have wide ranging impacts, and consideration of performance-based initiatives would be only tangentially related to most of them. No specific changes to the guidelines were made in consideration of these comments.

Process and Case Studies Applying High-Level Guidelines

The purpose of this attachment is to present case studies in which the high-level guidelines are applied to specific regulatory provisions. The guidelines to assess viability are emphasized because they represent what is distinctive regarding identifying and assessing performance-based activities. The guidelines were applied to two areas. The first was based on a postulated set of regulatory requirements which the staff hypothesized may be identified as performance-based candidates. The second was a retrospective evaluation of a regulation recently promulgated to assess whether the changes could be seen as having made the existing regulation more performance-based.

Process, Concepts and Definitions

The high-level guidelines to assess viability center on selection or formulation of performance parameters and associated performance criteria. Application of these guidelines depend on certain definitions, which are developed below.

Kinds of "Performance"

In formulating a concept for performance, the staff has drawn on ideas used in the Revised Reactor Oversight Process, in which "performance" refers to those activities in design, procurement, construction, maintenance, and operation that support achievement of the objectives of the cornerstones of safety in the Reactor Oversight Process. In an analogous manner, other applications would entail identification of key aspects of performance and focus on activities which are important to safety.

Risk-significant performance changes generally affect system characteristics such as frequency of events and reliability, availability, or capability of systems, structures, and components (SSCs). Here, "capability" refers to the physical capacity of the system to accomplish a given function, such as "deliver required flow at a given pressure," "successfully bear a given load," or "effectively filter air taken into a breathing apparatus." Availability refers to the fraction of time that the SSC is capable of performing its function. Reliability refers to the probability that a given SSC will function on demand and during the required mission time, given that it was available.

Many kinds of performance affect the system characteristics including such factors as human performance, and the condition in which equipment is left after preventive or corrective maintenance (recognizing that the conduct of testing and maintenance itself affects availability). Ultimately, licensee corrective action programs also affect reliability and availability. Even spare parts management can affect availability.

Characteristics of Functional Safety Requirements

A complete functional safety requirement includes the following:

(1) A definition of the safety mission to be carried out.

This entails at least an implicit specification of the physical challenge that needs to be met. Meeting the challenge will require a level of performance characterized in terms of one or more physical parameters such as flowrate at a particular pressure, or heat removal rate. The system performance specification may be made implicitly, as when a functional outcome is mandated, conditional on a specific challenge (such as maximum peak clad temperature following a specific LOCA, or "no containment failure due to hydrogen combustion" following major core damage).

(2) An indication of the required degree of assurance (functional reliability) that the mission will be carried out successfully.

Assurance of successful performance has previously been approached using concepts such as redundancy (single-failure proof design), special treatment requirements (in procurement, installation, and surveillance), and limiting conditions of operation (so that individual trains or channels of the system cannot be out of service longer than allowed outage times). Surveillance testing or inspection may be mandated at specified intervals so that the probability of undetected faults is limited. System reliability can be promoted by requirements on redundancy, QA, surveillance testing, and allowed outage times.

Implementation Phases of Functional Safety Requirements

There are two distinct kinds of activities involved in implementation of functional safety requirements involving performance parameters. The first kind of activity is associated with design and construction (includes design, procurement, installation and gaining assurance that system design is capable of achieving the desired reliability). The second kind of activity is operational and aimed at maintaining the required reliability and availability. It includes such things as surveillance testing, preventive maintenance, corrective maintenance, and corrective action programs. In the regulatory sphere the first kind of activity is generally associated with licensing. Later plant modifications may also be included. The first kind of activity includes formulation, initial achievement, and subsequent modification of a safety case; the second kind of activity is aimed at keeping the current safety case valid.

Hierarchy of Regulatory Framework

Current regulatory requirements are formulated at several distinct levels which are termed as the hierarchical structure within the regulatory framework. Rules generally state high-level requirements, while lower-level guidance documents provide more specific guidance, including examples of acceptable ways to meet requirements. Technical Specifications and other license conditions also play a role in imposing requirements on licensees. It is found that assessment of the viability of performance-based approaches in a given area is best discussed in light of a comprehensive picture of requirements existing at all of these levels.

Rule Level

The rule states the mission, including the challenges to be addressed and the definition of successful performance. Some existing rules explicitly quantify physical success criteria, such

as peak clad temperature, or percentage of metal assumed to react with water to produce hydrogen in certain scenarios.

Evaluation Guidance Level

At this level, which includes both regulatory guides and standard review plans, numerical success criteria are given if they were not stated as part of the rule. These may relate to capability requirements or reliability requirements. Guidance at this level does not have the standing of rules, but it may articulate standards that are considered to be a way to satisfy the intent of rules.

Guidance on acceptable evaluation methods is also provided, including conservative analysis assumptions that may be required in order to assure that conclusions based on the evaluations are robust.

Operational Level (Technical Specifications, Commitments, other elements of the Licensing Basis, etc.)

At this level, requirements are aimed at assuring that assumptions related to safety are upheld. Requirements may be imposed on surveillance test interval and/or test protocol. Technical Specifications may limit the amount of time that the plant is allowed to operate with certain equipment trains out of service. Consensus standards cited by rules are also effectively operational level guidance.

Case Study 1: Combustible Gas Control

This case study applies the viability guidelines to a hypothetical new requirement concerning combustible gas control. The purpose of this hypothetical requirement is to control the probability of containment failure from uncontrolled burns of combustible gas which can occur under certain scenarios in certain containment designs. If the requirement satisfies the viability guidelines concerning measurable performance parameters, objective performance criteria, licensee flexibility, and safety margin, this is an indication that the requirement can be made performance-based.

The case study assumes the following:

- For plants with certain containment designs, some risk-significant scenarios lead to the burning of combustible gas at levels that can threaten containment integrity.
- A technical basis exists for identifying and quantifying risk-significant scenarios and their elements on a plant-specific basis.
- A technical basis exists for quantifying the amounts and rates of generation of combustible gases, and modeling the phenomenology of burns (including the resulting loads).

- A technical basis exists for analysis of containment response to loads caused by combustion of gas.

- A technical basis exists for establishing a needed functional reliability. This could be derived from an argument based on the Quantitative Health Objectives (QHOs), the frequency at which this function is challenged, and the expected radiological consequences of functional failure of combustible gas control, given that it is challenged.

Formulation of a Requirement on Combustible Gas Control

For purposes of this illustration, a hypothetical requirement on combustible gas control has been formulated that would be applicable to specific classes of plants. This hypothetical requirement on combustible gas control is characterized as follows in terms of the concepts discussed above.

The Safety Issue:

The safety issue is prevention of failure of containment due to loads caused by burning of combustible gases in conjunction with other loads (e.g., steam pressurization, HPME) during risk-significant core damage scenarios that produce significant amounts of combustible gas. The emphasis on "risk-significant" core damage scenarios means that station blackout sequences need to be addressed (including the availability of power for ignition systems) and the phenomenology of core damage scenarios needs to be allowed for, including the amounts and rates of hydrogen generation and the severity of the environments that result. It is also necessary to include methodology for evaluation of containment loads resulting from burns, and specification of required margin on containment performance, if this is warranted.

Physical Definition of Success:

A possible definition of success is "Prevention of containment failure from burning of combustible gas concurrent with other containment loadings, given severe core damage with accompanying evolution of gas."

This is to be assessed using evaluation methods and assumptions mandated in specification of the safety issue (above), and depends on technology. For igniters, it will be necessary to specify physical ignition capability: surface temperature, number, and distribution.

Depending on implementation of technology selected, Technical Specifications on capability may be warranted (specification of the physical ignition capability required to be confirmed by test).

Specification of Functional Reliability Needed To Meet Requirement:

As discussed earlier, the desired functional reliability can be determined from such considerations as the QHOs, the consequences of functional failure, and the frequency of challenges to this function (the frequency of severe core damage). In the discussion that follows, it is assumed that such a determination has been carried out, and that for plants in the

class subject to this requirement, the overall functional failure probability is to be maintained well below 0.1. This probability is conditional on the scenario ingredients called out previously, such as station blackout. This assumption bears on licensee flexibility and on the feasibility of detecting performance changes within a reasonable time.

As formulated, this hypothetical requirement specifies evaluation methodologies with respect to the challenge and definition of success. These evaluations could be carried out on a plant-specific basis, or for classes of plants; for purposes of the present case study, it is tacitly assumed that each plant carries out the evaluations according to the acceptable methodologies. The performance parameters thus derived will take credit for aspects of containment performance that are themselves the subject of other requirements, which may be prescriptive. The hypothetical requirement does not force a choice of technology.

Application of the Viability Guidelines

The following aspects of the overall requirement, as hypothesized, warrant consideration as areas that could be performance-based: igniter capability, functional reliability, division reliability, and division availability. (For this case study, the choice of igniter technology is presumed, although this choice might not be made in all cases.) Atmospheric mixing is a related area that could be performance-based, but it is not treated here. The following discussion applies the four viability guidelines to each potential performance-based area in turn.

Igniter Capability:

In order to succeed, the igniter function must provide sufficient physical capability (e.g., enough surface area at a sufficiently high temperature). The functional reliability associated is discussed separately.

> Guideline IA: Several capability parameters exist: surface temperature, number, and distribution.
>
> Guideline 1B: Criteria for each of these parameters can be developed based on ignition phenomenology.
>
> Guideline IC: Within igniter technology, relatively little flexibility in achieving these parameters may exist, but choice of technology itself may be allowed.
>
> Guideline ID: Provided that performance is actually monitored periodically, so that the failure is detected in test and not in an actual accident scenario, not meeting the criterion does not immediately cause a safety concern. This is based on the fact that the frequency of severe core damage is itself limited.

Functional Reliability:

Here, the phrase "functional reliability" refers to the probability that the ignition function will be carried out successfully, given that a need for the function arises. Since the function may be performed by a collection of SSCs, which may be designed to allow for some failures, the

functional reliability depends on lower-level figures of merit such as division-level, train-level, or component-level reliability and availability.

Guideline IA: This guideline is met. At the functional level, for this case, it would be calculated from division and component level performance and availability data.

Guideline IB: This guideline is met. Functional reliability criterion is derivable as indicated above from QHO arguments, or could be formulated based on other lines of reasoning.

Guideline IC: Choice of technology is one level of flexibility. Within igniter technology, there is flexibility in system redundancy and in licensee management of division availability.

Guideline ID: Declining reliability is not an immediate safety concern. This is based on the fact that the frequency of severe core damage is itself limited.

Division Reliability:

Here, the phrase "division reliability" refers to the reliability of a functional subset of the igniter function. In fact, divisional redundancy may not be required for this function – it is possible that a single division might meet the requirement. The present discussion tacitly assumes that some redundancy would be incorporated into the design. Depending on the design, the functional reliability requirement would then be decomposed into division reliability requirements and division availability requirements.

Guideline IA: Division reliability would be calculated from component level performance data.

Guideline IB: An objective criterion can be developed based on the functional reliability criterion discussed above.

Guideline IC: There is flexibility in design and in operational practices to meet this requirement.

Guideline ID: Declining reliability is not an immediate safety concern. This is based on the fact that the frequency of severe core damage is itself limited.

Division Availability:

Here, the phrase "division availability" refers to the availability of a functional subset of the igniter function. In fact, divisional redundancy may not be required for this function - it is possible that a single division might meet the requirement. The present discussion tacitly assumes that some redundancy would be incorporated into the design.

Guideline IA: Division availability would be evaluated directly from test and maintenance records.

Guideline IB: An objective criterion would be developed, based on system redundancy, the functional reliability criterion and the division reliability criterion discussed above.

Guideline IC: Flexibility exists in licensee management of maintenance.

Guideline ID: Not meeting the availability criterion would not be an immediate safety concern. In addition to factors cited above for other parameters, the availability criterion has the property of being relatively easily observable, in that changes in performance are not masked by statistical fluctuations.

Summary

For active ignition technology, several capability parameters were identified. These satisfy some of the remaining guidelines in that they are measurable, criteria exist, and failure to meet performance criteria does not result in an immediate safety concern. However, within igniter technology, there may not be very much flexibility in meeting these criteria. Other technologies could be considered. Inquiry needed to establish the practicality or necessity of monitoring the efficacy of atmospheric mixing was not carried out.

Reliability parameters satisfy three of the four guidelines and might satisfy the fourth. Criteria can be derived, flexibility is afforded, and failure to satisfy reliability requirements is not an immediate safety concern. However, whether it is practical to confirm reliability through monitoring is a plant-specific evaluation. Viability requires that unacceptable performance cause enough failure events within a reasonable monitoring time to manifest the current (degraded) performance level. For this system, it is expected that quantitative evaluation would lead to a satisfactory finding for this guideline as well.

Therefore, the viability guidelines are substantially satisfied by several key elements of this requirement. A substantially performance-based version of this requirement would be viable. However, as noted previously, the evaluations carried out for this area will take credit for passive containment performance under severe conditions including high temperatures. Performance-basing of requirements on these less-testable aspects of containment integrity may not be viable. Moreover, this hypothetical requirement mandates evaluation of the frequency of this particular functional challenge (i.e., the frequency of severe core damage events that challenge this function). This frequency itself reflects credit for satisfaction of requirements that may not be performance-based. Nevertheless, the utility of the guidelines has been demonstrated to identify elements of the regulatory framework which can be made substantially performance-based.

Case Study 2: Respiratory Protection and Controls to Restrict Internal Exposure in Restricted Areas

This case study applies all three groups of guidelines to examine the recent changes to 10 CFR 20, Subpart H, Respiratory Protection and Controls to Restrict Internal Exposures. The stated goals of the revision were to revise the requirements to reflect current guidance (ANSI

and OSHA) and to make the requirements for radiological protection less prescriptive while reducing unnecessary regulatory burden without reducing worker protection. A review of the changes made to the requirements indicates three generic types of changes:

- Administrative changes that clarify the requirements,
- Regulatory framework changes to the structure of the requirements resulting in a more logical order (e.g., moving Appendix A footnotes to the regulatory text), and
- Regulatory changes that actually change the requirements explicitly identified in the rule and thus may impact the licensees' regulatory burden.

The purpose of this case study is to apply the three groups of guidelines to specific regulatory requirements and determine whether the revised rule can be judged to be more performance-based than the prior version of the rule. Hence, the guidelines are being applied as an assessment tool to the changes made to the rule by the recent revision, and not to the rule as a whole. The assessment was performed using a sampling approach. To assess the impact of the change to Subpart H, three of the changes to the rule were analyzed. The three changes selected were of the third type above. One change reflected an increased regulatory burden, one a reduction in regulatory burden, and one an overall neutral impact on the regulatory burden.

Application of the Viability Guidelines

The sample of three rule changes are examined below:

(i) A provision to reduce regulatory burden was contained in §20.1702(b), which added text to permit licensees to consider safety factors other than radiological factors when performing an ALARA analysis to determine whether or not respirators should be used. Applying the viability guidelines to assess this change results in the following:

> Guideline I.A.: The parameters should reflect licensee performance of the ALARA program as well as consider non-radiological factors that affect worker safety. Under the original rule requirements, the non-radiological factors had to be considered, but were divorced from the radiological ALARA determination. This could have resulted in reduced worker protection from non-radiological factors while licensees sought to meet ALARA requirements. Measurable or calculable parameters would be available from performance history associated with the non-radiological and ALARA factors. When compared to the prior version of the Subpart H requirements, the revised requirement would only require identification of parameters associated with non-radiological safety factors, such as trending of occupational health and safety incidents, in addition to parameters associated with radiological factors.
>
> Guideline I.B.: Objective criteria to assess performance of a licensee's ALARA program exist in the form of past performance. Objective criteria on performance of a licensee's ALARA program could be based on trending of worker doses.

Guideline I.C.: The prior version of the requirement allowed licensee flexibility by the definition of ALARA. The revised requirement provides another degree of freedom for the ALARA analysis by including non-radiological safety factors. Under the revised requirement, it is possible for the ALARA analysis to result in higher doses to workers but lower overall risk to the workers once non-radiological safety factors are included. By allowing slightly higher worker doses in this scenario, the NRC has provided the licensee increased flexibility. Thus, flexibility is increased with the revised requirement.

Guideline I.D.: By definition, the ALARA program operates in a dose regime that does not correspond to an immediate safety concern. Generally, the airborne concentrations of radioactive material are such that failure of performance criteria will not result in an immediate safety concern. By including non-radiological safety factors, the revised requirement should result in lower total risk. Thus, the revised requirement should generally increase the safety margin. On occasion, hazards may be such that a failure of equipment might result in a relatively small safety margin. These rare cases result in more prescriptive requirements for equipment that will be discussed in further detail in the next requirement change example.

Summary – This change expands the scope of the ALARA analysis by including non-radiological safety factors. This introduces greater flexibility by not requiring respirator use in some circumstances in which it would previously have been required. The licensee may, however, expend some extra effort in justification. The net effect may be to decrease overall licensee burden. In summary, this change satisfies the viability guidelines, making the revised rule more performance based than the prior version.

(ii) A provision that increased regulatory burden was contained in §20.1703(c)(6) which added text to require fit testing before first field use of tight-fitting, face sealing respirators and at least annual testing thereafter. The quantitative criteria for successful fit testing are also codified. The prior version of the rule only included a requirement that the licensee's respiratory protection program include written procedures for fitting. The revised rule does not alter these requirements, but includes specific requirements for fit testing frequency and quantitative criteria for test fit factors that must be achieved during testing in order to use the Appendix A APFs. These new specific requirements explicitly provide lower-level (less outcome-oriented) objective criteria for assessing fit testing. Both the prior version of the rule and the revised rule included a requirement that the licensee include surveys and bioassays, as necessary, to evaluate actual intakes in the respiratory protection program. Applying the viability guidelines to assess this change results in the following:

Guideline I.A.: The parameters that measure desired outcomes associated with this requirement, dose due to internal exposure, are not affected by this change. The revised requirement explicitly mentions lower-level parameters for monitoring performance, but these parameters do not measure outcomes and were implicit in the prior version of the rule.

Guideline I.B.: Objective criteria to assess performance of a licensee's fit testing exist. The revision simply explicitly stated some of the objective criteria for fit testing.

Guideline I.C.:The prior version of the rule allowed licensee flexibility by only specifying that a written procedure for fitting be included in the respiratory protection program. The revision adds requirements at a lower level: it increases the specificity of requirements imposed by the rule. Thus, application of the third viability guideline would indicate that the revised rule may be less performance-based.

Guideline I.D.: For performance in the area of respirator equipment fitting, sufficient safety margin may not exist when performance criteria are not met. As discussed above in the analysis of the ALARA program, hazards may be such that a failure of the respirator fitting properly may result in a relatively small safety margin. In addition, time is not available for taking corrective action due to the nature of the hazards, such as internally deposited radioactive material or non-radioactive airborne materials, and the typical frequency of surveys and bioassays. These scenarios require prescriptive requirements for fit testing. In addition, since proper fit is assumed when making dose calculations for legal records, prescriptive requirements are necessary to provide the proper assurance of accuracy. This guideline therefore corresponds to the motivation for the rule change.

Summary – This revision to the rule does not make the rule more performance-based. However, the reason for this is that sufficient safety margin and time for taking corrective action do not exist in the event the performance criteria are not met. The viability guidelines indicate that this area of the rule is not suitable for performance-based activities and support the motivation for the rule change.

(iii) A provision considered neutral relative to regulatory burden was included in the rulemaking relative to §20.1703(a)(6) [which becomes §20.1703(e) in the revised rule] such that text was added to require consideration of low temperature freezing of exhaust valves on negative pressure respirators, and removed text that specified protection against skin contamination. The only difference between the prior version of the rule and the revised rule for this particular change is the list of requirements explicitly mentioned by the rule that need to be considered when selecting respiratory protection equipment. Adding the requirement for consideration of low temperature work environments increases the analysis effort explicitly required. Removing the requirement for consideration of skin contamination requires the licensee to address skin contamination using means other than respiratory equipment. Applying the viability guidelines to assess this change results in the following:

Guideline I.A.: The parameters would be equivalent for the prior version of the rule and the revised rule.

Guideline I.B.: The objective criteria may be based on performance history.

Guideline I.C.: Although the list of requirements explicitly mentioned changes, the net affect on licensee flexibility is negligible. The level of specificity of the explicit requirements does not change. Since the objective criteria remain equivalent, the flexibility is unchanged by the change to the Subpart H requirements.

Guideline I.D.: Failure to meet the performance criteria of either the prior version of the rule or the revised rule could lead to situations that do not provide sufficient safety margin

or time for taking corrective actions. For example, failure to consider low temperature work environments could result in exhalation valves on negative pressure respirators to freeze in the open position due to moisture from exhaled air when temperatures are below freezing. This situation would provide a pathway for airborne hazards, such as radioactive material, to bypass the respirator filter without the users knowledge. Thus, requirements are necessary to provide worker protection while in radioactive areas. This guideline therefore corresponds to the motivation for the rule change.

Summary – The revised rule is neither more or less performance-based than the prior version of the rule. The specific requirements changed in this example are prescriptive due to the fact that sufficient safety margin and time for taking corrective action do not exist in the event the performance criteria are not met. This example does demonstrate the validity of using the viability guidelines to assess performance-based activities and support the motivation for the rule change.

Conclusion: Application of the guidelines to the three selected changes to the rule indicates that the changes appear to comport with the guidelines. A premise in the testing of the guidelines was that the process of testing may indicate a need to change one or more of the guidelines. The guidelines worked well as they are and no changes are proposed as a result of the testing.

Application of the Guidelines to Assess Performance-Based Regulatory Change

For completeness, the changes to the requirements of Subpart H were evaluated against the remaining performance-based guidelines to verify that the changes resulted in a net regulatory benefit. For this evaluation, the composite of all the changes must be evaluated to provide the integrated consideration required, rather than evaluating each change individually. Thus, the results of the sampling approach above are extrapolated to include all changes to the rule when necessary. However, this evaluation is based primarily on the existing results contained in the staff's Statement of Considerations and the Regulatory Analysis for the amendment of Subpart H requirements.

Guideline II.A.: The following factors were noted:

- Allowing the consideration of non-radiological safety factors when performing an ALARA analysis results in an overall reduction in the worker's risk from all hazards;
- Explicitly identifying fit test criteria, intended to ensure that sufficient margin of safety (specifically, proper fit) is maintained under field and work conditions, increases assurance that respiratory equipment will perform as expected during use;
- Explicitly identifying environmental factors, such as low temperatures, for consideration in determining respiratory protection increases assurance that the proper operation of respiratory equipment will not be adversely affected during use.

Guideline II.B.: The following factors were noted:

- Identifying regulatory requirements in the amended rule text and removing guidance from the rule, such as moving some of the Appendix A footnotes to the regulatory text and deleting some that are addressed in the Regulatory Guide, clarifies the requirements and reduces confusion;

- Recognizing new devices and new technologies updates the rule to reflect current practices by licensees;

- Allowing use of single-use disposable masks when ALARA analysis indicates that respiratory protection is not necessary, provides a means for addressing respiratory protection equipment when requested by the worker.

Guideline II.C.: The following factors were noted:

- Including decontamination to reduce resuspension of radioactive material in the work place provides an effective and efficient means of controlling internal dose instead of using respirators;

- Adopting the existing guidance of ANSI, such as reduced equipment assigned protection factors (APFs) provides consistency;

- Adopting the existing requirements of OSHA, such as fit testing frequency and fit factors for positive pressure, continuous flow, and positive-demand devices, provides consistency.

Guideline II.D: The following was noted:

- Each amendment to the rule was reviewed by the staff to determine the impact on licensee burden and the conclusion was that 13 amendments reduced burden, 3 amendments increased burden, and 36 amendments had no impact on burden; with the net result being a reduction in licensee burden.

Guideline II.E: The following was noted:

The backfit analysis performed by the staff for the amendments concluded that the changes constitute not only a burden reduction, but also a substantial increase in the overall protection of public (worker) health and safety. Based on a review of public comments, public confidence is not significantly affected by the rule amendments. However, it is assumed that the substantial increase in the overall protection of worker health and safety would result in an associated increase in public confidence. The Regulatory Analysis estimated a net benefit of $1.5 million per year, including the cost to revise licensee procedures. Finally, since this is an amendment to an existing rule, the regulatory framework can inherently incorporate the approach into the existing regulatory framework. Thus, the existing Regulatory Analysis adequately addresses the regulatory improvement guidelines, demonstrating that the amendments to the rule result in a net regulatory benefit.

Application of the Guidelines to Assure Consistency with Other Regulatory Principles

The revision is inherently consistent with other regulatory principles. However, use of the guideline will support the assertion that the guideline is valid for evaluating future performance-based activities. The revised rule is consistent with 1992 American National Standards Institute (ANSI) guidance for respiratory protection and respiratory protection regulations published by Occupational Safety and Health Administration (OSHA). The findings of the environmental assessment analysis state that the revised rule is expected to result in a decrease in the use of respiratory protection and an increase in engineering and other controls to reduce airborne contaminants while maintaining total occupational dose as low as reasonably achievable. Thus, subject to the limitations of the sampling approach used, the revision to the rule is consistent with other regulatory principles.

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON D.C 20555-0001

June 22, 2000

The Royal College of Physicians and Surgeons of Canada
774 Promenade Echo Drive
Ottawa, ON Canada KIS 5N8

SUBJECT: RECOGNITION OF BOARDS

Dear Sir:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

I am writing to notify you of our intent to initiate the recognition process immediately. Other specialty boards whose diplomates are likely to seek authorization are being similarly notified. If you are interested in having your board recognized by the NRC, please submit a letter to me listing each training and experience section of the rule for which you believe your Board's diplomates should be deemed to have met the requirements. Enclosures 1 and 2 should assist you in preparing your letter. Enclosure 1 lists all areas where NRC plans to recognize boards. Enclosure 2 is a copy of the draft final regulatory text that lists the training and experience criteria for authorized medical physicists, authorized nuclear pharmacists, authorized users, and Radiation Safety Officers.

Your letter should clearly state that an individual must have completed the training and experience required by a particular section prior to receiving board certification. For example, if your board would like to be recognized under 10 CFR 35.390, "Training for use of unsealed byproduct material for which a written directive is required," the letter should state: (the name of your organization) has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this section prior to being certified by our board."

The letter should be dated and signed by the chief executive of your board. If you have any

questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

Enclosures:
1. Areas where NRC plans to recognize boards
2. Draft Final Regulatory Text - Training and Experience Criteria

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON D.C 20555-0001

June 22, 2000

The American Board of Medical Physics, Inc.
c/o Credentialing Services, Inc.
ATTN: Dr. Larry Reinstein
Chairman
P.O. Box 1502
Galesburg, IL 61402-1502

SUBJECT: RECOGNITION OF BOARDS

Dear Dr. Reinstein:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

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(the name of your organization) has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this

section prior to being certified by our board."
The letter should be dated and signed by the chief executive of your board. If you have any questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

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UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON D.C 20555-0001

June 22, 2000

American Board of Health Physics
ATTN: Mr. Richard J. Burke, Jr.
Executive Director
1313 Dolly Madison Boulevard, Suite 402
McLean, Virginia 22101

SUBJECT: RECOGNITION OF BOARDS

Dear Mr. Burke:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

I am writing to notify you of our intent to initiate the recognition process immediately. Other specialty boards whose diplomates are likely to seek authorization are being similarly notified. If you are interested in having your board recognized by the NRC, please submit a letter to me listing each training and experience section of the rule for which you believe your Board's diplomates should be deemed to have met the requirements. Enclosures 1 and 2 should assist you in preparing your letter. Enclosure 1 lists all areas where NRC plans to recognize boards. Enclosure 2 is a copy of the draft final regulatory text that lists the training and experience criteria for authorized medical physicists, authorized nuclear pharmacists, authorized users, and Radiation Safety Officers.

Your letter should clearly state that an individual must have completed the training and experience required by a particular section prior to receiving board certification. For example, if your board would like to be recognized under 10 CFR 35.390, "Training for use of unsealed byproduct material for which a written directive is required," the letter should state: (the name of your organization) has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this section prior to being certified by our board."

The letter should be dated and signed by the chief executive of your board. If you have any questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

Enclosures:
1. Areas where NRC plans to recognize boards
2. Draft Final Regulatory Text - Training and Experience Criteria

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON D.C 20555-0001

June 22, 2000

Board of Pharmaceutical Specialties
ATTN: Mr. Richard Bertin
Executive Director
2215 Constitution Avenue, NW
Washington, DC 20037-2985

SUBJECT: RECOGNITION OF BOARDS

Dear Mr. Bertin:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

I am writing to notify you of our intent to initiate the recognition process immediately. Other specialty boards whose diplomates are likely to seek authorization are being similarly notified. If you are interested in having your board recognized by the NRC, please submit a letter to me listing each training and experience section of the rule for which you believe your Board's diplomates should be deemed to have met the requirements. Enclosures 1 and 2 should assist you in preparing your letter. Enclosure 1 lists all areas where NRC plans to recognize boards. Enclosure 2 is a copy of the draft final regulatory text that lists the training and experience criteria for authorized medical physicists, authorized nuclear pharmacists, authorized users, and Radiation Safety Officers.

Your letter should clearly state that an individual must have completed the training and experience required by a particular section prior to receiving board certification. For example, if your board would like to be recognized under 10 CFR 35.390, "Training for use of unsealed byproduct material for which a written directive is required," the letter should state:
(the name of your organization) has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this section prior to being certified by our board."

The letter should be dated and signed by the chief executive of your board. If you have any questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

Enclosures:
1. Areas where NRC plans to recognize boards
2. Draft Final Regulatory Text - Training and Experience Criteria

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

June 22, 2000

The American Board of Radiology
ATTN: Dr. M. Paul Capp
Executive Director
5255 E. Williams Circle, Suite 3200
Tucson, AZ 85711-7409

SUBJECT: RECOGNITION OF BOARDS

Dear Dr. Capp:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

I am writing to notify you of our intent to initiate the recognition process immediately. Other specialty boards whose diplomates are likely to seek authorization are being similarly notified. If you are interested in having your board recognized by the NRC, please submit a letter to me listing each training and experience section of the rule for which you believe your Board's diplomates should be deemed to have met the requirements. Enclosures 1 and 2 should assist you in preparing your letter. Enclosure 1 lists all areas where NRC plans to recognize boards. Enclosure 2 is a copy of the draft final regulatory text that lists the training and experience criteria for authorized medical physicists, authorized nuclear pharmacists, authorized users, and Radiation Safety Officers.

Your letter should clearly state that an individual must have completed the training and experience required by a particular section prior to receiving board certification. For example, if your board would like to be recognized under 10 CFR 35.390, "Training for use of unsealed byproduct material for which a written directive is required," the letter should state:
"(the name of your organization) has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this section prior to being certified by our board."

The letter should be dated and signed by the chief executive of your board. If you have any questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

Enclosures:
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UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON D.C 20555-0001

June 22, 2000

American Osteopathic Board of Radiology
ATTN: Ms. Pamela Smith
Executive Director
119 East Second Street
Milan, MO 63556-1331

SUBJECT: RECOGNITION OF BOARDS

Dear Ms. Smith:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

I am writing to notify you of our intent to initiate the recognition process immediately. Other specialty boards whose diplomates are likely to seek authorization are being similarly notified. If you are interested in having your board recognized by the NRC, please submit a letter to me listing each training and experience section of the rule for which you believe your Board's diplomates should be deemed to have met the requirements. Enclosures 1 and 2 should assist you in preparing your letter. Enclosure 1 lists all areas where NRC plans to recognize boards. Enclosure 2 is a copy of the draft final regulatory text that lists the training and experience criteria for authorized medical physicists, authorized nuclear pharmacists, authorized users, and Radiation Safety Officers.

Your letter should clearly state that an individual must have completed the training and experience required by a particular section prior to receiving board certification. For example, if your board would like to be recognized under 10 CFR 35.390, "Training for use of unsealed byproduct material for which a written directive is required," the letter should state: "(the name of your organization) has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this section prior to being certified by our board."

The letter should be dated and signed by the chief executive of your board. If you have any questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

Enclosures:
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UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON D.C 20555-0001

June 20, 2000

American Osteopathic Board of Nuclear Medicine
Chairman: T. Bryson Struse III, D.O.
142 E. Ontario Street
Chicago, IL 60611

SUBJECT: RECOGNITION OF BOARDS

Dear Dr. Struse:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

I am writing to notify you of our intent to initiate the recognition process immediately. Other specialty boards whose diplomates are likely to seek authorization are being similarly notified. If you are interested in having your board recognized by the NRC, please submit a letter to me listing each training and experience section of the rule for which you believe your Board's diplomates should be deemed to have met the requirements. Enclosures 1 and 2 should assist you in preparing your letter. Enclosure 1 lists all areas where NRC plans to recognize boards. Enclosure 2 is a copy of the draft final regulatory text that lists the training and experience criteria for authorized medical physicists, authorized nuclear pharmacists, authorized users, and Radiation Safety Officers.

Your letter should clearly state that an individual must have completed the training and experience required by a particular section prior to receiving board certification. For example, if your board would like to be recognized under 10 CFR 35.390, "Training for use of unsealed byproduct material for which a written directive is required," the letter should state: _(the name of your organization)_ has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this section prior to being certified by our board."

The letter should be dated and signed by the chief executive of your board. If you have any questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

Enclosures:
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UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON D.C 20555-0001

June 22, 2000

The American Board of Nuclear Medicine
ATTN: Dr. Ronald L. Van Heertum
Chairman
900 Veteran Avenue
Los Angeles, CA 90024-1786

SUBJECT: RECOGNITION OF BOARDS

Dear Dr. Van Heertum:

As you know, the Nuclear Regulatory Commission (NRC) is revising its medical use regulations in 10 CFR Part 35, "Medical Use of Byproduct Material." I anticipate the Commission will publish the final rule in the Federal Register in 2000, with an effective date 6 months after publication. As part of this revision, the regulatory text will no longer incorporate a listing of the specific boards whose diplomates automatically fulfill the training and experience requirements for an authorized medical physicist, authorized nuclear pharmacist, authorized user, or Radiation Safety Officer. Rather, the NRC will recognize certification boards that require individuals to complete the training and experience requirements specified in the regulatory text. Once recognized, the board's name will be placed on the list of recognized boards maintained on the NRC website. This change is being made to eliminate the need for a rulemaking each time a board is added or deleted.

I am writing to notify you of our intent to initiate the recognition process immediately. Other specialty boards whose diplomates are likely to seek authorization are being similarly notified. If you are interested in having your board recognized by the NRC, please submit a letter to me listing each training and experience section of the rule for which you believe your Board's diplomates should be deemed to have met the requirements. Enclosures 1 and 2 should assist you in preparing your letter. Enclosure 1 lists all areas where NRC plans to recognize boards. Enclosure 2 is a copy of the draft final regulatory text that lists the training and experience criteria for authorized medical physicists, authorized nuclear pharmacists, authorized users, and Radiation Safety Officers.

Your letter should clearly state that an individual must have completed the training and experience required by a particular section prior to receiving board certification. For example, if your board would like to be recognized under 10 CFR 35.390, "Training for use of unsealed byproduct material for which a written directive is required," the letter should state:
(the name of your organization) has reviewed 10 CFR 35.390 and has determined that our certification process requires an individual to meet all the requirements in paragraph (b) of this section prior to being certified by our board."

The letter should be dated and signed by the chief executive of your board. If you have any questions or comments, please contact Ms. Catherine Haney of my staff (301-415-6825 or E-mail at cxh@nrc.gov) .

Sincerely,

Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety

Enclosures:
1. Areas where NRC plans to recognize boards
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The American Board of Nuclear Medicine

A Member Board of the American Board of Medical Specialties

Chairman
Ronald L. Van Heertum, M.D.
New York, New York

Vice Chairman
Robert E. Carretta, M.D.
Roseville, California

Secretary-Treasurer
Martin L. Nusynowitz, M.D.
Galveston, Texas

Paul V. Dubovsky, M.D.
Birmingham, Alabama

Michael M. Graham, M.D.
Iowa City, Iowa

Lawrence E. Holder, M.D.
Baltimore, Maryland

Mary H. Maurer, M.D.
Philadelphia, Pennsylvania

David C. Price, M.D.
San Francisco, California

[illegible] Sandler, M.B., Ch.B.
Memphis, Tennessee

Leonard B. Silberstein, M.D.
Cincinnati, Ohio

Andrew E. Taylor, M.D.
Atlanta, Georgia

S. Ted Treves, M.D.
Boston, Massachusetts

Executive Director
William H. Blahd, M.D.
Los Angeles, California

Associate Executive Director
Heinrich R. Schelbert, M.D.
Los Angeles, California

Administrator
Gloria W. Gorden, M.P.H.
Los Angeles, California

Please Address All Communication To:

900 Veteran Avenue
Los Angeles, CA 90024-1786
Telephone (310) 825-0787
Fax (310) 825-0435

July 10, 2000

Donald A. Cool
Director, Division of Industrial
and Medical Nuclear Safety
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Mr. Cool:

I am responding to your letter of June 22, 2000 concerning the recognition of boards whose diplomates automatically fulfill the training and experience requirements for authorized use of byproduct materials. I am writing to you on behalf of the American Board of Nuclear Medicine (ABNM), which is a medical specialty certifying board recognized by the American Board of Medical Specialties, the American Medical Association, and the Council of Medical Specialty Societies. Since its inception in 1971, ABNM has examined and certified approximately 5000 physicians as specialists in the clinical use of byproduct materials. Certification by ABNM has been recognized in the past by the NRC as sufficient indication of competence in the safe uses of byproduct materials, and it has issued licenses to physicians certified by the ABNM for all categories of use of unsealed byproduct materials

In conjunction with the Council on Medical Education of the American Medical Association and the Society of Nuclear Medicine, the ABNM sponsors a Nuclear Medicine Residency Review Committee that establishes criteria for residency training in nuclear medicine. The Residency Review Committee currently oversees 69 nuclear medicine residency training programs. All nuclear medicine training programs are monitored and routinely audited by the Accreditation Council on Graduate Medical Education.

Nuclear Medicine programs comprise three years of training, which includes one year of preparatory clinical experience and two years of full-time nuclear medicine instruction. They are highly structured educational programs that encompass both basic science and clinical instruction. Basic science instruction includes the following areas: radiation physics and instrumentation, radiation protection, mathematics pertaining to the use and measurement of radioactivity, radiation biology and radiation dosimetry, and substantially exceed 200 hours of didactic instruction. In addition, residents receive

more than 700 hours of training and experience in basic radionuclide handling techniques that are applicable to the medical use of unsealed byproduct material for imaging and localization studies, and for radionuclide therapy that requires a written directive. The programs also provide training in radiation safety, including shipping, receiving, and assaying of radioactive materials and the use of instrumentation, such as survey meters and calibration meters. Instruction in the prevention of radionuclide contamination, proper decontamination procedures, and the disposal of byproduct material also are included. Upon the completion of training and to obtain certification as nuclear medicine specialist physician's must pass a rigorous eight-hour examination on all aspects of nuclear medicine.

Accordingly, the ABNM requests formal recognition under 10 CFR Part 35-Medical Use Of Byproduct Material. We have reviewed the area listed where NRC plans to recognize boards and have determined that the ABNM certification process requires an individual to meet all of the requirements in the following subsections of Part 35:

35.190 Training for uptake, dilution, and excretion studies.
35.290 Training for imaging and localization studies.
35.390 Training for use of unsealed byproduct material for which a written directive is required.
35.392 Training for the oral administration of sodium iodide I-131 requiring a written directive in quantities less than or equal to 1.22 gigabecquerels (33 millicuries).
35.394 Training for the oral administration of sodium iodide I-131 requiring a written directive in quantities greater than 1.22 gigabecquerels (33 millicuries).

Your favorable consideration of our request to be listed as a recognized board that provides training and experience in the above use of byproduct materials will be most sincerely appreciated.

Sincerely,

Ronald L. Van Heertum

Ronald L. Van Heertum, M.D.
Chairman
American Board of Nuclear Medicine

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

September 28, 2000

Ronald L. Van Heertum, M.D.
Chairman
American Board of Nuclear Medicine
900 Veteran Avenue
Los Angles, CA 90024

Dear Dr. Van Heertum:

This letter acknowledges our receipt of the letter you sent, on behalf of the American Board of Nuclear Medicine (ABNM), to Donald A. Cool requesting formal recognition by the Nuclear Regulatory Commission of the ABNM's certification process.

Your letter will be reviewed by my staff. NRC expects to begin listing the names of recognized boards on an NRC website prior to the effective date of the final rule. I anticipate the Commission will publish the final rule in the Federal Register by spring 2001, with an effective date 6 months after publication.

If you have any questions, please contact Sam Jones of my staff (301- 415-6198 or e-mail SZJ@NRC.gov).

Sincerely,

Patricia Holahan, Branch Chief
Rulemaking and Guidance Branch
Division of Industrial and
Medical and Nuclear Safety
Office of Nuclear Material Safety
and Safeguards

bps Board of Pharmaceutical Specialties

September 7, 2000

Donald A. Cool
Director, Division of Industrial and Medical Nuclear Safety
United States Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Mr. Cool:

The Board of Pharmaceutical Specialties (BPS) thanks you for the opportunity to respond to the NRC for recognition of our organization in its process to recognize pharmacists as specialists in the practice of nuclear pharmacy.

Through requirements established by our Nuclear Pharmacy Specialty Council, including eligibility criteria and our written examination process, we grant the credential Board Certified Nuclear Pharmacist (BCNP) to qualified licensed pharmacists. Before receiving this recognition, each candidate must submit proof of being a licensed pharmacist, have competed a minimum of 4000 hours of training and experience in the field of nuclear pharmacy, and have passed the rigorous written BPS examination. In order to retain certification, a BCNP must also meet defined recertification requirements.

The Board of Pharmaceutical Specialties has reviewed 10 CFR 35.50 *Training for Radiation Safety Officer* and 10 CFR 35.55 *Training for an authorized nuclear pharmacist* and determined that our certification process requires an individual to meet all the requirements in paragraph (b) of these sections prior to being certified by our board.

If you have any further questions, please contact me at 202-223-7192 or rjb@mail.aphanet.org.

Sincerely,

Richard J. Bertin

Richard J. Bertin, PhD, RPh
Executive Director

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

October 16, 2000

Richard J. Bertin, PhD, RPh
Executive Director
Board of Pharmaceutical Specialities
2215 Constitution Avenue, NW
Washington, D.C.20037-2985

Dear Dr. Bertin:

This letter acknowledges our receipt of the letter you sent, on behalf of the Board of Pharmaceutical Specialities (BPS), to Donald A. Cool requesting formal recognition by the Nuclear Regulatory Commission of the BPS certification process.

Your letter will be reviewed by my staff. NRC expects to begin listing the names of recognized boards on an NRC website prior to the effective date of the final rule. I anticipate the Commission will publish the final rule in the Federal Register by spring 2001, with an effective date 6 months after publication.

If you have any questions, please contact Sam Jones of my staff (301- 415-6198 or e-mail SZJ@NRC.gov).

Sincerely,

Patricia K. Holahan

Patricia Holahan, Branch Chief
Rulemaking and Guidance Branch
Division of Industrial and
Medical and Nuclear Safety
Office of Nuclear Material Safety
and Safeguards

THE AMERICAN BOARD OF MEDICAL PHYSICS
C/o Credentialing Services, Inc.
P.O. Box 1502, Galesburg, Illinois 61402-1502
Telephone: (309) 343-1202 Fax: (309) 344-1715

July 20, 2000

Donald A. Cool, Director
Division of Industrial and Medical Nuclear Safety
United States Nuclear Regulatory Commission
Washington, D.C. 20555-0001

Dear Mr. Cool:

I received your letter dated June 22, 2000 on the subject of "Recognition of Boards". As you probably know, certification by the ABMP is currently considered sole evidence for recognition as a "Qualified Medical Physicist" (QMP) by several state regulatory agencies as well as by the American Association of Physicists in Medicine (AAPM) and the American College of Medical Physics (ACMP). Thus I am writing to let you know that it is totally proper and appropriate for the American Board of Medical Physics to be fully recognized by the Nuclear Regulatory Commission.

I will respond to your request for information after I circulate the enclosures you sent to me amongst my board and the specialty panel chairmen, and ask them to review and assist me with this.

Please let me know what your time frame is and I will try to meet any deadline imposed.

Sincerely,

Lawrence E. Reinstein, Ph.D.
Chairman

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

September 28, 2000

Lawrence E. Reinstein, Ph.D., Chairman
The American Board of Medical Physics
C/o Credentialing Services, Inc.
P.O. Box 1502
Galesburg, Illinois 61402-1502

Dear Dr. Reinstein:

This letter is to acknowledge our receipt of the letter dated July 20, 2000, you sent on behalf of The American Board of Medical Physics (ABMP), to Donald A. Cool regarding recognition of the ABMP's certification process by the Nuclear Regulatory Commission (NRC).

In regard to your question concerning NRC's time frame and deadline, there is no required time frame or deadline for the ABMP to submit the information to the NRC because submitting such information to the NRC would be a voluntary action by the ABMP. The June 22, 2000, letter was provided to your board to provide early notification of the expected change in NRC's process for recognizing boards. I anticipate that the Commission will publish the final rule in the Federal Register by spring 2001 with an effective date 6-months after publication. The NRC expects to begin listing the names of recognized boards on an NRC website prior to the effective date of the final rule. Thus, the timing for the ABMP to submit the information to be recognized is at your discretion.

If you have any questions, please contact Sam Jones of my staff (301-415-6198 or e-mail SZJ@NRC.gov).

Sincerely,

Patricia Holahan, Branch Chief
Rulemaking and Guidance Branch
Division of Industrial and
Medical Nuclear Safety, NMSS

From: <efmaher@dukeengineering.com>
To: <cxh@nrc.gov>
Date: Thu, Aug 10, 2000 3:49 PM
Subject: Recognition of Boards, NRC Letter dated 6/22/2000

Dear Ms. Haney:

I sending you this e-mail in my capacity as the Chairperson, American Board of Health Physics (ABHP). The ABHP is the certifying body of the American Academy of Health Physics (AAHP). The ABHP grants the credentials of Certified Health Physicist (CHP).

I have read and subject letter and I am dismayed by the very prescriptive approach that the NRC has taken in recognizing certification boards under the revised 10 CFR Part 35. Specifically, ABHP certified health physicists have traditionally been accepted as qualified radiation safety officers (RSOs) for Part 35 licenses by virtue of their ability to meet the experience, education, testing, and other professional requirements that the ABHP has established as essential to the comprehensive practice of health physics.

Under the revised 10 CFR 35, we believe that ABHP certification meets the intent of the revised 10 CFR 35.50, but not always the letter of the regulation. Specifically, ABHP certification does not require "One year of full-time radiation safety experience under the supervision of an individual identified as the Radiation Safety Officer on a Commission or Agreement State license that authorizes similar types(s) of use(s) of by-product material..." ABHP certification does require that an individual be involved in the professional, full-time practice of health physics for a minimum of six years." The latter, although not meeting the "letter" of the regulation does meet or exceed the "intent" of the regulation.

In another example of meeting the intent, but not the letter, ABHP certification does not require a written certificate, signed by a preceptor Radiation Safety Officer, that the individual has satisfactorily completed the requirements in Paragraph (b)(1)....." ABHP certification does require that the CHP follow the AAHP's Code of Ethics and not practice in areas that they are not competent. The requirement to follow the AAHP Code of Ethics, combined with the training, experience, submittal of professional report(s) and passing of two written examinations does ensure the ABHP certification meets and exceed the intent of 10 CFR Part 35.50.

My purpose in providing you this information is to ask you for a preliminary read of the following questions: First, if meeting the intent, if not always the letter (as described above) sufficient for the NRC to recognize the American Board of Health Physics? Secondly, can this draft final rule be modified at this point or is past that time?

Finally, the ABHP would like to know if it should formally respond to the NRC's

letter with a detailed description of how we meet the intent of the regulation, but not always the letter of the regulation, or will recognition be based on a narrow interpretation of 10 CFR Part 35.50 as currently stated in the draft final revision? Your letter appears not to provide the measure of latitude that we had hoped for in demonstrating equivalent training and experience for 10 CFR Part 35 RSO qualifications.

Please contact me at (978) 568-2522 of via this e-mail address. Thank you for this consideration and I eagerly wait your response.

Respectfully,

Edward F. Maher, Sc.D., CHP
Chairperson
American Board of Health Physics

CC: <ceroessl@frontiernet.net>, <njohnson@burkinc.com>...

MEDICAL COLLEGE OF WISCONSIN

Office of Research,
Technology and Informatics
8701 Watertown Plank Road
Milwaukee, WI 53226
Phone: 414/456-4402
FAX: 414/456-6554
e-mail: whendee@mcw.edu

September 15, 2000

Donald A. Cool
Director, Division of Industrial and Medical Nuclear Safety
Nuclear Regulatory Commission
Washington, DC 20555-0001

Dear Mr. Cool:

I am writing in response to your letter of June 22, 2000 to Dr. Paul Capp of the American Board of Radiology (ABR). Your letter, and the Draft Final Regulatory Text: Training and Experience Criteria, were the subject of intense discussion among trustees of the ABR at our meeting in Santa Fe on September 8-10, 2000. This discussion yielded two questions that must be answered before the ABR can completely address the issues raised in your letter. These two questions are:

35.50: Training for Radiation Safety Officer
Medical physicists frequently serve as Radiation Safety Officers in healthcare institutions. To be eligible for ABR certification in Medical Nuclear Physics, a physicist must have a graduate degree in medical physics or related discipline, and 3 years of clinical experience. The educational requirements for certification include all of the items in (b.1.i), and the three years of clinical experience include all of the items in (b.1.ii.A-G). The three years of clinical experience are obtained under the supervision of a Radiation Safety Officer. However, the experience is usually embedded within a set of clinical responsibilities that extend beyond the specific duties of a Radiation Safety Officer. Strict interpretation of Section 35.50 could imply that such individuals would not satisfy the requirement of one year of full-time radiation safety experience. We wish to know whether the educational and clinical experience of a physicist eligible for certification in Medical Nuclear Physics will be interpreted by the Nuclear Regulatory Commission as satisfying the requirement of one year of full-time radiation safety experience.

35.51: Training for an Authorized Medical Physicist
Medical physicists who are certified in Therapeutic Radiological Physics by the ABR satisfy the requirements described in (b)(1) to be authorized medical physicists for therapeutic medical units as described in (b)(2). Some physicists certified in Therapeutic Radiological Physics also meet the education and clinical experience requirements described in 35.50, with the possible exception of one year of full-time experience in radiation safety, as described in the preceding paragraph. We wish to know whether these physicists satisfy the requirements of the Nuclear Regulatory Commission to serve as an institutional Radiation Safety Officer.

We look forward to your response to these two questions.

Sincerely,

William R Hendee

William R. Hendee, Ph.D.
Senior Associate Dean and Vice President
Vice President, ABR

cc: Philip O. Alderson, M.D.
M Paul Capp M.D.
Ms. C. Haney
Guy H. Simmons, Ph.D.

The American Board of Radiology

Diagnostic Radiology Radiation Oncology Radiologic Physics

M. Paul Capp, M.D., Executive Director

October 3, 2000

Dr. Sam Jones
Nuclear Regulatory Commission
Washington, D.C. 20555-0001

Dear Dr. Jones:

This letter is in response to your request that I send you a list of my concerns regarding the proposed revisions in the NRC medical use regulation 10 CFR part 35. I should point out that I did not originally call you to express concerns. I called you for clarification regarding the wording so that I could determine whether I do have any concerns about the proposed revisions. I was specifically calling for clarification regarding how specific the work experience hour requirements would be. I am speaking as a private radiation oncologist, not as a training director, chair of a training program, member of ASTRO, or trustee of the American Board of Radiology.

I believe that the following sections of 35 apply to radiation oncology training programs: Paragraph 35.390, "Training for use of unsealed byproduct material for which a written directive is required; 35.392, "Training for the oral administration of sodium iodide I-131 requiring a written directive in quantities less than or equal to 33 millicuries; 35.394, "training for the oral administration of sodium iodide I-131 requiring a written directive in quantities greater than 33 millicuries; 35.490, "training for use of manual brachytherapy sources; 35.491, "training for opthalmic use of strontium-90; 35.690, "training for use of remote afterloader units, teletherapy units, and gamma stereotactic radiosurgery units.

In most of these sections, a specific number of hours of training is required, (usually 700 hours, of which 200 hours must be spent in the classroom, and 500 hours may be spent as work experience under the supervision of an authorized user). I do not personally perceive the classroom hours to be a problem, although other radiation oncology training directors may. The question I have relates to how specific the work experience must be. I would have concerns if this document intends that authorized users must have the following: 500 hours of work experience specifically in the use of unsealed by-product material for which a written directive is required, plus significant experience specifically in the oral administration of sodium iodide in quantities less than 33 millicuries, plus experience specifically relating to the administration of I-131 in quantities greater than 33 millicuries, plus 500 hours work experience specifically in manual

brachytherapy sources, plus 500 hours of work experience specifically in the use of remote afterloader units, teletherapy units and gamma stereotactic radiosurgery units. I believe that many radiation oncology residency programs would not be able to meet these requirements if the work experience requirements for each section is specific to the procedure under consideration.

On the other hand, I would have no concerns if the work experience for each section were broader in scope, and allowed experiences such as that described in paragraph (b) (2) of section 35.490, which states: "has obtained three years of supervised clinical experience in radiation oncology, under an authorized user who meets the requirements in paragraph 35.490 or equivalent agreeing with state requirements as part of a formal training program approved by the Residency Review Committee for Radiation Oncology of the ACGME or the Committee on Post-doctoral Training of the American Osteopathic Association."

As I mentioned to you in a previous call, several other radiation oncologists have expressed concerns about training program graduates meeting the requirement 35.690 relating to gamma knives if they trained in a radiation oncology program whose stereotactic radiosurgery program is linear accelerator based. However, this is not as great a concern as the work experience hour requirements.

Thank you for your attention.

Sincerely,

David H. Hussey M. D.

DHH:sd

From: "Dr. David Hussey" <husseyd@TheABR.ORG>
To: <szj@nrc.gov>
Date: Thu, Oct 5, 2000 3:58 PM
Subject: you asked me

Dear Dr. Jones:
You asked me to list my concerns regarding part 35. Please see attached document. I am sending another copy by U.S. mail.

Thank you for your help.

David H. Hussey, M.D.

October 3, 2000

Dr. Sam Jones
Nuclear Regulatory Commission
Washington, D.C. 20555-0001

Dear Dr. Jones:

This letter is in response to your request that I send you a list of my concerns regarding the proposed revisions in the NRC medical use regulation 10 CFR part 35. I should point out that I did not originally call you to express concerns. I called you for clarification regarding the wording so that I could determine whether I do have any concerns about the proposed revisions. I was specifically calling for clarification regarding how specific the work experience hour requirements would be. I am speaking as a private radiation oncologist, not as a training director, chair of a training program, member of ASTRO, or trustee of the American Board of Radiology.

I believe that the following sections of 35 apply to radiation oncology training programs: Paragraph 35.390, "Training for use of unsealed byproduct material for which a written directive is required; 35.392, "Training for the oral administration of sodium iodide I-131 requiring a written directive in quantities less than or equal to 33 millicuries; 35.394, "training for the oral administration of sodium iodide I-131 requiring a written directive in quantities greater than 33 millicuries; 35.490, "training for use of manual brachytherapy sources; 35.491, "training for opthalmic use of strontium-90; 35.690, "training for use of remote afterloader units, teletherapy units, and gamma stereotactic radiosurgery units.

In most of these sections, a specific number of hours of training is required, (usually 700 hours, of which 200 hours must be spent in the classroom, and 500 hours may be spent as work experience under the supervision of an authorized user). I do not personally perceive the classroom hours to be a problem, although other radiation oncology training directors may. The question I have relates to how specific the work experience must be. I would have concerns if this document intends that authorized users must have the following: 500 hours of work experience specifically in the use of unsealed by-product material for which a written directive is required, plus significant experience specifically in the oral administration of sodium iodide in quantities less than 33 millicuries, plus experience specifically relating to the administration of I-131 in quantities greater than 33 millicuries, plus 500 hours work experience specifically in manual brachytherapy sources, plus 500 hours of work experience specifically in the use of remote afterloader units, teletherapy units and gamma stereotactic radiosurgery units. I believe that many radiation oncology residency programs would not be able to meet these requirements if the work experience requirements for each section is specific to the procedure under consideration.

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expressed concerns about training program graduates meeting the requirement 35.690 relating to gamma knives if they trained in a radiation oncology program whose stereotactic radiosurgery program is linear accelerator based. However, this is not as great a concern as the work experience hour requirements.

Thank you for your attention.

Sincerely,

David H. Hussey M. D.

DHH:sd

Received: from igate2.nrc.gov
(igate.nrc.gov [148.184.176.31])
by nrcgwia.nrc.gov; Thu, 05 Oct 2000 15:57:27 -0400
Received: from nrc.gov
by smtp-gateway ESMTPœ id PAA08407
for <szj@nrc.gov>; Thu, 5 Oct 2000 15:56:47 -0400 (EDT)
Received: from husseyd ([198.182.109.24]) by Opus1.COM (PMDF V5.2-33 #9830)
with SMTP id <01JUZ91NWO6KBCKTYA@Opus1.COM> for szj@nrc.gov; Thu,
5 Oct 2000 12:57:19 MST
Date: Thu, 05 Oct 2000 14:57:43 -0700
From: "Dr. David Hussey" <husseyd@TheABR.ORG>
Subject: you asked me
To: szj@nrc.gov
Message-id: <000201c02f17$4a91db40$186db6c6@medicine.uiowa.edu>
MIME-version: 1.0
X-MIMEOLE: Produced By Microsoft MimeOLE V5.00.2314.1300
X-Mailer: Microsoft Outlook CWS, Build 9.0.2416 (9.0.2911.0)
Content-type: multipart/mixed; boundary="Boundary_(ID_+2PqGWoAfTkV4glfH0oUtA)"
Importance: Normal
X-Priority: 3 (Normal)
X-MSMail-priority: Normal

Licensing of Intravascular Brachytherapy for Routine Use

NRC Requirements

Robert L. Ayres, Ph.D.

Two Classes of NRC Licensees

- Broad Scope Medical Licensees.
  - No license amendment normally required to conduct intravascular brachytherapy.
- Limited Specific Scope licensees.
  - License amendment (NRC authorization) required to conduct intravascular brachytherapy.

Four Criteria for Authorizing Participation of Limited Specific Scope Licensees

- Sealed source(s) and device evaluation and Registration
- FDA approved PMA
- **Appropriately qualified physician (Authorized User)**
- Exemption to the requirements of 10 CFR 35.400 required

Three Levels of Licensing Complexity

- Simple – Traditional photon emitting sealed sources
- Moderate – Pure Beta emitting sealed sources
- Complex – Unsealed sources of byproduct material

New Section 35.1000

- Added to accommodate emerging technologies
- Allows considerable flexibility in establishing regulatory requirements through custom license conditions
- First applicable existing requirements are applied and then specific conditions are established for unique aspects of the new technology

Present Status of FDA Approvals

- Numerous systems in ongoing clinical trials
- Two vendors have submitted trail results for PMA authorization
  - Best/Cordis Ir-192 seeds in nylon ribbons
  - Novoste Sr-90 seeds in hydraulically driven remote afterloading device
- In both cases the FDA's Circulatory System Devices Panels have recommended approval with conditions

Best/Cordis System

- Recommended approval with conditions on June 19, 2000:
  - Label changes
  - Continue patient follow-up out to 5 years
  - Require team consisting of Interventional Cardiologist, Radiation Oncologist, and Medical physicist
- Approval for the treatment of In-Stent Restenosis only

Novoste System

- Recommended for approval with conditions on September 11, 2000:
  - Approval restricted to 30-mm device
  - Labeling changes to include team consisting of Interventional Cardiologist, Radiation Oncologist, and Medical Physicist
  - Continue patient follow-up out to 5 years
  - Require post-market surveillance to more fully characterize device failure and malfunction events
- Approved for the treatment of In-Stent Restenosis only

Licensing Issues - 1

- Conditions of Use
  - Treatment of In-Stent Restenosis
  - Unrestricted Intravascular use
- Specific Safety Precautions
  - Finger dosimeters
  - Adequate fluid supply
  - Introducer sheaths

Licensing Issues –1

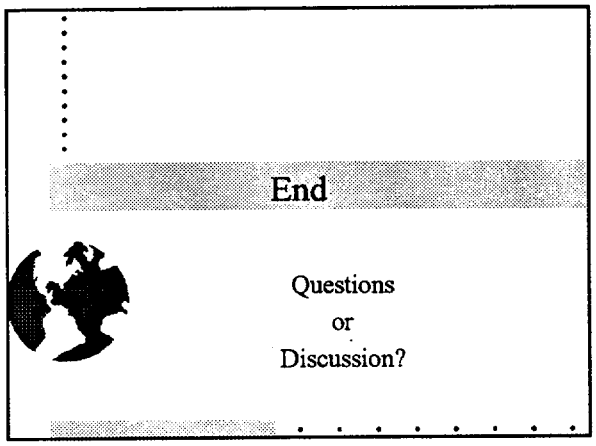
- Amendment of QMP
- Written Directives
- Misadministrations and related dose calculations
- Emergency procedures and response training
- Use in unshielded Cath labs

New Part 35 T&E Issues

- New Part 35 establishes separate training and experience requirements for manual brachytherapy (35.400) and remote afterloading brachytherapy (35.600)
- Some IVB system will be licensed under 35.400 and others under 35.600

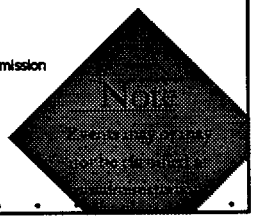
Distribution Issues

- Manufacture & distribution of radioactive drugs authorized under 10 CFR 32.72
- Manufacture & distribution of sources or devices authorized under 10 CFR 32.74
  - Traditionally view as applicable to sealed sources only
  - Or, those devices that use sealed sources
- "Contained" sources – no authorization for manufacture and distribution


End
Questions
or
Discussion?

Misadministrations/Events in Vascular Brachytherapy Trials

•Robert L. Ayres, Ph.D.
•U.S. Nuclear Regulatory Commission



Misadministration or Event What's the Difference?

- An event can be any unusual occurrence - does not require error in dose delivery to a patient
- A misadministration is defined by NRC regulations and requires an error in dose delivery to a patient, most commonly:
  - delivered doses greater than, or less than, 20% of the prescribed dose; or,
  - wrong treatment site

Introduction

- To Date - 16 Misadminstrations or Events and Counting
- 7 Misadministrations/Events in one Trial
- 4 Misadministration/Events in a second Trial
- 3 Misadministrations/Events in a third Trial
- 3 Single Misadministrations/Events in 3 additional Trials
- A Total of 5 Separate Trials Involved

How Can Event Information Be Used?

- To alert other users of potential problems and possible corrective actions
- To develop appropriate regulations governing device approvals and use
- To improve device designs or study protocols

Device And Trials For Which Event Reports Have Been Received

- Novoste Beta-Cath / BERT Trial (7)
- Guidant (3)
- Angiorad (USSC) (4)
- Radiant (USSC) (1)
- Nucletron / PARIS (1)
- Re-188 - MAG_3 / SABER (1)

Novoste Beta-Cath BERT Trial Misadministrations

- On 1/16/98 an NRC licensee reported a patient receiving a unintended dose to the wrong treatment site
- On 2/9/98, the State of Washington reported a patient received an unintended 7.8 Gy dose to the wrong treatment site
- Both events were attribute to a failure of the source transport system

Investigation of the NRC Licensee Reported Misadministration

- Root Cause
- Possible source transport failure modes
- Factors contributing to the reported misadministration
- Licensee proposed corrective actions

Root Cause

- Over-tightening of the Touhy-Bourst value around the catheter
  - Produced a crimp in the Novoste catheter blocking return of the sources to their storage position
  - Partial blockage allowing saline flow but no source movement
- Second event may have had the same root cause but actual root cause has not been determined

Possible Source Transport Failure Modes - 3 Identified

- Over tightening of the Touhy-Bourst valve
- Premature depletion of the saline transport fluid if too much pressure applied to supply syringe
- Over-tightening of the syringe Luer to the extension connector causing the sterile sleeve to be pinched, resulting in the inability to produce sufficient hydraulic pressure

Factors Contributing To The Misadministration

- Device design allows over-tightening of Touhy-Bourst valve
- Excessive time interval between training and start of clinical procedures
- Less than optimal didactic and practical training
- Limited opportunities for self-practice and rehearsal
- Lack of detailed operational and emergency checklists

Proposed Corrective Actions - 1

- Improve radiation oncology training
  - review of relevant interventional cardiology procedures
  - realistic training exercises in a cath lab environment
- Be conscious of possible treatment catheter damage before & during treatment
- Develop a checklist of essential steps, checks, & precautions to followed in executing treatments

Proposed Corrective Actions - 2

- Develop appropriately modified version of AAPM's device quality assurance protocol
  - Daily testing of all treatment units
  - Testing of treatment catheter before positioning in patient
  - Testing position catheter with a dummy source train for unobstructed passage
  - Verification of source strength and/or prescription dose rate

Proposed Corrective Actions - 3

- Develop a mechanism for facilitating self-initiated practice and procedure review
- Redesign the treatment-to-guide catheter interface to eliminate the possibility of catheter damage

Comments On Corrective Actions

- The first 3 of the proposed corrective actions can be unilaterally implemented by the licensee
- The remaining 3 proposed corrective actions require the approval and support of the trial sponsor

Summary of Beta -Cath Misadministrations

- Extensive write-up of these 2 misadministrations contained in NRC Information Notice 98-10
  - Available on the NRC Website
  - http:/www.nrc.gov
- Purpose of the IN - To make licensees aware of the potential for such failures and the corresponding potential for patient harm

AngioRad ARTISTIC Trial Event

- On 11/17/98 an NRC licensee reported that, during a patient treatment, the radioactive source stuck in the delivery catheter when the drive cable jammed
- However, the 500 mCi Ir-192 source was not located in the patient at the point of the jam

Probable Cause

- Source wire behaves like a stiff rod when encountering an obstruction near the proximal end of the extension catheter
- As a result the force exerted upon encountering the obstruction is transferred up the wire causing the wire to jump the track where the wire enters the spool
- Clutch safety mechanism is "to slow" to prevent catastrophic failure

Additional Similar Failures

- Licensee reported that an identical failure occurred during demonstration/training
  - This failure involved a non-certified "demonstrator" device
  - The failure was not reported to the licensee's radiation safety committee prior to project approval
- Licensee has since learned of two, apparently similar, failures in non-clinical uses at other institutions

Sequence of Events - 1

- Radiation Oncologist indicated the cranking action did not "feel right" as the source was advanced
- Source position could not be verified with fluoroscopy
- Further attempt to advance the source into the fluoroscopy field was unsuccessful

Sequence of Events - 2

- Immediate attempt to retract the source was unsuccessful
- Catheter removed from the patient and entire device, including afterloader, moved to an adjacent room
- Lead shields installed around device
- Attempts to locate the source using a GM survey meter were unsuccessful (meter off scale >200 mr/hr)

Sequence of Events - 3

- HDR emergency procedures implemented
  - Housing of afterloader removed to visualize the source position
  - Source wire was observed to have come off of guide track and become entangled in the winding mechanism
  - Source wire determined to be located a few inches outside the tungsten safe
  - Wire was cut and source secured in HDR safety pig

Radiation Exposures

- Maximally exposed licensee personnel
  - Whole body - 131 mRem
  - Extremity - 87 mRem
- Patient
  - Whole body - 4 mRem
  - Extremity - same

Proposed Corrective Actions

- Suspension of protocol pending USSC root cause analysis
- Reapplication to Radiation Safety Committee required for protocol restart
- Written emergency procedures for various failure modes
- Personnel to be instructed to report important information, such as, "demo" failures, unusual occurrences, and procedure changes to RSC

Radiant Re-188 Balloons

- On 1/7/99 an Agreement State reported a medical misadministration when an angioplasty balloon broke releasing 2 to 4 mCi of Re-188 perrhenate into the patients coronary artery
- Radiation dose estimates to the patient have not yet been provided but could be upwards of 50 cGy to the bladder

Probable Cause

- Ruptures of angioplasty balloons are an expected event of relatively low frequency
- Trial sponsor implemented additional procedures in their protocol to minimize balloon ruptures
  - Pre-inflation to burst pressure of the balloon immediately prior to usage
  - Limiting inflation pressure during treatment to 3 atm

Re-188MAG$_3$ SABER Trial

- In March 1998, a contamination event occurred in a cath lab after completion of patient treatment
  - Occurred during removal of treatment catheter from patient
  - Floor of cath lab contaminated with Re-188
- Contamination was not removable - Cath lab closed for ~1 week for radioactive decay

Lessons Learned From This Event

- Contamination events can readily occur when working with unsealed sources of radioactive materials
- If you cannot tolerate the loss of a cath lab for a week or more consideration should be given to not using unsealed sources
- Although contamination events can occur with sealed sources, they are much more unlikely

Guidant/Nucletron Trials

- On 2/8/99 an Agreement State reported a misadministration wherein a patient was treated 34 cm proximal to the intended treatment site with a 150 mCi P-32 source
- Estimated dose to the vessel wall ranges from 70 to 108 Gy

Sequence of Events -1

- On 16 December1998, Guidant introduced a new type catheter and provided training for the licensee's personnel
  - Supervised the use of the new system during a patient treatment
  - Although licensee was unsure if source was observed on fluoro, treatment was given

Sequence of Events -2

- On 11 January 1999, Guidant informed the licensee that the new catheter required the use of a different connector on the front of the afterloader
  - Proper connector not used on 16 December treatment
  - Failure to use proper connector would place source at the wrong treatment site
- On 13 January1999, licensee confirmed that the 16 December treatment was ~34 cm from the intended treatment site

Major Issues

- The failure to confirm the location of the source with fluoro, when fluoro visualization is an integral part of the protocol
- The incomplete training and direction provided the licensee by the Guidant personnel when the device equipment was changed on 16 December

Two Additional Guidant Misadministrations/Events

- Source stuck outside of HDR safe during source exchange by vendor - minimum radiation exposure to service representative
- Patient randomized to receive 20 Gy received 0 Gy instead - Error in programming the HDR by the medical physicist

What is NRC's Prospective On All These Events/Misadministrations

- Are they of unusually high frequency? - Yes, compared to comparable HDR Oncology procedures
- Can the frequency of occurrence be reduced? - Yes, through better review of investigative protocols and appropriate implementation of improved training, emergency procedures, and checklists

NRC's Prospective (Cont.)

- What other actions can be taken to reduce frequency?
  - Broadscope RSC should perform appropriate radiation safety evaluations before authorizing participation in one of these protocols
  - NRC's expectations from broadscope licensees using these un-reviewed and un-registered devices are set forth in Information Notice 99-24 and include:
    - Better performance by the licensee's radiation safety committee in the review & approval these sources & devices
    - If unresolved safety issues - then deny participation

END

Questions
Or
Discussion?

US NUCLEAR REGULATORY COMMISSION

ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

NEW TECHNOLOGY - THE THERASPHERE® DEVICE
November 8, 2000

1. REGULATORY GUIDANCE FOR THERASPHERE® DEVICE USE

New advances in medicine and technology have resulted in rapidly emerging research, development, and use of new modalities to treat disease. One of the novel systems devised to deliver therapeutic radiation doses for medically indicated curative or palliative purposes is the TheraSphere®* device. The TheraSphere device consists of an administration kit and a dose vial containing Y-90 embedded in insoluble glass microspheres. It is designed to provide *in situ* radiation treatment of hepatic tumors for which no viable alternative medical treatment exists, and for which without intervention, death is imminently certain. TheraSphere is currently registered with the FDA as a Humanitarian Use Device (HUD) under a Human Device Exemption (HDE), and is registered in the U.S. Nuclear Regulatory Commission (NRC) sealed source and device registry.

TheraSphere does not share many attributes with conventional medical radioactive sources or treatment modalities. The TheraSphere device and its method of delivery appear to be a hybrid between traditional brachytherapy and delivery mechanics associated with radiopharmaceutical therapy. Therefore, TheraSphere does not fit exclusively within a single categorically identifiable use in Subparts D through I in 10 CFR 35, "Medical Use of Byproduct Materials." Because the definitions for misadministration, prescribed dose, written directive, and the training and experience requirements are tied to individual categories identified in these subparts, these terms and requirements are not defined for TheraSphere. In addition, the unique characteristics of this device may present some safety concerns which are not addressed in the current regulations. Further, the characteristics inherent to a device granted Humanitarian Use Device (HUD) status by the FDA, as is TheraSphere, may introduce additional radiation safety concerns.

NRC staff therefore concluded that regulatory guidance specific to the TheraSphere device should be developed to ensure that its manner of use is consistent with the fundamental premise of 10 CFR 35, "...These requirements and provisions provide for the protection of the public health and safety (§35.1)," as well as the NRC Strategic Goals for Nuclear Materials Safety. The proposed guidance was developed by tailoring the rule language of Part 35 to fit the unique attributes of the TheraSphere device. This guidance will ensure that the TheraSphere device is used safely and properly, in accordance with the standards required in 10 CFR 35.

The NRC needs to develop licensing guidance applicable to the TheraSphere device now since two broad scope licensees are using the device, several are planning to use it, and limited specific licenses may also want to use it. The proposed guidance will require all licensees to submit a license amendment based upon §35.400 regulations.

Brachytherapy rule language that has been modified to accommodate the unique characteristics of the TheraSphere device and satisfy the basic radiation safety principles outlined in Part 35. The license amendment may be in the form of either license conditions or the licensee's adoption of a radiation safety program.

The following issues and items are identified for ACMUI consideration in assisting the staff formulate this guidance:

1. TheraSphere is a sealed source for brachytherapy use, not a drug for radiopharmaceutical therapy use
2. Licensee experience using the TheraSphere device
3. Guidance recommended to be implemented as a license amendment; either by specific license conditions, or by an equivalent commitment by the licensee in the amendment application. License exemptions are not recommended
4. Guidance for broad scope and limited specific licenses for TheraSphere:
   a. Definition of misadministration
   b. Definition of written directive
   c. Definition of prescribed dose
   d. Authorized user training and experience requirements for TheraSphere
5. Generic licensing guidance for other emerging technologies

*The registered trademark ® is assumed throughout this document.

2. THERASPHERE IS A SEALED SOURCE DEVICE USED FOR BRACHYTHERAPY

Initial staff discussions centered on whether the TheraSphere device was a "brachytherapy" sealed source regulated under 10 CFR 35.400*, or a "radiopharmaceutical" for therapy regulated under 10 CFR 35.300.* TheraSphere delivery was considered by some to be consistent with conventional radiopharmaceutical "drug" therapy. However, the attributes of the ^{90}Y microspheres are technically consistent with the definition of a "device," not a "drug." The TheraSphere manufacturer is registered with FDA under the medical device regulations, the product meets the FDA definition of a device, and the product was approved by the FDA Center for Devices and Radiological Health. TheraSphere is also registered by the NRC as a sealed source. Materials regulated under §35.300 are radioactive drugs. §35.300 requires that unsealed byproduct material for therapeutic administration must be obtained from, pursuant to §32.72, a manufacturer registered or licensed with the FDA as a drug manufacturer. Therefore, §35.300 is not applicable for TheraSphere.

Within the current regulatory language of 10 CFR 35, NRC staff consider the TheraSphere device to be a sealed source for brachytherapy use for the following reasons:

1. It is consistent with the definition of a sealed source, in 10 CFR 35.2, "any byproduct material that is encased in a capsule designed to prevent leakage or escape of the byproduct material." Y-90 does not leach from the glass matrix (microspheres) in which it is embedded.

2. It is consistent with the definition of a brachytherapy source, 10 CFR 35.2, "an individual sealed source or a manufacturer-assembled source train that is not designed to be disassembled by the user."

3. It is inconsistent with the FDA definition of a radioactive drug (Attachment 2) because the microspheres are not biologically active, nor are they biodegradable. They remain permanently *in situ.*

Although the TheraSphere device is consistent with the generic of brachytherapy and sealed source definitions, the associated regulations in §35.400, do not provide for many of the attributes of this device.

At least four exemptions to the regulations associated with brachytherapy use, and significantly more for those associated with therapeutic use of unsealed material, would have to be issued to account for the unique characteristics of the microspheres.

The staff therefore concluded that the TheraSphere device should be considered an emerging technology, for which a specific radiation safety program should be developed. This program must be consistent with the radiation safety principles in 10 CFR Part 35.

*Titles of cited regulations, and Part 35 sections containing associated training and education requirements.

10 CFR Part	Title/Content	T&E 10 CFR Part
§35.200	Use of unsealed byproduct material for imaging and localization studies	§35.920
§35.300	Use of unsealed byproduct material for therapeutic administration	§35.930
§35.400	Use of sources for brachytherapy	§35.940

3. LICENSEE EXPERIENCES

I. TWO MISADMINISTRATIONS:

Only two licensees, University of Pittsburgh (Region 1) and University of Maryland (Agreement State) are currently using the TheraSphere device. Many other licensees are planning to use TheraSphere in the near future.

TheraSphere (a HUD) may be used clinically or for human research. The FDA does not require informed consent the for clinical use of a HUD.

The Internal Review Board (IRB) of both licensees have required informed consent as a condition of their approval to perform the TheraSphere procedure. NRC staff members involved with the TheraSphere issue appreciate the IRBs' decision to require informed consent for TheraSphere use, and are hopeful that future users will do the same, for the following reasons:

- The distinction between clinical use and human research use of the TheraSphere device is somewhat ambiguous at the present time.
- The FDA approves HUDs for clinical use based on an abbreviated version of the detailed application requirements for premarket approval of medical devices (Attachment 3). The summaries, results, and clinical trials for the TheraSphere device were performed outside of the United States. Each of the two licensees who are currently using TheraSphere in the U.S. have encountered several problems during TheraSphere administration.
- Although TheraSphere use is indicated for terminally ill patients for whom no alternative medical treatments exist, TheraSphere administration will likely cause mild to moderate side-effects, can cause serious side-effects, and, if improperly used, can cause radiation-induced death.

University of Pittsburgh experienced a misadministration during the first use of the TheraSphere device, on August 15, 2000. Significant bremsstrahlung radiation was detected in the device administration kit, at the stopcock, after the TheraSphere administration was thought to be completed. It is believed that the licensee's use of a smaller-than-normal arterial catheter was a primary contributing factor to the misadministration. More recent, but still preliminary, evaluation of this incident indicates that apparently 62 percent of the intended activity reached the liver and 38 percent of the dose remained in the administration set/catheter. Sixty days after the TheraSphere administration, the licensee concluded that the patient benefitted from the TheraSphere treatment. The significance of arterial catheter composition is also being considered.

University of Maryland performed 10 uneventful administrations prior to reporting an apparent misadministration (under-dose) on October 18, 2000. Preliminary licensee report data proposed that this misadministration may have been attributed to an air leak in the source vial rubber cap, at the site of needle insertion. The licensee suspects that the inlet needle and the outlet needle may have been positioned too closely to each other, which caused the rubber cap to lose its self-sealing capability. The licensee and the State of Maryland are conducting an investigation of this incident.

During their first TheraSphere administration, University of Maryland observed ^{90}Y microspheres pooling in the blue stopcock of the TheraSphere administration assembly. Normal sized arterial catheters were used. The licensee subsequently replaced the TheraSphere administration set's 5-ml syringe (see Attachment 4, TheraSphere Package Insert, page 15, item number 6 on diagram), with a 20-ml syringe and flushed the administration assembly with 50 to70 milliliters of normal saline. This procedure differed from the manufacturer's package insert, written in accordance with their FDA Humanitarian Device Exemption (HDE) approval, which states in the "Administration Instructions" on page 9, "The directions for administration should be followed to ensure accurate delivery of the calculated dose. Approximately 96% of the radioactivity in the TheraSphere® dose vial will be delivered to the patient using the recommended technique." The TheraSphere administration procedure would normally require using the provided 5-ml syringe to flush 5 ml of normal saline twice through the administration assembly (for a total of 10 ml).

The manufacturer subsequently took sensitive detectors to University of Maryland and they could easily detect the TheraSpheres pooling in the blue stopcock. The manufacturer concurred that the larger volume of saline was necessary to effectively flush the TheraSpheres from the administration set.

The manufacturer reported that the flow of microspheres through the stopcock was also affected by the angle of the stopcock and that changes in flow resulted from tapping on the stopcock by the physician.

The manufacturer is assisting with the evaluation of these events, and will address the TheraSphere administration assembly design. In the interim, the FDA has determined that the TheraSphere device will continue to be available, but proposes that the manufacturer provides more intensive training to the administering physicians on how to most effectively use the administration kit and to therefore minimize TheraSphere pooling within the assembly. This training will include instructions to "tap" on the stopcock during the infusion process.

TheraSphere administration difficulties have not been reported by users in Canada or Hong Kong, where TheraSphere has been used since 1991 and 1995, respectively. *The manufacturer performed bench-top experiments to conclude that approximately 96% of the radioactivity in the TheraSphere dose vial will be delivered to the patient using the recommended administration technique. Equivalent data was not collected during clinical trials.*

II. POSSIBLE SOURCES OF ERROR DURING THE ADMINISTRATION PROCEDURE:

1. Using administration materials other than those included in the TheraSphere device kit Administration Set.

2. During the following specific steps itemized in the "TheraSphere Package Insert, Instructions for Use, Administration Instructions" (Attachment 4):

- *Item 7*: "The 20-gauge needle at the free end of the inlet line is carefully inserted through the center of the TheraSphere dose vial septum and pushed to the bottom of the vee at the base of the vial."

- *Item 11*: "The 20-gauge needle at the free end of the outlet line is carefully pushed through the septum of the TheraSphere dose vial until it is just visible below the level of the seal."

- *Item 14*: "Fluid from the syringe is slowly forced through the inlet line, into the TheraSphere dose vial, and out through the outlet and vent lines until all air is exhausted from the system and fluid has entered the empty vial. **NOTE: A low flow rate and gently tapping of the TheraSphere dose vial will reduce the possibility of premature introduction of spheres in to the outlet line**.

- *Item 15*: "The outlet needle is pushed half way into the TheraSphere dose vial. The purpose of this step is to eliminate the possibility of sweeping air that may be trapped near the top of the TheraSphere dose vial into the catheter."

- *Item 20*: "After verifying that both stopcocks are correctly positioned, **the fluid in the syringe is expressed at a rate of approximately 1 ml per second.** This flow rate will carry the spheres out of the TheraSphere dose vial, through the outlet line, and into the catheter.

In addition, procedures 7, 11, and 15 require close hand and eye contact to the unshielded TheraSphere source vial during precise placement of needles into the vial. An applicable shielding design should be employed for these procedures.

III. ADDITIONAL INFORMATION:

A. Licensee ability to efficiently and accurately quantify TheraSphere activity:

It is not known yet if the two licensees had a procedure in place, prior to using the TheraSphere device, to quantify ^{90}Y microsphere activity which was either administered or "not" administered.

In the amendment request to use the TheraSphere device, a licensee committed to the condition, as part of the definition of a misadministration, "when the administered dosage differs from the prescribed dosage by more than 20 percent." This licensee experienced a TheraSphere misadministration which was discovered by gross exposure rate measurements originating from the administration assembly, after the TheraSphere administration was thought to be completed. The manufacturer immediately assisted with the incident follow-up, and it is not yet known whether or not the licensee would have been able to independently quantify the amount of TheraSphere (^{90}Y microspheres) remaining in the administration assembly.

The physical and radiological attributes of the TheraSphere device make measuring the ^{90}Y microsphere activity somewhat difficult, but not impossible. Residual ^{90}Y microsphere activity could be determined in at least two ways:

1. The licensee or the manufacturer could determine residual ^{90}Y microsphere activity left within the administration assembly (as a whole or in parts) by developing a bremsstrahlung - residual ^{90}Y microsphere "calibration curve." This would entail measuring the bremsstrahlung radiation produced by known quantities of ^{90}Y microspheres which are purposefully infused into the administration assembly.

2. Alternatively, residual ^{90}Y microsphere activity within the administration assembly could be determined by thoroughly flushing the assembly components with an appropriate solution, and measuring an aliquot of the flush in a liquid scintillation counter which is pre-calibrated for such measurements. The accuracy of this method could be determined by comparing the acquired results with known quantities of ^{90}Y microspheres infused into the administration assembly.

B. Approximate exposure rates* associated with TheraSphere administration, per licensee:

1. The exposure rate from the dose vial containing 135 mCi (5 GBq) (inside plastic shield but not in a lead pig) was approximately 7 mR/h at 30 cm. During administration, the exposure rate reached several hundred mR/h to several R/h at a distance of 30 cm or so from the apparatus. The licensee reported that this will vary greatly due to the beta contribution and the type of survey instrument used.

2. The exposure rate from a patient who was administered 48 mCi was 4 mR/h on contact from the right side of the body.

3. The exposure rate from a patient who was administered 130 mCi measured 9 mR/h on contact from the right side, 4 mR/h on contact from the front and 0.8 mR/h at 1 meter.

The total (integrated) dose**, D_T, accrued at a given distance from the radiation source (the patient) over a time interval T (which begins at the time of administration when the instantaneous source dose rate is at its maximum, D_o) is:

$$D_T = D_o / \lambda \, [1-e^{-(\lambda T)}]$$

where λ is the decay constant ($0.693/T_{1/2}$).

When $T>>1/\lambda$, (or when the exposure time interval is much longer than the half life) this equation becomes the total (infinite) dose; the total possible dose accrued during the period of complete decay (about 7 half-lives ~ 1% activity remaining):

$$D_T = D_o / \lambda$$

The dose rate, and total doses at other distances from the patient can be approximated by using the inverse square law: $I_1 D_1^2 = I_2 D_2^2$, where I_1 and I_2 are the dose (or dose rates) rates at distances D_1 and D_2, respectively.

^{90}Y activity (mCi)	D_o at 1 m (mrem/h)	D_o at 1 ft (mrem/h)	Total dose accrued over 8 hours (T=8) at 1 ft (mrem/h)
130	0.8	8.6	66
176	1.1	11.8	90
250	1.5	16.1	123
300	1.85	19.9	152
400	2.5	26.9	206

* The general conditions under which these measurements were taken, patient physical attributes, accuracy of activity and distances reported, and the survey instrument used are unknown at this time.

**assume exposure ~ dose

4. LICENSING AND REGULATORY ISSUES FOR MEDICAL USE TYPE A BROAD SCOPE AND LIMITED SPECIFIC LICENSEES

I. BOTH BROAD SCOPE AND LIMITED SPECIFIC LICENSEES NEED LICENSE AMENDMENTS TO USE THERASPHERE

1. Possession and medical use of ^{90}Y:

   a. The *Type A Broad Scope* Radiation Safety Committee is expected to review and approve the licensee's safety evaluation of proposed uses of material (§33.13(C)(3)). Usually a new authorization for the use of ^{90}Y is not needed unless it is to increase the amount of material. Also authorization to use the material for medical use is already covered by the broad medical use authorization.

   b. The *Limited Specific* licensee needs approval to use ^{90}Y in the form of sealed microspheres for the brachytherapy because this material is not already authorized on limited specific licenses.

2. *Both licensees* need definitions for TheraSphere misadministrations, prescribed dose, and written directive because these are not appropriately defined in 10 CFR Part 35.

3. *Both licensees* need to describe the training and experience requirements necessary to authorize a physician to use the TheraSphere device.

4. *Both licensees* need to commit to following the requirements for brachytherapy sources, and permanent implant brachytherapy uses included in 10 CFR 35, and other radiation safety procedures that the NRC deems necessary for the safe use of TheraSphere.

II. MISADMINISTRATION DEFINITION:

1. Current Brachytherapy Misadministration Definition in 10 CFR 35.2:

Misadministration means the administration of: (5) a brachytherapy radiation dose:

(i) Involving the wrong individual, wrong radioisotope, or wrong treatment site (excluding, for permanent implants, seeds that were implanted in the correct site but migrated outside the treatment site);

(ii) Involving a sealed source that is leaking,... or

(iv) When the calculated administered dose differs from the prescribed dose by more than 20 percent of the prescribed dose.

2. Suggested Misadministration Definition for TheraSphere Use:

For ^{90}Y microspheres, misadministration is defined as:

(i) Involving the wrong individual, wrong radioisotope, or wrong treatment site *for permanent implantation of Y-90 microspheres (including migration to the wrong treatment site if the preliminary shunt test was not performed, not performed properly, or results were not used prior to treatment);*

(ii) When the calculated administered dose *to the liver* differs from the prescribed dose by more than 20 percent of the prescribed dose,

(iii) *When the Y-90 dosage or total dose to the lung exceeds 15.6 mCi or 30 Gy, respectively, in a single treatment.*

III. WRITTEN DIRECTIVE DEFINITION:

1. Current Definition of a Permanent Implant Brachytherapy Written Directive in 10 CFR 35.2:

Written directive means an order in writing for a specific patient or human research subject, dated and signed by an authorized user

(6) for all other brachytherapy:

(i) Prior to implantation: the radioisotope, number of sources, and source strengths; and

(ii) After implantation but prior to completion of the procedure: the radioisotope, treatment site, and total source strength and exposure time (or, equivalently, the total dose).

2. Suggested Written Directive Definition for TheraSphere Use:

Written directive for *TheraSphere* means an order in writing for a specific patient or human research subject, dated and signed by an authorized user, *conditional on results of preliminary shunt tests*:

(i) Prior to the implantation: *the source strength, the treatment site(s) and fraction(s) of total activity and total dose to treatment site(s)*; and

(ii) After implantation: *the total activity and total dose to the treatment site(s).*

IV. PRESCRIBED DOSE DEFINITION:

1. Current Definition of Brachytherapy Prescribed Dose in 10 CFR 35.2:

(3) For brachytherapy, either the total source strength and exposure time or the total dose, as documented in the written directive.

2. Suggested Prescribed Dose Definition for TheraSphere:

For ^{90}Y microsphere brachytherapy, the total dose or total activity *as documented in the written directive.*

V. QUALITY MANAGEMENT PROGRAM:

Licensees will need to review and update their quality management program (QMP), §35.32, to ensure it addresses any unique properties of the TheraSphere device which is not covered by the current brachytherapy QM program. In addition, licensees will have to include TheraSphere use in their annual QMP review of representative sample administrations.

VI. AUTHORIZED USER TRAINING AND EXPERIENCE:

Recommended Training and Experience Requirements for Authorized Use of TheraSphere (^{90}Y Microspheres):

Use of the TheraSphere device (^{90}Y microsphere therapy) should be performed by a team consisting of at least a ***§35.200 authorized user and a §35.400 authorized user.*** *The rationale is provided below.*

The ^{90}Y microsphere therapy treatment is an emerging technology that requires multiple skills for safe use. The performance and evaluation of the prescreening test is critical to the determination of whether the patient is a candidate for the therapy treatment. **The equipment and computer programs needed to evaluate the prescreening test is best performed by a §35.200 physician authorized user. However, this physician does not have training in calculating therapy doses and making therapy treatment medical decisions.** If an error occurs and it is not possible to image the TheraSpheres, this physician also does not have extensive experience in the use of phantoms to evaluate the probable locations and dose effects of beta emitters.

The §35.300 radiopharmaceutical therapy physician has the narrowest training and experience of the §35.200, §35.300, and §35.400 physician authorized users. To date, this physician **is involved in use of radioactive drugs that preferentially find their way to the target tissue.** Biodistribution tables are available to aid the physician in determining doses to other important organs.

The §35.400 brachytherapy physician lacks experience in the skills needed to perform the prescreening test and to obtain quantitative data from the resulting images. However, the §35.400 physician is best qualified to determine the doses to normal tissues and sensitive organs using the prescreening tests data. *The brachytherapy physician's extensive clinical training provides the skills necessary to make therapy treatment medical decisions. This physician also has the skills needed to determine the dose and evaluate the biological effects if an error is made.*

The brachytherapy medical physicist should have the skills to determine doses to tumors, normal tissues and sensitive organs when provided the quantitative data from the prescreening images. This individual also has the skills needed to model, measure, and estimate doses from radiation measurements made from phantoms and patients. **However, this individual can not make medical judgments.**

*Titles of cited regulations, and Part 35 sections containing associated training and education requirements.

10CFR Part	Title/Content	T&E 10 CFR Part
§35.200	Use of unsealed byproduct material for imaging and localization studies	§35.920
§35.300	Use of unsealed byproduct material for therapeutic administration	§35.930
§35.400	Use of sources for brachytherapy	§35.940

The following tables compare physician training and education for each task of each phase required for TheraSphere administration. These tables were used by the staff to recommend at team consisting of at least a §35.200 authorized user and a §35.400 authorized user.

PHASE 1 - PRESCREENING:

STEP	TASK	PURPOSE	TRAINING NEEDED
Prescreening for extrahepatic shunting to liver, GI tract or other tissues.	Inject ^{99m}Tc MAA spheres (^{99m}Tc- macroalbumin)	Deliver ^{99m}Tc MAA spheres to hepatic artery.	Medical personnel with experience finding hepatic artery and delivering material to the artery.
	Locate ^{99m}Tc MAA.	Determine biodistribution of MAA.	§35.200 nuclear medicine imaging.
	Evaluate localization of biodistribution.	Quantify the amount of labeled MAA spheres going to lung, GI tract, or other site.	§35.200 nuclear medicine localization calculations.
	Calculate dose to non-liver sites.	Determine doses to normal liver and other tissue and radiation sensitive organs to determine potential effects of ^{90}Y microspheres on these sites. Ensure the GI tract does not receive any (or minimal -benefit vs risk) dose, and that the lung does does not exceed 30 Gy	Equations are straight forward: §35.200 Nuclear medicine physician can make calculations from localization data §35.400 Therapeutic brachytherapy dose calculation: Brachytherapy physician and medical physicist both with experience in similar type of dose calculations.
	Calculate dose to liver sites.	Determine dose to liver tumors to determine potential effects of ^{90}Y microspheres on liver tumor.	Equations are straight forward: §35.200 Nuclear medicine physician can make calculations from localization data. §35.400 Therapeutic brachytherapy dose calculation: Brachytherapy physician and medical physicist both with experience in similar type of dose calculations.

PHASE 2 - DETERMINE PATIENT ELIGIBILITY AND PERFORM TREATMENT

Reject or approve patient for ^{90}Y Therapy	Evaluate the prescreening data	Determine if patient is candidate for TheraSphere therapy. Ensure dose to normal tissue and sensitive organs is not more harmful than liver therapy benefit.	§35.400 Therapeutic Brachytherapy Physician to evaluate effects of doses to liver and other tissues and organs to determine if ^{90}Y therapy is appropriate for patient.
Perform ^{90}Y Therapy	Inject TheraSphere	Deliver therapeutic dose to liver without delivering life threatening dose to other tissues or organs, ensure occupational doses are ALARA.	Medical personnel with experience finding hepatic artery and delivering material to the artery. This may include experience in balloon blockage or other arterial pathways. Training and clinical experience under direction of manufacturer or experienced ^{90}Y microsphere user to ensure proper delivery.

PHASE 3 - EMERGENCY RESPONSE AFTER ADMINISTRATION PROBLEMS AND TREATMENT.

STEP	TASK	PURPOSE	TRAINING NEEDED
	Determine initial medical consequences for patient.		§35.400 Brachytherapy physician with experience making medical decisions based on therapy doses.
	Treat patient.		Specialist for area of concern.

PHASE 4 - RESPONDING TO ADMINISTRATION PROBLEMS AND ACCURATE EVALUATION OF MEDICAL EFFECTS

STEP	TASK	PURPOSE	TRAINING NEEDED
Evaluate effects of errors in delivery or misadministration.	Quantify the amount of ^{90}Y left in delivery devices.	Determine fraction of TheraSphere activity that was not administered.	Medical physicist with experience determining activity measuring and evaluating betas and bremsstrahlung emissions.
	Determine where ^{90}Y spheres went in patient.	Locate microspheres in the patient.	Imaging and localization either by §35.200 nuclear medicine, or other imaging modality.
	Quantify the amount of spheres at each location.		Quantify by imaging modality specialist.
	Collect phantom data.	Quantify radiation measurements from patient if microspheres locations cannot be imaged.	Brachytherapy physician or brachytherapy medical with phantom development and dose calculation.s
	Determine dose to organs of interest.		If imaged by nuclear medicine dose may be calculated from images, otherwise brachytherapy dose calculations comparing other imaging data or phantom data with patient measurements.
	Determine if misadministration.		

STRENGTHS AND WEAKNESSES OF NRC AUTHORIZED USERS WITH RESPECT TO THERASPHERE DEVICE USE (^{90}Y Microsphere Therapy)

INDIVIDUAL	STRENGTHS	WEAKNESSES
Nuclear Medicine Physician	1. Imaging experience 2. Computerized localization programs 3. Computerized quantification programs 4. Injection experience 5. Experience in evaluating case histories to determine suitability for radioisotope diagnostic tests	1. Not trained to make radiation therapy treatment medical decision 2. Not trained in pure beta emitter dosimetry 3. Not trained in evaluation of radiation therapy injury to unintended site
Radiopharmaceutical Therapy Physician	1. Trained to make radioactive drug therapy medical decision 2. Trained in handling and administering radionuclides in solution or suspension	1. Limited radiation training 2. Clinical experience limited to a few drugs and treatment sites 3. Limited experience with dose calculations to non-target tissues 4. Limited phantom development and calibration experience 5. If correct drug is given its biologically activity takes it to intended site
Brachytherapy Physician	1. Trained to make therapy treatment medical decision 2. Extensive radiation safety training 3. Extensive clinical training in evaluating dose effects on non target tissues 4. Extensive complex dose determination experience for wide variety of body parts 5. Dose modeling and phantom experience 6. Extensive experience in determining suitability, limitations, and contraindications of Brachytherapy treatments	Limited experience with beta dosimetry
Brachytherapy Medical Physicist	1. Extensive radiation safety training 2. Extensive complex dose determination experience for wide variety of body parts 3. Extensive dose modeling and phantom use experience	1. Cannot make medical judgment decision 2. Lack of familiarity with catheter based infusion systems

Not all NRC staff concur with the recommendation to ACMUI that the use of the TheraSphere device (^{90}Y microsphere therapy) should be performed by a team consisting of at least a §35.200 authorized user and a §35.400 authorized user.

The training requirements for each authorized user is provided below for reference.

Following these requirements, the position that a §35.300 physician is most suitable to be the authorized user for the TheraSphere device is discussed under the "comment" headings, and the counterpoint follows as the "response."

§35.920 Training for imaging and localization studies *(§35.200* uses).
Except as provided in Sec. 35.970 or 35.971, the licensee shall require the authorized user of a radiopharmaceutical, generator, or reagent kit in Sec. 35.200(a) to be a physician who:

(a) ... [certification options]...; or

(b) Has had classroom and laboratory training in ***basic*** radioisotope handling techniques applicable to the use of ***prepared radiopharmaceuticals***, generators, and reagent kits, supervised work experience, and supervised clinical experience as follows:

(1) ***200*** hours of classroom and laboratory training that includes:

(i-iv) Radiation protection; Mathematics...; ***Radiopharmaceutical chemistry***; Radiation biology; and

(2) ***500*** hours of supervised work experience under the supervision of an authorized user that includes:

(i) Ordering, receiving, and unpacking radioactive materials safely and performing the related radiation surveys;

(ii) Calibrating dose calibrators and diagnostic instruments and performing checks for proper operation of survey meters;

(iii) Calculating and safely preparing patient or human research subject ***dosages***;

(iv) Using administrative controls to prevent the misadministration of byproduct material;

(v) ***Using procedures to contain spilled byproduct material safely and using proper decontamination procedures***; and

(vi) Eluting technetium-99m ...; and

(3) ***500*** hours of supervised clinical experience under the supervision of an authorized user that includes:

(i) Examining patients or human research subjects and reviewing their case histories to determine their suitability for radioisotope diagnosis, limitations, or contraindications;

(ii) Selecting the suitable ***radiopharmaceuticals*** and calculating and measuring the dosages;

(iii) Administering dosages to patients or human research subjects and using syringe radiation shields;

(iv) ***Collaborating with the authorized user in the interpretation of radioisotope test results***; and

(v) Patient or human research subject follow up; or

(c) Has successfully completed a six-month training program in nuclear medicine that has been approved by the Accreditation Council for Graduate Medical Education and that included classroom and laboratory training, work experience, and supervised clinical experience in all the topics identified in paragraph (b) of this section.

§35.930 Training for Therapeutic use of unsealed byproduct material *(§35.300* uses).

(a) ... [certification options]...; or

(b) Has had classroom and laboratory training in ***basic*** radioisotope handling techniques applicable to the use of radiopharmaceuticals, and supervised clinical experience as follows:

(1) *80* hours of classroom and laboratory training that includes:

(i-iv) Radiation physics and instrumentation; Radiation protection; Mathematics...; Radiation biology; and

(2) Supervised clinical experience under the supervision of an authorized user at a medical institution that includes:

(i) Use of iodine I-131 for diagnosis of thyroid function and treatment of hyperthyroidism or cardiac dysfunction in 10 individuals; and

(ii) Use of iodine-131 for treatment of thyroid carcinoma in 3 individuals.

§35.940 Training for use of brachytherapy sources *(§35.400* uses).

(a) ... [certification options] ...; or

(b) ***Is in the active practice*** of therapeutic radiology, has had classroom and laboratory training in radioisotope handling techniques applicable to the therapeutic use of brachytherapy sources, ***supervised work experience***, and clinical experience as follows:

(1) ***200*** hours of classroom and laboratory training that includes:

(i-iv) Radiation physics and instrumentation; Radiation protection; Mathematics...; Radiation biology; and..;

(2) ***500 hours*** of supervised clinical experience under the supervision of an authorized user at a medical institution that includes:

(i) ***Ordering, receiving, and unpacking*** [ram] ... and... [performing radiation surveys];

(ii) Checking survey meters fro proper operation;

(iii) ***Preparing, implanting***, and removing sealed sources;

(iv) Maintaining running inventories of material on hand; and

(v) ***Using administrative controls to prevent the misadministration of byproduct material***; and

(vi) ***Using emergency procedures to control byproduct material***; and

(3) Three years of supervised clinical experience that includes on year in a formal training program approved by the ... and an addition two years of clinical experience in therapeutic radiology under the supervision of an authorized user at a medical institution that includes:

(i) ***Examining individuals and reviewing their case histories to determine their suitability for brachytherapy treatment, and any limitations or contraindications***;

(ii) Selecting the proper brachytherapy sources and dose and method of administration;

(iii) ***Calculating the dose***; and

(iv) ***Post-administration follow up and review of case histories in collaboration with the authorized user***.

The the position that a §35.300 physician is most suitable to be the authorized user for the TheraSphere device is discussed under the "comment" headings, and the counterpoint follows as the "response."

Comment:

The TheraSphere is more appropriately administered under the supervision of a §35.300 qualified physician who has received the manufacturer's training, but proposes to the *ACMUI that this modality be placed into the "emerging technology" category and that the NRC develop specific guidance on how to license its use.* This will avoid difficulties with the FDA's designation of TheraSphere as a device and NRC's Sealed Source and Device review and, at the same time, require every licensee to come in for an amendment of the license to authorize the use of TheraSphere. If NRC determines that a §35.300 or §35.400 physician qualifies as a TheraSphere Authorized User, then TheraSphere can be used without notifying the NRC, which may not be desirable for some limited scope licensees.

Response: *The NRC proposal that all licensees who use TheraSphere amend their license is not based solely on the training and education requirement issues. The amendment proposal is also based upon the need to include device-specific definitions for misadministration, prescribed dosage, written directive, and to incorporate any other specific conditions the Commission deems necessary for the medical use of this device. The NRC would therefore be notified of all licensee TheraSphere use, regardless of the authorized user qualifications.*

Comment: Regarding Phase 1 - Prescreening: Once the §35.200 qualified physician identifies the liver and non-liver sites where the MAA localized and quantifies the amount of MAA at each site, the estimation of dose to these sites resulting from TheraSphere administration is a straight forward calculation (using the formula described in the Humanitarian Device Exemption) that can be made by anyone. Because this calculation is critical to the patient treatment, I would expect that it be made by, or reviewed by, the authorized user for the therapy, whether it be a §35.300 qualified physician or a §35.400 qualified physician. (Almost all §35.300 physicians are also qualified to perform §35.100 and §35.200 procedures).

Response: *NRC staff agrees that the liver dose calculation is straightforward and that it is critical that the data collected for the equation variables is accurate. Doses to the GI tract (stomach, duodenum, etc.) can cause chronic pain, ulceration, and bleeding which may be mild, severe (treatable with surgery), or lethal. TheraSphere shunting to the lungs can cause edema and fibrosis that may not be reversible. Radiation pneumonitis has been observed in patients receiving doses to the lungs greater than 30 Gy in a single treatment. The staff recommends that a §35.400 physician review the prescreening data, the dose calculation, and the final doses expected, before TheraSphere administration occurs.*

The staff disagrees that "almost all §35.300 physicians are also qualified to perform §35.200 procedures."

Comment: Regarding Phase 2 - Determine Patient Eligibility and Perform Treatment:
§35.300 physicians are more qualified than §35.400 physicians to determine patient eligibility for TheraSphere therapy based on radiation exposure to the liver and other tissues. Y-90 is a pure beta emitter and most §35.400 physicians have little or no experience with beta emitters. Conversely, §35.300 physicians have had extensive experience using beta emitters for therapy (strontium-89, phosphorus-32, samarium-153, yttrium-90, etc.) and concern for the radiation exposure of other critical tissues/systems is a critical factor in the decision to treat a particular patient. A good example of this is the use of strontium-89 for palliative treatment of bone pain. A critical factor in the decision to treat a patient or continue treatment is the patient's red blood cell count.

Response: *Beta emitting radionuclides are used frequently in brachytherapy. Examples include: ^{32}P, ^{90}Sr, and ^{90}Y (all pure beta emitters) for intravascular brachytherapy, and ^{32}P and ^{90}Y for permanently implanted radioactive stents.*

Unsealed byproduct materials (radiopharmaceuticals) used by §35.300 physicians distribute and localize in accordance with their biochemical properties. Localization is predictable and doses to target tissues are well established and documented. §35.400 physicians have experience in calculating short-range doses and dose rates, such as beta doses to immediately surrounding tissue, and to other tissues/organs as a result of unexpected localization elsewhere in the body.

Comment: §35.300 physicians are more qualified than §35.400 physicians to perform treatment using TheraSphere because of their experience using beta emitters in therapy and because the standard dose, in all likelihood, would have to be reduced based on the specific requirements of the patient. The dose reduction (volume reduction) would have to be based on the manufacturer's assay (millicuries per milliliter) or on the in-house dose calibrator assay. §35.400 physicians are not experienced with the handling of unsealed materials nor are they trained to use a dose calibrator.

Response: *The TheraSphere device is a sealed source. Therefore, the unit dose distributed by the manufacturer is not to be altered by the licensee. Also, the manufacturer will provide the licensee with the requested TheraSphere unit dose activity.*

§35.400 physicians and medical physicists have expertise in measuring photon and electron (beta) kerma, exposure, and absorbed dose (and rates) in air, water, and various phantom compositions, with consideration given to radiation scatter, buildup, attenuation, and surface transition effects, when applicable. The types of detection devices they employ include ion chambers, thimble chambers (condenser, Farmer), electrometers, calorimeters, chemical dosimetry, TLDs, film, as well as conventional dose calibrators. The training and education requirements for §35.300 and §35.400 physicians do not specify dose calibrator training, nor handling of unsealed materials.

Comment: Regarding Phase 3 - Emergency Response After Administration Problems and Treatment, and Phase 4 - Responding to Administration Problems and Refinement for the Evaluation of Medical Effects: §35.300 physicians are more qualified than §35.400 physicians to respond to emergencies because they are experienced with the use of beta emitters for medical treatment in patients and they are experienced in the use of unsealed material and the handling of contamination.

Response: *The qualifications required of §35.300 physicians are much less demanding than those for §35.200 and §35.400 physicians. The qualifications for §35.300 physicians consist of 80 hours of classroom and laboratory training, and require supervised clinical experience with only I-131. No other radiopharmaceutical experience is required.*

5. GENERIC LICENSING GUIDANCE FOR EMERGING TECHNOLOGIES

To be discussed.

ATTACHMENT 1

SPECIFIC CHARACTERISTICS OF THE THERASPHERE DEVICE (A supplement follows)

- Device generic name: Yttrium-90 Glass Microspheres
- Device Trade Name: TheraSphere®
- HDE holder: MDS Nordion, Inc., Ontario, Canada. FDA CDRH Humanitarian Device Exemption (HDE no. H980006, approval to applicants on 12/10/99)
- NRC: Registry of Radioactive Sealed Source and Devices, NR-0220-D-113-S, February 15, 2000
- TheraSphere is a brachytherapy sealed source.

TheraSphere consists of insoluble glass microspheres in which Y-90 is embedded, and is intended to be used to treat a liver tumors. The microspheres are delivered into the hepatic artery which provides the main blood supply to the tumor in the liver. The microspheres become physically "trapped" in the tumor vasculature by arteriolar capillary blockage, and the Y-90 beta particle delivers a localized radiotherapeutic dose to tumor tissue. The glass microspheres are not biologically active or biodegradable. They remain in place in the capillary bed and do not redistribute to other organs of the body.

The TheraSphere *device* consists of the TheraSphere dose and a preassembled single use administration kit. TheraSphere was intended to be administered using the administration kit provided with each dose.

The FDA approved conditions of TheraSphere use is: "TheraSphere is indicated for radiation treatment or as a neoadjuvant to surgery transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters."

TheraSphere may be used for clinical or human research use.

The TheraSphere package insert states that TheraSphere is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi), and 20 GBq (540 mCi). However, the manufacturer is currently providing licensed users with other dosages (e.g., 80 mCi and 400 mCi) based upon specific patient medical conditions.

The dose is supplied in 0.05 ml of sterile, pyrogen-free water contained in a 0.3 ml vee-bottom vial secured within a 12 mm clear lucite vial shield. Each milligram contains between 22,000 and 73,000 microspheres (mean diameter 25 μm each).

Additional information and a schematic of the TheraSphere dose vial and administration kit are found in the attached "Summary of Safety and Probable Benefit" document.

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Yttrium-90 Glass Microspheres

Device Trade Name: TheraSphere®

Applicant's Name and Address:

MDS Nordion, Inc.
447 March Road
Kanata, Ontario Canada
K2K 1X8

Humanitarian Device Exemption (HDE) Number: H980006

Date of Humanitarian Use Device Designation: Dec. 1, 1997

Date of Panel Recommendation: Not applicable (Refer to Section XI for discussion).

Date of Good Manufacturing Practices Inspection: September 10, 1999

Date of Notice of Approval to Applicant: DEC 10 1999

II. INDICATIONS FOR USE

TheraSphere® is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.

III. DEVICE DESCRIPTION

TheraSphere® is a therapeutic device consisting of insoluble glass microspheres in which the radionuclide yttrium-90 (Y-90) is an integral constituent. The microspheres have a mean (±SD) diameter of 25 μm (±10 μm, with less than 5% below 15 μm and less than 10% above 35 μm). Each milligram contains between 22,000 and 73,000 microspheres. The TheraSphere® dose is supplied in 0.05 mL of sterile, pyrogen-free water contained in a 0.3-mL vee-bottom vial secured within a 12 mm clear lucite vial shield. TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi), and 20 GBq (540 mCi). Each dose of TheraSphere® is supplied with an administration set. The administration set is a single use delivery system designed to deliver TheraSphere® to the disease site and to minimize radiation exposure to administering personnel. The pre-assembled administration set has inlet and outlet lines that facilitate infusion of the microspheres from the dose vial.

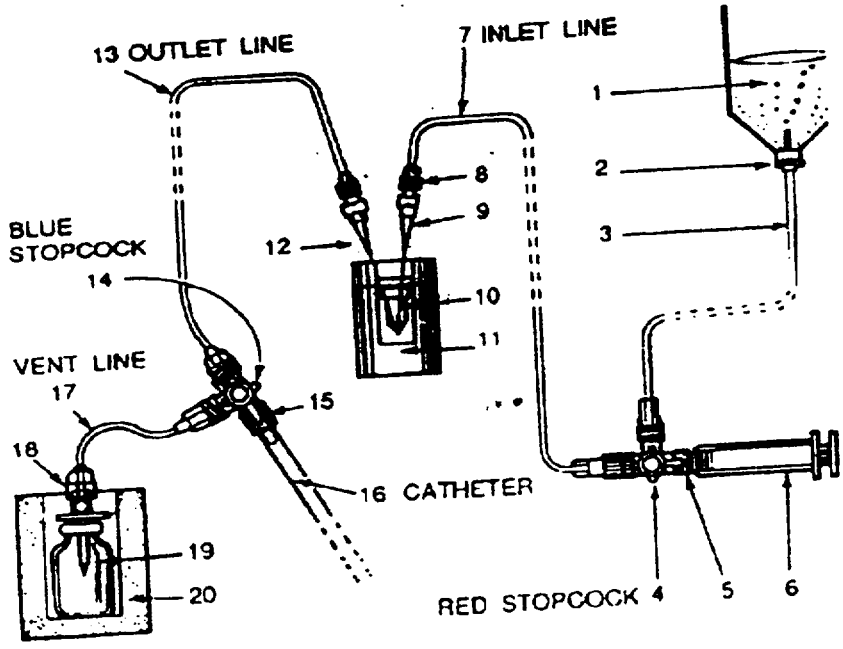
Radiation Dosimetry

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.2 hours (2.68 days). The average energy of the beta emissions from Y-90 is 0.9367 MeV. The average range of the radiation in tissue is 2.5 mm, with a maximum range less than 1 cm. One GBq (27 mCi) of Y-90 per kg of tissue gives an initial radiation dose of 13 Gy (1,297 rad) per day. The mean life of Y-90 is 3.85 days. Thus, the radiation dose delivered by Y-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5,000 rad).

Administration Set

The TheraSphere® administration set is a single use delivery system consisting of an inlet set and an outlet set. The inlet set and the outlet set are made up of pre-assembled sterile, apyrogenic components hermetically sealed in a bag and ethlyene oxide sterilized. Each dose is supplied with all the components required for administration exclusive of items utilized in the catheterization procedure. Figure 1 is a diagramatic representation of the contents of the administration set.

Figure 1. TheraSphere® Administration Set



The numbers refer to the following items: 1 - fluid source, 2 - piercing pin, 3 - fluid line, 4 - red three-way stopcock, 5 - free port on the red three-way stopcock, 6 - 5 mL syringe, 7 - inlet line, 8 - check valve, 9 - 20 gauge needle at the free end of the inlet line, 10 - TheraSphere® dose vial, 11 - acrylic vial shield, 12 - 20 gauge needle at the free end of the outlet line, 13 - outlet line, 14 - blue three-way stopcock, 15 - freeport

on the blue three-way stopcock, 16 - catheter, 17 - vent line, 18 - filter vent assembly, 19 - sterile empty vial and 20 - lead pot.

Principles of Operation of the Device

TheraSphere® is delivered into the liver tumor through a catheter placed into the hepatic artery. This artery provides the main blood supply to the tumor in the liver, as opposed to normal liver parenchyma, which is dependent on the portal vein. TheraSphere®, being unable to traverse the tumor vasculature, is embolized within the tumor and exerts a local beta radiation radiotherapeutic effect with relatively limited concurrent injury to surrounding normal tissue.

Properties of the Device Relevant to the Treatment of the Disease

TheraSphere® is used to treat liver tumors where the blood supply is delivered by the hepatic artery. The size of the microspheres causes them to be embolized in the tumor vasculature and hence, retained within the tumor. The microspheres are not biodegradable and do not redistribute to other organs of the body. The administration set facilitates the transfer of the radioactive microspheres from their container into the tumor via a catheter inserted in the hepatic artery.

Yttrium-90 is an integral component of the glass matrix. Yttrium-90 is a radioisotope well suited for localized radiation therapy. The beta particle emitted during radioactive decay has an average tissue penetration of 2.5 mm and a maximum tissue penetration less than 1 cm. Therefore, this radioisotope is suitable to deliver highly localized radiation doses to tumors while minimizing the damage to surrounding healthy liver tissue.

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

The use of TheraSphere® is contraindicated in patients:

- whose Tc-99 macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract which cannot be corrected by angiographic techniques.
- who show shunting of blood to the lungs which could result in delivery of greater than 16.5 mCi of radiation to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment.
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities, bleeding diathesis, or portal vein thrombosis.
- who have severe liver dysfunction or pulmonary insufficiency.

Precautions /Warnings

- Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.

- Adequate shielding and precautions for handling radioactive material must be maintained.

- The TheraSphere® dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The vial should always be stored in a shielded location away from personnel.

- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately following good radiation safety practices and the area monitored for contamination at the end of the procedure.

- As in the use of any radioactive material, care should be taken to insure minimum radiation exposure to the patient extraneous to the therapeutic objective and to insure minimum radiation exposure to workers and others in contact with the patient.

- Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.

- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Based on clinical and preclinical animal experience with TheraSphere® and other yttrium-90 microspheres, certain adverse reactions have been identified [1-7]. Adverse events that occurred in the 100 Gy HCC (N=22) [8], the Pilot HCC (N=9) [3], and the Mixed Neoplasia (N=4) [9,10] studies are summarized by severity in Table 1.

Table 1
Incidence[a] of Treatment-Emergent Adverse Events From Three Studies[b] (N=35), SWOG Toxicity Grading System

Adverse Event	Mild	Moderate	Severe	Life Threatening	Lethal/Fatal	Total
Increased Transaminase (SGOT/SGPT)[c]	14 (40.0%)	14 (40.0%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	33 (94.3%)
Increased Alkaline Phosphatase	18 (51.4%)	9 (25.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	30 (85.7%)
Increased Lactic Dehydrogenase	19 (54.3%)	2 (5.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	24 (68.6%)
Increased Bilirubin	0 (0.0%)	9 (25.7%)	6 (17.1%)	4 (11.4%)	1 (2.9%)	20 (57.1%)
Abdominal Pain	6 (17.1%)	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	16 (45.7%)
Decreased Hemoglobin	8 (22.9%)	4 (11.4%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	15 (42.9%)
Nausea	9 (25.7%)	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	13 (37.1%)
Anorexia	11 (31.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Malaise/Fatigue/Lethargy	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Other Pain[d]	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Decreased White Blood Cell	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (28.6%)
Fever, Absence Infection	4 (11.4%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.7%)
Increased Creatinine	6 (17.1%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Increased Prothrombin Time	5 (14.3%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Edema	3 (8.6%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	7 (20.0%)
Weight Gain	5 (14.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (20.0%)
Gastric Ulcer	1 (2.9%)	0 (0.0%)	4 (11.4%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Other Liver[d]	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Vomiting	4 (11.4%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (17.1%)
Anxiety/Depression	4 (11.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Hemorrhage (Clinical)	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Other Gastrointestinal[d]	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Decreased Platelet	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Cough	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Dyspnea	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Insomnia	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Weight Loss	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Constipation	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Diarrhea	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Hyponatremia	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Pneumonia	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	3 (8.6%)
Sweats	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Dysrhythmia	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
Headache	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
Infection	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)

Abbreviations: SWOG, Southwest Oncology Group; HCC, hepatocellular carcinoma; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

[a] For each patient, the highest severity of an adverse event was counted once. Adverse events that were reported by at least two patients in the total population are summarized.

[b] Studies: 100 Gy HCC (N=22), Pilot HCC (N=9), and Mixed Neoplasia (N=4).

[c] If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

[d] Other pain included pain in back/lower back (3), epigastric (2), chest (1), legs (1), shoulder (1), stomach (1), toe (1), and musculoskeletal (1). Other liver included hepatitis (2) and ascites (4). Other gastrointestinal included abdominal discomfort (1), early satiety (1), heartburn (1), duodenal ulcer (1), and burping (1).

The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract can cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs can cause edema and fibrosis that may not be reversible. Extrahepatic shunting may be identified through the injection of Tc-99 MAA into the hepatic artery [11, 12]. Flow of radioactivity to the

gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [13]. The use of this product leads to irradiation of both tumorous and normal liver parenchyma. As a result, patients with diseases which compromise the functioning of the non-tumorous liver parenchyma or with very small lesions scattered throughout the normal parenchyma may be at greater risk of liver function impairment.

VI. ALTERNATE PRACTICES AND PROCEDURES

Surgery

The standard curative therapy for hepatocellular cancer is complete resection of the tumor in a patient who has not developed metastatic disease. However, only15% of patients in high incidence countries and 30% of cases in western countries are candidates for attempts at curative resection. Liver transplantation is an option for the cure of patients with liver-confined hepatocellular cancer who cannot have curative partial hepatectomy. Because of limited access to transplant centers and limited availability of donor organs, liver transplantation benefits only a small minority of patients with hepatocellular carcinoma.

Non-surgical Treatments

Other therapies for hepatocellular cancer includes: 1) systemic chemotherapy, 2) hepatic artery embolization with materials such as lipiodol, angiostat, and gel foam, and 3) chemoembolization where chemotherapeutic agents are mixed with embolizing material.

Chemotherapy

Both single agent therapy with drugs such as FUDR and combination therapy with combinations of drugs including mitomycin, 5-FU, FUDR, doxorubicin, and cisplatin have been used in the treatment of hepatocellular cancer. Single agent therapy with FUDR,[14, 15] a drug which is particularly attractive for intrahepatic therapy because of a 95% first pass hepatic extraction, is capable of inducing responses in as many as 50% of patients; median survivals range from six to seven months. With combination chemotherapy,[16,17] high orders of response in the range of 60-70% have been reported in small studies. Median survivals for these studies, however, are only approximately eight months. Long-term survival is very rare and intrahepatic chemotherapy is not considered useful except as a palliative measure in hepatocellular cancer.

Embolization and Chemoembolization

Because of the vascular nature of hepatocellular cancer, controlling the tumor by hepatic arterial embolization has been of considerable interest. Embolization of materials such as lipiodol, angiostat, and gel foam have been used to devascularize hepatocellular cancer.[18 - 20]. These approaches result in decreases in serum

alpha fetoprotein (AFP) in as many as 50-90% of cases and patients selected for this treatment have one year survivals ranging from 30-50%. When chemotherapeutic agents are mixed with the embolizing material, anti-tumor responses of 40-90% have been noted [21, 22] and some patients have survival well beyond one year, although median survival rates are less than 12 months. Because of the ability of embolization and chemoembolization to produce substantial anti-tumor responses and some improvement in survival, they have been used as initial therapy in patients who are candidates for hepatic transplantation. This strategy is aimed at controlling the hepatocellular cancer in the liver while the patient awaits an available liver for orthotopic transplantation. Survival data are difficult to interpret in embolization/chemoembolization therapy since some patients are subsequently transplanted. Since transplant is known to have curative potential, it is not possible to assess whether the pretransplant therapy had significant impact on long term survival. In considering survival results reported for embolization, chemoembolization, or any other hepatic directed therapy, it is important to note that there are significant and important patient selection factors which may result in these patients having better survival potential than the general population of patients with hepatocellular cancer. For example, patients with severe underlying liver disease are not candidates for these therapies. Patients for hepatic directed therapies must have good performance status, no extrahepatic tumor and relatively good hepatic function without severe portal hypertension. These patients also must possess the intellectual ability and personal support systems to comply with a complex medical intervention.

Embolization and chemoembolization may be associated with significant toxicity. These therapies cause fever and pain in the post-therapy period in all patients. "Clinical" hepatitis, i.e., elevation in transaminases and/or bilirubin is common. Infections may occur and these therapies are not applicable to patients with portal vein obstruction and must be used with caution in patients with portal hypertension.

VI. MARKETING HISTORY

MDS Nordion has had TheraSphere® available for sale in Canada since 1991. Syncor International, MDS Nordion's distributor for Asia and Mexico, has had TheraSphere® available for sale in Hong Kong since 1995. TheraSphere® has recently been approved for use in Mexico and will be made available for sale by Syncor International.

TheraSphere® has not been withdrawn from marketing for any reason relating to safety or probable benefit of the device.

VIII. SUMMARY OF PRECLINICAL STUDIES

In Vitro Studies

In vitro laboratory testing of TheraSphere® demonstrated excellent chemical and physical stability under simulated use conditions. The results at pH 7 indicated that

the solubility of yttrium from the glass matrix becomes extremely small as the dissolution medium approaches physiologic pH. The release of Y-90 from the activated glass microspheres comprising TheraSphere® production batches was evaluated also. The mean ratio of Y-90 in solution at pH 6 to that in the glass microspheres was 0.00093. This result was in good agreement with the pH 6 removal data obtained with the nonradioactive spheres. This test was performed at pH 6 because at pH 7 and above the solution activity became too small to quantify.

In Vivo Studies

1) An evaluation was performed to examine the translocation of Y-90 from TheraSphere® in Sprague-Dawley rats. The Y-90 was injected via the caudal vein so that the microspheres lodged in the vasculature of the lungs. An average of 90% (SD=11) of the activity delivered (the difference between the activity in the syringe before and after delivery) could be accounted for. Considering the differences between the geometry and composition of the various samples and containers involved, this is a very satisfactory result. In only one case, Rat 11, was activity detected outside the lungs. In this case the activity was around the delivery site. Except for this one case, activity was confined to the lungs. The extent of translocation in the test animals was below the limits of detection using this protocol. No detectable activity was found in the liver of any animal at any time. These results lead to the conclusion that the extent of translocation was 0.1% or less of the total amount delivered. This is a level, which should produce no adverse health effects.

2) Another preclinical study (liver distribution study) evaluated TheraSphere® in normal and tumor-bearing New Zealand white rabbits. The glass microspheres were introduced directly into the hepatic artery of New Zealand white rabbits by means of a catheter placed in the gastroduodenal artery, and were evaluated specifically for their ability to distribute throughout the liver in relative proportion to hepatic blood flow without inducing any acute changes in systemic hemodynamic stability and without inducing changes in local hepatic perfusion due to excessive occlusion of capillary beds.

The results from this study demonstrated that: 1) administering either 140,000 or 460,000 glass microspheres to the rabbit's liver (average weight between 70 and 100 grams) by direct hepatic arterial delivery does not acutely alter systemic blood pressure or heart rate, nor does it occlude the hepatic capillary bed significantly so as to induce alterations in regional hepatic perfusion; 2) although the glass microspheres do not necessarily distribute throughout the liver in direct proportion to regional blood flow patterns as determined by administration of tracer resin microspheres, they do adequately distribute to all lobes of the liver including caudal aspects and peripheral edges; and 3) the glass microspheres tend to be delivered in higher concentrations to central regions of the liver, and to regions with relatively higher local blood flow. This might be of some advantage, as tumors tend to have relatively higher local blood flows.

3) A small study examined the tolerance of TheraSphere® administration via the hepatic artery in dogs.

The radioactive glass microspheres, in the quantities with the specific activities administered (See Table 3), were well tolerated in all dogs. Signs referable to toxicity were not observed although some abnormalities were observed in serum biochemical parameters. An increase in SGPT was measured in dog 234I. SGPT is an enzyme located in the cytosol of hepatocytes. An elevation is indicative of hepatocellular injury with leakage of the enzyme. Serum alkaline phosphatase consists of several isoenzymes; induction of hepatic alkaline phosphatase is the likely cause of the SGPT elevation in dog 234I. The increased hepatic alkaline phosphatase production observed was probably induced by increased intracanicular hydrostatic pressure. The mechanism in this case is hepatocellular swelling which can occlude bile canaliculi. Taken together these elevated enzymes suggest hepatocellular damage and swelling.

Table 3. Radioactivity Administered to Foxhounds

Dog	Weight (kg)	Mass of Spheres	Activity in Vial	Activity Delivered	Activity in Liver
234C	40	116 mg	52.0 mCi	96	50.0 mCi
234I	25	75 mg	33.6 mCi	95	32.0 mCi
34K	29	79 mg	35.2 mCi	95	33.0 mCi

The extent of hepatocellular damage may be estimated from the SGPT elevation in that the degree of elevation parallels the number of hepatocytes affected. The SGPT elevation does suggest some degree of damage. The elevated SAP (serum alkaline phosphatase) indicates hepatocellular swelling, but the degree of pressure on bile ducts was not severe enough to result in hyperbilirubinemia.

The amylase elevation observed in dog 234C suggests distribution of some microspheres to the pancreas. Amylase is a leakage enzyme that rises in serum in cases of pancreatic cell damage. The pancreatic duodenal artery, a branch of the gastroduodenal, which branches from the common hepatic artery, supplies the pancreas. A mechanism therefore exists for distribution of some glass microspheres to the pancreas. The elevation was small and with the absence of clinical signs indicates minimal damage to the pancreas.

The observation that all hematologic parameters monitored remained within normal limits implies asepsis of the product and delivery procedure. The duration of this preliminary study was insufficient to evaluate any effect on bone marrow stem cells.

4) The appearance of radioactivity in the blood of dogs following administration of Tc-99 MAA microspheres and TheraSphere® via the hepatic artery was also assessed. The data in Table 4 provide some insight into the release of Y-90 from TheraSphere® in vivo. Dogs B & H did not receive any radionuclides; thus their

blood samples represent an estimate of background in this system. The samples from C, I, and K measured through 1/27/86 were all higher than those for B and H. By 2/10/85 all samples had roughly comparable values to those from B and H. This seems to indicate that some Y-90 activity was indeed present following the delivery of TheraSphere®. If the long-lived isotope Tc-99 MAA had been responsible for the initial activity above background, the 14-day decay period would not have resulted in the change observed (neglecting all other elimination mechanisms for Tc-99 MAA). Assuming the worst case, i.e., all elevated activity was due to Y-90, and assuming that the activities observed on 2/10/85 were essentially background, then the blood activity elevation relative to background can be calculated. The column "Elevation" gives the ratio of the initial activity to background indicating that on average the TheraSphere® elevated the blood activity by only 90 percent of background. This indicates a very low level of mobile Y-90 from TheraSphere® delivery into the hepatic artery. This result is in qualitative agreement with the in vitro release studies, which indicate a very low Y release rate at physiological pH. Quantitative comparison would require detailed knowledge of Y absorption and elimination kinetics -- information that is not available.

Table 4. Activity in Blood

Activity observed in serum and plasma samples obtained from dogs in acute toxicity tests.

Date	Dog	Sample	Initial	Activity Decayed	Differ.	Elevat.
1/23	B	Ser	2.5	2.2	0.3	1.1
1/23	H	Ser	2.5	2.2	0.3	1.1
1/23	C	Ser	4.0	2.5	1.6	1.6
1/23	I	Ser	3.9	2.4	1.5	1.6
1/23	C	Pla	3.6	2.1	1.5	1.8
1/23	I	Pla	3.5	1.9	1.5	1.8
1/23	K	Pla	3.2	1.9	1.3	1.6
1/24	C	Pla	4.6	2.5	2.1	1.8
1/24	I	Pla	6.5	2.5	4.0	2.6
1/24	K	Pla	5.3	2.4	2.9	2.2
1/25	C	Pla	4.6	2.3	2.3	2.0
1/25	I	Pla	5.2	2.3	2.9	2.2
1/25	K	Pla	4.3	2.3	2.0	1.9
1/26	C	Pla	4.5	2.3	2.2	2.0
1/26	I	Pla	4.7	2.3	2.4	2.1
1/26	K	Pla	4.5	2.3	2.2	2.0
1/27	C	Pla	3.4	2.3	1.1	1.5
1/27	I	Pla	3.6	2.0	1.6	1.8
1/27	K	Pla	2.8	2.4	0.5	1.2

Initial, Decayed and Difference are activities given in curies times 1011, i.e., 10^{-5} microcuries, per ml sample.
Date indicates when sample was drawn.

Elevation gives the ratio of the initial activity to the background (Decayed Activity).

There is some indication that the activity levels were highest at 48 through 72 hours after delivery. A linear release rate model predicts a maximum activity outside the liver at 96 hours.

Detailed interpretation of the results of this study must be kept in perspective. The fact is, the activity observed in the blood of dogs C, I, and K were in all cases less than 3 times background. This leads to a large uncertainty in the measurements, making only gross trends observable. The amount of Y-90 in circulation in the dogs studied was extremely small -- very near current limits of detection.

5) A subsequent study evaluated the reaction of canines to the administration of non-radioactive glass microspheres through surgically implanted hepatic arterial catheters. Two dogs were administered at 1.5 times the currently proposed human dose of 5 million spheres and two at 6 times this dose. On a liver weight basis, the dog doses were 3 times and 12 times more than any patient will receive. All dogs were sacrificed one-month post treatment. Liver function tests showed minor changes only, and, at autopsy, there was no evidence of cirrhosis or portal fibrosis in any of the dogs.

6) Additionally, four dogs had hepatic arterial catheters placed angiographically (procedure to be used for most human patients) and were administered glass microspheres at a level 2.5 times (5 times on a liver weight basis) the currently proposed-human dose. The tissue damage observed at necropsy following sacrifice at 48 hours post administration varied from no evident damage to extensive infarction of the gall bladder with focal hepatic infarcts.

7) Pulmonary toxicity was assessed also in dogs. Six dogs were divided into two groups of three each: a high dose group receiving doses of 120, 130 and 168 Gy and a low dose group receiving doses of 31, 33, and 33 Gy. TheraSphere® was delivered into the cephalic vein. In the high dose group, the 168 Gy dog was near death from pulmonary failure on day 96 and was euthanized. The other two dogs in this group were euthanized at day 108. The 120 and 130 Gy dogs showed x-ray changes consistent with pulmonary fibrosis as well as minor blood gas abnormalities. Dogs receiving 31 and 33 Gy showed no changes on chest x-ray or in blood gases or clinical status. Routine pathological examination of the lungs of dogs receiving 31 and 33 Gy were normal (identical to untreated dogs). The high dose dogs had extensive fibrosis. The maximum dose (10 millicuries, ca. 18 - 20 Gy) allowable for patients is below that generating significant symptomatic permanent injury in dogs.

8) Biodistribution was examined in five New Zealand white rabbits which were infused via the hepatic artery with 10 milligrams (1 millicurie) of TheraSphere®. The study organs can be divided into two groups, those with an arterial supply arising at or below the celiac axis and those with an arterial supply outside this region. The first group of organs can contain radioactive glass microspheres and in some cases was observed to contain radioactivity. The other group of organs should

not contain any glass microspheres and, in fact, no activity was observed in any sample. The first group of organs in this study consisted of the spleen, duodenum, pancreas, stomach, colon, ileum, gall bladder, and bile duct while the second group consisted of the lungs and bone marrow. This biodistribution study supports the contention that the rate of release of Y-90 from TheraSphere® is extremely low.

9) Biocompatibility was not tested directly for TheraSphere® but is inferred from extensive studies done with glass fiber, a close analogue to the glass microspheres. These studies found very low pulmonary toxicity. A two-year inhalation study [23] in which animals were allowed to live out their lives found only minimal macrophage reaction without pulmonary fibrosis even at fiberglass dust concentrations in excess of 100 mg/m^3. Also no neoplastic reactions were observed. A study of workers with a mean exposure of 20 years showed no significant difference in pulmonary disease over a carefully matched control group [24]. To test for the biocompatability and tissue reactions of TheraSphere®, four dogs had nonradioactive TheraSphere® delivered through surgically implanted hepatic arterial catheters to evaluate subacute tissue reactions. Each set of two dogs had 3 and 12 times the proposed human dose of 5 million glass microspheres delivered into their livers. All dogs were sacrificed one-month post treatment. Liver function tests showed minor changes only and, at autopsy, there was no evidence of cirrhosis or portal fibrosis in any of the dogs.

Summary of Findings from the Preclinical Studies

A number of preclinical studies were completed on different animal species: rats, dogs, and rabbits. In the rat studies TheraSphere® was delivered into the caudal vein and trapped in the capillaries of the lungs. The activity of the liver, cranial section, caudal section and tail (delivery site) were below the detection limit of the measuring equipment used. An average of 90% of the activity delivered could be accounted for in the lungs since no activity was found in other body parts, the fact that the activity balance did not account for 100% of the activity indicates a systematic error in the bremsstrahlung measurements involved. The dog study determined the radioactivity in the blood of dogs following delivery of TheraSphere® via the hepatic artery. On average, the blood activity was found to be two times background. This indicates a very low level of mobile Y-90 from TheraSphere® into the hepatic artery. The rabbit study involved measurement of the distribution of TheraSphere® in organs. TheraSphere® was delivered into the hepatic artery of white rabbits. The study organs were divided into two groups. Those organs that had an arterial supply at or below the celiac axis, which could convey microspheres, were observed to contain some radioactivity. The second group of organs has their arterial supply outside of the celiac axis. No activity was observed in any sample from these organs. The release of Y-90 from TheraSphere® appears to be negligible. In summary, the preclinical studies have shown that the irradiated yttrium (Y-90) is not displaced from the glass matrix under clinically relevant conditions.

IX. SUMMARY OF CLINICAL STUDIES

A. Overview of TheraSphere® Clinical Studies

Three clinical studies have been conducted with TheraSphere®. All three studies were observational with mortality, response to treatment, and safety as major endpoints. Six study centers participated in these studies with five from Canada and one from the United States (US). All studies were performed in patients with unresectable liver cancer (HCC and metastatic).

The first protocol to begin enrollment was "Phase I Study of Hepatic Arterial Yttrium-90 Glass Microsphere (TheraSphere®) Therapy for Liver Neoplasia", and will be referred to as the "mixed neoplasia study". The mixed neoplasia study recruited patients with carcinoid and colorectal metastatic disease to the liver, as well as primary hepatobiliary carcinoma. The second protocol entitled "A Pilot Trial of Yttrium-90 Microspheres in the Treatment of Primary Hepatocellular Carcinoma" will be referred to as the "pilot HCC study". This study targeted HCC patients. Both protocols required beginning at an initial nominal liver dose of 50 Gy. Based on accumulating multicenter safety data, the dose was escalated in increments of 25 Gy not exceeding a target dose of 100 Gy. These two protocols resulted in 111 patients being treated with TheraSphere®, and comprised the data upon which TheraSphere® gained Canadian approval in 1991. Treated patients from these two protocols are intended to provide supporting safety data.

The third protocol entitled "Phase II Trial of Yttrium-90 Microspheres in the Treatment of Primary Hepatocellular Carcinoma" was approved by the Toronto Hospital Committee for Research on Human Subjects in January 1992, and the first patient was treated on April 3, 1992. Based on the encouraging safety results of the pilot HCC study, the nominal liver dose was set at 100 Gy. This study will be referred to as the "100 Gy HCC study". The last patient under this protocol was treated on April 10, 1996. This study provides the primary clinical safety and probable benefit data.

The main differences between the three protocols, besides dose escalation, are that prior chemotherapy and/or radiation therapy were not allowed in the 100 Gy HCC study. Compared to the pilot HCC study, the mixed neoplasia study required that all patients be evaluated pretreatment with a radionuclide liver scan and be angiographically assessed for lesion vascularity. The 100 Gy HCC and Mixed Neoplasia studies required a pretreatment Tc-99 MAA scan to predict the activity to be delivered to the lungs from the treatment dose. All three protocols were single treatment protocols.

The treatment indication sought for TheraSphere® is for HCC. Diagnosis of HCC was based on cytology, pathology, or the confirmation of a dominant liver mass with an associated serum AFP greater than 1000 ng/dL. The distribution of hepatocellular carcinoma cases from each protocol is as follows: four cases from the mixed neoplasia

study, nine cases from the pilot HCC study, and 22 cases from the 100 Gy HCC study.

B. Mixed Neoplasia [9, 10] and the Pilot HCC [3] Studies

Mixed Neoplasia Study: Objectives and Patient Selection/Exclusion Criteria

The objectives of the mixed neoplasia study were to evaluate the toxicity of Y-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of Y-90 glass microspheres administered by hepatic arterial infusion that would be suitable for Phase II-III studies in a similar patient population.

Eligibility criteria for the mixed neoplasia study included:

- histological proof of surgically unresectable metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobiliary carcinoma
- hepatic arterial angiography or Tc-99 MAA hepatic arterial perfusion to demonstrate that the hepatic tumor was vascular
- Karnofsky performance status equal to or greater than 60
- peripheral leukocyte count greater than 4,000/mm^3
- granulocyte count greater than 2,000/mm^3
- platelet count greater than 150,000/mm^3
- serum albumin greater than 2.5 g/dL
- bilirubin less than 2 mg/dL
- SGOT less than 6 x normal
- prothrombin time within 3 seconds of control (or correctable with Vitamin K to same)
- serum creatinine less than 2.0 mg/dL.

Patients also had to have a hepatic arterial perfusion scan using Tc-99 MAA or albumin microspheres showing complete perfusion of both lobes of the liver, an F (fraction of Tc-99 MAA activity observed in the lungs relative to the total Tc-99 MAA activity observed) times A (the Y-90 activity to be injected) product of 10 mCi or less, and no detectable Tc-99 MAA activity in the stomach and/or duodenum by gastric air contrast scan. Patients must have terminated any previous chemotherapy or non-hepatic radiation therapy at least four weeks before entering the study and they must have recovered from all toxicity from the previous therapy. Patients who had received previous hepatic radiotherapy were excluded from the study.

Pilot HCC Study: Objectives and Patient Selection/Exclusion Criteria

The objectives of the pilot HCC study were to define the activity of Y-90 microspheres administered by hepatic arterial infusion to patients with hepatocellular carcinoma and to evaluate the toxicity of Y-90 microsphere therapy.

Patients eligible for the pilot HCC study had to have histologic or cytologic proof of primary hepatocellular carcinoma and the disease must have been measurable. The

inclusion and exclusion criteria for this study were comparable to those enumerated above for the mixed neoplasia study.

Population Description and Treatment Administration

From July 1986 to December 31, 1989, a total of 111 patients were treated in these two studies with TheraSphere® in North America. One hundred (100) patients were evaluable (Table 5). The evaluable patients were divided into three categories of tumor type: adenocarcinoma, hepatocellular carcinoma and all other tumor types. The patients were further divided into two dose ranges: less than 80 Gy (35 to 79 Gy) and equal to or greater than 80 Gy (80 to 150 Gy).

Table 5. Evaluable Patients

	<8,000 rads	≥8,000 rads	Totals
Adenocarcinoma	22	50	72
Hepatocellular	7	6	13
Other Tumor Types	5	10	15
Total	34	66	100

Summary of Safety Data

Two patients died during the follow-up period. The deaths were attributed to elevated bilirubin (elevated before TheraSphere® treatment that increased in severity 2 days after treatment and continued until the patient's death 2 weeks later; judged as possibly related to TheraSphere®), and pneumonitis, (death approximately 6 weeks after TheraSphere® treatment; judged as possibly related to TheraSphere®).

In the group of 34 patients treated at < 80Gy 13 patients (38%) had gastric complications, 2 patients (6%) had fevers lasting between 1 and 6 days, and 3 patients (9%) had complications classified as "other." Of those patients with gastric complications 9 had grade 1-2 symptoms and 4 patients developed ulcers. Two of the ulcer patients were managed with medication and 2 required surgical intervention. Of those patient complications listed as other one was ascites. A second patient experienced lethargy and confusion that extended over a nine-day period.

In the group of 66 patients treated at 80 Gy or more 15 (23%) experienced gastric symptoms. This apparently lower incidence of gastric complications may be due to the adoption of a different catherization technique. A balloon catheter was employed whenever possible in these latter patients to prevent any of the microspheres from entering the right gastric artery. Five of the 15 patients with gastric complications developed ulcers. Three were medically managed and two required surgical intervention. One of the 66 patients experienced a fever possibly due to tumor necrosis as a result of the Y-90 therapy.

Five (8%) of the 66 patients developed complications classified as "other". Two patients developed a "red line" rash on the skin in the area where the catheter used to deliver the spheres was left in place. Normally the catheters are removed

immediately and disposed of with the other radioactive waste. Residual radioactivity remaining in the catheters even after flushing probably resulted in the erythema. One patient had an elevated WBC ascribed to tumor necrosis and one patient had RUQ pain thought due to rapid and significant tumor shrinkage. A fifth patient developed a measles-like rash that was probably due to an antihistamine reaction.

Summary of Probable Benefit Data

Table 6. Therasphere® Median Survival (months)

	Dose < 80 Gy	Dose ≥ 80 Gy
Adenocarcinoma	9.1 (n=22)	9.7 (n=50)
Hepatocellular	3.6 (n=8)	11.1 (n=7)

The fifty adenocarcinoma patients treated at doses of 80 Gy or more had a median survival of 9.7 months and those treated at < 80 Gy had a median survival of 9.1 months (see Table 6). Hepatocellular patients treated at < 80 Gy had a median survival of 3.6 months but those treated at ≥ 80 Gy had a median survival of 11.1 months. Survival of the adenocarcinoma patients is comparable to published survival data for the systemic and intrahepatic infusion of chemotherapeutic agents for the treatment of metastatic liver cancer.

Conclusions for Mixed Neoplasia and Pilot HCC Studies

The data derived from these two studies support the following conclusions with respect to the use of TheraSphere® in the treatment of liver neoplasia:

- TheraSphere® appears to be more efficacious at a dose range of 80 to 150 Gy than at lower doses.
- TheraSphere®, when administered at the 80 to 150 Gy dose range according to the directions does not cause unacceptable toxicities or complications.

C. 100 Gy HCC Study [8]

The objectives of the study were to define the activity of Y-90 microspheres given by the hepatic artery infusion to a previously untreated patient with primary hepatocellular carcinoma, to evaluate the survival of patients treated with Y-90 microspheres, and to evaluate the toxicity of Y-90 microsphere therapy.

Patient Selection and Exclusion Criteria

Eligible patients had to have

- histologically confirmed unresectable hepatocellular carcinoma confined to the liver and at least one measurable lesion
- ECOG performance status 0-3,
- estimated life expectancy greater than 12 weeks.

- absolute granulocyte count 2.0 x 10^9/L or greater,
- platelet count 100 x 10^9/L or greater,
- prothrombin time (PT) and activated partial thromboplastin time (aPTT) within normal limits,
- bilirubin less than 1.5 x upper normal limit,
- aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP) less than 5 x upper normal limit
- normal pulmonary function defined as no more than 30% greater or less than the expected normal.

Exclusion criteria included

- previous chemotherapy or radiation,
- any contraindication to hepatic artery catheterization such as vascular abnormalities, bleeding diathesis, allergy to contrast dye, or portal vein thrombosis,
- any medical or psychosocial condition, which would not permit the patient to be managed according to the protocol.

Population Description and Treatment Administration

Twenty-two patients were treated in the 100 Gy HCC study. Two patients were excluded from the efficacy analysis due to an unconfirmed diagnosis of HCC. Patient 11017 did not have cytology or pathology results and had an AFP of 35 ng/dL. Patient 11019 had a pathology diagnosis of cholangiocarcinoma. Twenty patients received one TheraSphere® treatment; two patients received a second TheraSphere® treatment based on the principle investigator's discretion.

Three patients had undergone a prior right lobectomy and were being treated with TheraSphere® for a recurrence. The time from recurrence to TheraSphere® treatment was taken as the measure of treatment delay. Nine patients were classified as Okuda stage I and eleven patients as Okuda stage II. The median activity administered was 3.9 GBq and ranged from 2.0 GBq to 9.2 GBq, with two infusions injected into the left hepatic artery, three into the right hepatic artery, and fifteen infusions specified as hepatic artery only. The median liver dose was 104 Gy and ranged from 46 Gy to 145 Gy. All bremsstrahlung scan results were reported as comparable to the pretreatment Tc-99 MAA scans. One patient had known breast cancer at the time of treatment and another patient had prostate cancer. Three patients received either chemotherapy or immunotherapy for progression of their liver cancer after TheraSphere® treatment.

Summary of Safety Data

Three patients (11006, 11019 and 11026) died during the follow-up period. Patient 11026 died approximately two months after TheraSphere® treatment due to radiation pneumonitis (received estimated lung dose of 56.5 Gy); the investigator

judged the death to be definitely related to TheraSphere® treatment. Patient 11019 died approximately two months after TheraSphere® treatment due to a gastric ulcer; the investigator judged the death to be probably related to TheraSphere® treatment. Patient 11006 died approximately five months after TheraSphere® treatment due to hepatitis; the investigator judged the death to be possibly related to TheraSphere® treatment.

TheraSphere® treatment procedures were completed without complications; however, one patient (11013) suffered from a possible angiography contrast agent allergic grade 3 reaction. Seven patients exceeded the protocol stated lung shunt exclusion criteria of 10 mCi during the first treatment with TheraSphere® with activity levels of 11.2, 11.3, 11.8, 14.0, 14.3, 16.4, and 30.5 mCi. These patients received estimated lung doses of 20.8, 21.0, 21.8, 25.9, 26.4, 30.3, and 56.5 Gy, respectively. The accumulated lung doses for the two patients who underwent a second TheraSphere® treatment were 43 Gy (Pt. 11002) and 36 Gy (Pt. 11021).

There were twenty-four grade 3 toxicities in 11 patients, four grade 4 toxicities in four patients, and three grade 5 toxicities, for a total of 31 toxicities of grade 3 or higher in 14 patients. 45.2% of these toxicities were liver related and 19.4% were gastrointestinal. Liver toxicities were primarily elevated enzymes during the week after treatment, while the gastrointestinal toxicities included three ulcers, one ileus, and one nausea. Patient 11021 experienced grade 3 fatigue after the second TheraSphere® treatment.

Summary of Probable Benefit Data

As of February 14, 1997, only two patients remained alive resulting in a median survival of 378 days (95% CI, 209 - 719), with a minimum survival of 49 days and a maximum survival of 1265 days. Based on a stratified Cox survival analysis model; activity ratio, Okuda stage, and liver dose appeared to influence survival by approximately the same magnitude of effect. This effect was measured by the estimated risk ratio for activity ratio (.26), liver dose (.28) and the reciprocal of the estimated risk ratio for Okuda stage (.29).

A sensitivity analysis of the effect of liver dose on survival, taking into consideration the delay of treatment, was performed. The influence of treatment delay did not appear to confound the liver dose trend.

Two patients received a second TheraSphere® treatment. Patient 11002 received a total dose equal to the targeted dose of 100 Gy. However, patient 11021 received two approximately equal doses resulting in a total of 209 Gy.

X. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

Preclinical studies demonstrated that TheraSphere® is designed to prevent leakage of Y-90 from the glass microspheres, and that TheraSphere® is biocompatible and does not cause significant adverse tissue reaction.

The results from preclinical and clinical studies provide evidence of the safety of TheraSphere® in the treatment of patients with surgically unresectable hepatocellular carcinoma. In addition, the probable benefit from the use of TheraSphere® in this patient population outweighs the risks when compared to the safety and probable benefits of currently available alternative therapies.

XI. PANEL RECOMMENDATION:

This HDE was not taken to an Advisory Panel because other radioisotopes, for different etiologies in different patient populations, have been in use in the United States for many years. In addition, the use of embolization is a well-established therapeutic approach for treating other conditions such as vascular bleeding.

XII. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, TheraSphere® will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of injury or illness, and issued an approval order on DEC 10 1999.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See Package Insert (Attachment 1).

XIV. REFERENCES

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ATTACHMENT 2
DEFINITIONS OF DRUG AND DEVICE

TITLE 21 - FOOD AND DRUGS

CHAPTER 9 - FEDERAL FOOD, DRUG, AND COSMETIC ACT

SUBCHAPTER II - DEFINITIONS

(g)(1) The term ''drug'' means

(A) articles recognized in the official United States Pharmacopoeia, *official Homoeopathic Pharmacopoeia of the United States*, or official National Formulary, or any supplement to any of them; and

(B) *articles* intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) *articles (other than food)* intended to affect the structure or any function of the body of man or other animals; and

(D) *articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.*

(h) The term ''device'' (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) means an instrument, apparatus, implement, machine, contrivance, **implant**, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is -

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease *or other conditions*, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

ATTACHMENT 3
SUMMARY OF HDE/HUD (2 supplements follow)

TheraSphere is currently distributed under an FDA Human Device Exemption, and is registered with the FDA as a Humanitarian Use Device (HUD)*. The following is a summary of relevant HDE/HUD information. FDA regulations associated with premarket and HDE approval of medical devices are found in 21 CFR 814

1. **HDE (Humanitarian Device Exemption):** HDE provides incentive to manufacturers, for the development of devices for use for rare diseases/conditions in small populations, where device R&D costs shown to exceed potential market return.

2. **HUD (humanitarian use device):** A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year, and no comparable device is available.

3. FDA requires a **HUD to be used only in accordance with FDA approvable conditions of use.** An applicant seeking *a new indication* for use of an approved HUD shall obtain a new designation of HUD status *submit an original HDE (21 CFR 814.110).*

4. The FDA approves HUDs for clinical use based on an abbreviated version of the detailed application for premarket approval of medical devices (21 CFR 814.20) which includes elaborate discussions of summaries, conclusions, and results from clinical investigations. In lieu of these requirements , the HDE application shall include the summaries, conclusions, and results of all clinical experience or investigations (whether adverse or supportive) reasonably obtainable by the applicant that are relevant to an assessment of the risks and probable benefit of the device; ... (21 CFR 814.104).

5. **Institutional Review Board (IRB) requirements:** The HDE holder is responsible for ensuring that the approved HUD is administered only in facilities having an (IRB) which will provide continuous device review (21 CFR 814.124). The IRB has discretion to approve HUD use as it sees fit, e.g., the IRB may approve device use in general, for groups of patients meeting certain criteria, or for devices under a treatment protocol. An IRB may specify limitations on device use based upon any criteria determined appropriate. The IRB does not have to review and approve each individual use of the HUD.

6. **A HUD may be used administered without prior IRB approval,** if a physician determines that IRB approval cannot be obtained in time to prevent serious harm or death to a patient in an emergency. The physician shall subsequently provide written notification to the IRB chairman within 5 days after the use of the device (Sec. 814.124).

7. **An HDE holder shall maintain records of:** facility names and addresses to which the HUD has been shipped, correspondence with reviewing IRBs, and any other information requested by the FDA.

8. **Informed consent:** The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et. seq.) and the regulation ***do not require informed consent***, as the HDE provides for marketing approval and does not constitute research or an investigation which would normally require informed consent. If, however, the HUD is subject of a clinical investigation, i.e., safety and effectiveness data will be collected to support a premarket approval application or publication in a scientific journal, informed consent is required (21 CFR part 50). ***However, there is nothing in the act or regulation that preempts a State or institution from requiring such consent.***

*Applicable FDA regulations specific to HDE/HUD: 21 CFR 814.100-126. 21 CFR 814 last amended 1/1/99 (63 FR 59217).

Humanitarian Use Devices

- Agency Information Collection Activities: Proposed Collection; Comment Request; Medical Devices; Humanitarian Use Devices (Text or PDF)

General Information

On June 26, 1996, FDA issued a final rule to carry out provisions of the Safe Medical Devices Act of 1990 regarding humanitarian use devices (HUDs). This regulation became effective on October 24, 1996. An HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. A device manufacturer's research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. FDA, therefore, developed and published this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

The regulation provides for the submission of an humanitarian device exemption (HDE) application, which is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD must state that the device is an humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

Other HDE Information

- HDE Regulation Questions and Answers Text or PDF
- HDE Checklist for Filing Decisions Text or PDF

Listing of CDRH Humanitarian Device Exemption Summaries of Safety and Possible Benefit

Summaries are in pdf format. The HDE number is the indication of the link to the summary. Information about PDF Reader is available

HDE Number Approval Date, and Docket Number	Device Name	Company Name and Address	Device Description/Device Indications
H990012 11-May-00 Docket#00M-1354	TAS Ecarin Clotting Time Test	Cardiovascular Diagnostics, Inc.	To be used to determine the anticoagulant effect of recombinant hirudin (r-hirudin) during cardiopulmonary bypass in patients who have heparin induced thrombocytopenia (HIT).
H990014 31-March-00 Docket#00M-1451	Enterra™ Therapy System (formerly named Gastric Electrical Stimulation (GES) System	Medtronic, Inc.	For the treatment of chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.
H990008 09-March-00 Docket#:00M-1228	Telescopic Plate Spacer (TPS) Spinal System	Interpore Cross International	To replace normal body structures following a vertebrectomy/corpectomy of the spine for metastatic disease in the cervical and/or cervico-thoracic spine (C_3-T_2). The TPS Spinal System implants are intended to correct spinal alignment and stablize the spinal operative site during fusion. TPS Spinal S implants attach to the spine anteriorly by means of their trapezoidal shape and by screws joined with a plate and spacer component.
H990011 01-Feb-00 Docket#:00M-0599	CardioSEAL® Septal Occlusion System	Nitinol Medical Technologies, Inc.	For closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy.
H980006 10-Dec-99 Docket#:99M-5539	TheraSphere®	MDS Nordion, Inc., Kanata, Ontario, Canada	For radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters.
H990007 07-Dec-99	BioGlue®Surgical Adhesive	CryoLife, Inc.	For use as an adjunct in t' surgical repair of acute th c

http://www.fda.gov/cdrh/ode/h980006sum.html

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 10 1999

James Goin, Ph.D.
U.S. Representative for MDS Nordion, Inc.
c/o DataMedix Corporation
600 North Jackson Street, Suite 306
Media, Pennsylvania 19063

Re: H980006
TheraSphere®
Filed: August 11, 1998
Amended: September 14 and December 31, 1998; March 19 and April 8, 1999

Dear Dr. Goin:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for TheraSphere®. This device is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

The sale, distribution and use of this device are limited to prescription use in accordance with 21 CFR 801.109.

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/ode/hdeinfo.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact John C. Monahan at (301) 594-1212.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or

2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but

not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS

Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;

2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);

3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. **ADVERSE REACTION AND DEVICE DEFECT REPORTING**

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. **REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION**

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on April 11, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

(1) may have caused or contributed to a death or serious injury; or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, Maryland 20847-3002. For questions regarding the MDR regulation, please call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.

Copies of the MDR regulation and FDA publications, entitled "An Overview of the Medical

Device Reporting Regulation" and "Medical Device Reporting for Manufacturers," are available on the CDRH WWW Home Page (http://www.fda.gov/cdrh), through CDRH's Fact-on-Demand (FOD) at 800-899-0381 (FOD # 336, 1336, 509 and 987) or by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Lane
Rockville, Maryland 20850

ATTACHMENT 4
THERASPHERE USE TREATMENT PROTOCOL (A supplement follows)

Prescreening:

Per attached "TheraSphere Package Insert, Preliminary Patient Evaluation," page7: "Prior to the administration of TheraSphere® the patient should undergo hepatic arterial catheterization using a balloon catheter or other appropriate angiographic techniques to prevent extrahepatic shunting. Following the placement of the hepatic catheter, 75 MBq to 150 MBq (2 mCi to 4 mCi) of Tc-99m MAA is administered into the hepatic artery to determine the extent of A-V shunting to the lungs. Air contrast scintigraphic views of the stomach are also obtained to **confirm the absence of gastric and duodenal flow. If such flow is present and cannot be corrected using established angiographic techniques the patient is disqualified from treatment.**"

"The recommended dose to the liver is between 80 Gy to 150 Gy (8,000 rad to 15,000 rad). The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula, where F is the fraction of injected activity deposited into the lungs as measured by the Tc-99m MAA."

Activity Required (GBq) ={ [Desired Dose (Gy)] [Liver Mass (kg)]}/50 [1-F]

Determination of patient eligibility (page 1):

The use of TheraSphere is contraindicated in patients:

1. Whose Tc-99m MAA hepatic arterial perfusion scintigraphy shows ***any deposition to the GI tract which cannot be corrected by angiographic techniques.***
2. *Who show* ***shunting of blood to the lungs which could result in delivery of greater than 16.5 mCi of radiation to the lungs*** (will deliver ***30 Gy*****).** Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatments.
3. In whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities, bleeding diathesis, or portal vein thrombosis.
4. Who have severe liver dysfunction or pulmonary insufficiency."

TheraSphere Administration:

The administration assembly is shown on the last page of the package insert. All components are included in the TheraSphere kit except for the hepatic arterial catheter.

External Radiation Levels and Shielding:

In the US NRC Registry of Radioactive Sealed Sources and Devices, no. NR-0220-D-113-S, the manufacturer reported the following external radiation levels* for a TheraSphere device containing 515 mCi:

Distance from source (cm)	*Measured Radiation Levels from 515 mCi TheraSphere (mrem/h)*	
	Lucite Vial	Lucite Vial in F390 lead Pot
0	810	85
5	230	33
30	20	2.7
100	2.2	0.6

* Detector-type not identified.

http://www.fda.gov/cdrh/pdf/h980006c.pdf

Package Insert

TheraSphere® Yttrium-90 Glass Microspheres

Humanitarian Device.
Authorized by Federal Law for use in the radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable hepatocellular carcinoma (HCC) who can have placement of appropriately positioned hepatic arterial catheters. The effectiveness of this device for this use has not been demonstrated.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training and experience.

DESCRIPTION

TheraSphere® consists of insoluble glass microspheres where yttrium-90 is an integral constituent of the glass [1]. The mean sphere diameter ranges from 20 to 30 μm. Each milligram contains between 22,000 and 73,000 microspheres. TheraSphere® is supplied in 0.05 mL of sterile, pyrogen-free water contained in a 0.3 mL vee-bottom vial secured within a 12 mm clear acrylic vial shield. A pre-assembled single use administration set is provided with each dose. TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi) and 20 GBq (540 mCi).

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.2 hours (2.68 days). The average energy of the beta emissions from yttrium-90 is 0.9367 MeV.

Following embolization of the yttrium-90 glass microspheres in tumorous liver tissue, the beta radiation emitted provides a therapeutic effect [2-6]. The spheres are delivered into the liver tumor through a catheter placed into the hepatic artery that supplies blood to the tumor. The spheres, being unable to pass through the vasculature of the liver due to arteriolar capillary blockade, are trapped in the tumor and exert a local radiotherapeutic effect with some concurrent damage to surrounding normal liver tissue [7-14].

INDICATION

TheraSphere® is indicated for radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC who can have placement of appropriately positioned hepatic arterial catheters.

CONTRAINDICATIONS

The use of TheraSphere® is contraindicated in patients:

- whose Tc-99 MAA hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract which cannot be corrected by angiographic techniques (see Item 1 under **INDIVIDUALIZATION OF TREATMENT**);
- who show shunting of blood to the lungs which could result in delivery of greater than 16.5 mCi of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment (see Item 2 under **INDIVIDUALIZATION OF TREATMENT**);
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities, bleeding diathesis, or portal vein thrombosis; and

- who have severe liver dysfunction or pulmonary insufficiency.

PRECAUTIONS/WARNINGS

- Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides.
- Adequate shielding and precautions for handling radioactive material must be maintained.
- As in the use of any radioactive material, care should be taken to insure minimum radiation exposure to the patient extraneous to the therapeutic objective and to insure minimum radiation exposure to workers and others in contact with the patient.
- Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.
- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.
- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure.
- The TheraSphere® dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The vial should always be stored in a shielded location away from personnel.

ADVERSE REACTIONS

Based on clinical and preclinical animal experience with TheraSphere® and other yttrium-90 microspheres, certain adverse reactions have been identified [4-6, 15, 16, 17, 18]. Adverse events that occurred in the 100 Gy HCC (N=22), the Pilot HCC (N=9) [4], and the Mixed Neoplasia (N=4) [3, 11] studies are summarized by severity in Table 1.

The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract can cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs can cause edema and fibrosis that may not be reversible. Extrahepatic shunting may be identified through the injection of Tc-99 MAA into the hepatic artery [19, 20]. Flow of radioactivity to the gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [21]. The use of this product leads to irradiation of both tumorous and normal liver parenchyma. As a result patients with diseases which compromise the functioning of the non-tumorous liver parenchyma or with very small lesions scattered throughout the normal parenchyma may be at greater risk of liver function impairment.

Table 1
Incidence[a] of Treatment-Emergent Adverse Events From Three Studies[b] (N=35), SWOG Toxicity Grading System

Adverse Event	Mild	Moderate	Severe	Life Threatening	Lethal/Fatal	Total
Increased Transaminase (SGOT/SGPT)[c]	14 (40.0%)	15 (42.9%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	34 (97.1%)
Increased Alkaline Phosphatase	18 (51.4%)	9 (25.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	30 (85.7%)
Increased Lactic Dehydrogenase	19 (54.3%)	2 (5.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	24 (68.6%)
Increased Bilirubin	0 (0.0%)	8 (22.9%)	6 (17.1%)	4 (11.4%)	1 (2.9%)	19 (54.3%)
Abdominal Pain	6 (17.1%)	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	16 (45.7%)
Decreased Hemoglobin	8 (22.9%)	4 (11.4%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	15 (42.9%)
Nausea	9 (25.7%)	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	13 (37.1%)
Anorexia	11 (31.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Other Pain[d]	5 (14.3%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (31.4%)
Decreased White Blood Cell	8 (22.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (28.6%)
Malaise/Fatigue/Lethargy	5 (14.3%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (28.6%)
Fever, Absence Infection	4 (11.4%)	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (25.7%)
Increased Creatinine	6 (17.1%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Increased Prothrombin Time	5 (14.3%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
Edema	3 (8.6%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	7 (20.0%)
Weight Gain	5 (14.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (20.0%)
Gastric Ulcer	1 (2.9%)	0 (0.0%)	4 (11.4%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Other Liver[d]	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	1 (2.9%)	6 (17.1%)
Vomiting	4 (11.4%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (17.1%)
Anxiety/Depression	4 (11.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Hemorrhage (Clinical)	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Other Gastrointestinal[d]	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Decreased Platelet	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
Cough	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Dyspnea	0 (0.0%)	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Insomnia	4 (11.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Weight Loss	3 (8.6%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.4%)
Constipation	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Diarrhea	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Hyponatremia	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Pneumonia	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	3 (8.6%)
Sweats	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
Dysrhythmia	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
Headache	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
Infection	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)

Abbreviations: SWOG, Southwest Oncology Group; HCC, hepatocellular carcinoma; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

[a] For each patient, the highest severity of an adverse event was counted once. Adverse events that were reported by at least two patients in the total population are summarized.

[b] Studies: 100 Gy HCC (N=22), Pilot HCC (N=9), and Mixed Neoplasia (N=4).

[c] If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

[d] Other pain included pain in back/lower back (3), epigastric (2), chest (1), legs (1), shoulder (1), stomach (1), toe (1), and musculoskeletal (1). Other liver included hepatitis (2) and ascites (4). Other gastrointestinal included abdominal discomfort (1), early satiety (1), heartburn (1), duodenal ulcer (1), and burping (1).

CLINICAL STUDIES

1. 100 Gy HCC Study

- *Objectives:* To define the activity of yttrium-90 microspheres given by hepatic artery infusion to a previously untreated patient with primary hepatocellular carcinoma (HCC); to evaluate the survival of patients treated with yttrium-90 microspheres; and to evaluate the toxicity of yttrium-90 microsphere therapy.
- *Study Design:* Patients with HCC were treated with a target dose of TheraSphere® of 100 Gy by injection through the hepatic artery. Patients underwent laboratory tests, history and physical examinations, and liver ultrasounds or computerized tomography (CT) scans for up to 2 years after treatment. Response duration was calculated from the

date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the Southwest Oncology Group (SWOG; Operations Office, San Antonio, TX) grading system (last revised 12/94), i.e., grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and grade 5 = lethal/fatal. If a patient's transaminase was above normal at baseline and the patient experienced a further increase during the study, SWOG grading was not applied; rather, a grade 1 toxicity (mild) was defined as a 1-50% increase from baseline, a grade 2 toxicity (moderate) as a 51-200% increase from baseline, and a grade 3 toxicity (severe) as a >200% increase from baseline.

- *Patient Inclusion Criteria:* Presence of histologically confirmed unresectable HCC confined to the liver and at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status 0-3; estimated life expectancy greater than 12 weeks; absolute granulocyte count 2.0 x 10^9/L or greater; platelet count 100 x 10^9/L or greater; prothrombin time (PT) and activated partial thromboplastin time within normal limits; bilirubin less than 1.5 x upper normal limit; serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase less than 5 x upper normal limit; normal pulmonary function defined as no more than 30% greater or less than the expected normal.
- *Study Population and Treatment Administration:* Twenty-two patients were treated. Two patients were excluded from the efficacy analysis due to an unconfirmed diagnosis of HCC. Twenty patients received one TheraSphere® treatment; two patients received a second TheraSphere® treatment based on the principle investigator's discretion. Nine patients were classified as Okuda stage I and 11 patients as Okuda stage II. The median activity administered was 3.9 GBq (range, 2.0 GBq to 9.2 GBq). The median liver dose was 104 Gy (range, 46 Gy to 145 Gy).
- *Safety Results:* One patient suffered from a possible angiography contrast agent allergic reaction that was judged by investigator to be severe in nature. All 22 treated patients reported at least one treatment-emergent adverse event; however, the majority (85%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (45%) and gastrointestinal (19%). Liver toxicities were primarily elevated enzymes during the week after treatment. The gastrointestinal toxicities included three ulcers, one ileus, and one nausea. Three patients died during the follow-up period. The deaths were attributed to hepatitis (death approximately 5 months after TheraSphere® treatment; judged as possibly related to TheraSphere®), gastric ulcer (death approximately 2 months after TheraSphere® treatment; judged as probably related to TheraSphere®), and radiation pneumonitis (death approximately 2 months after TheraSphere® treatment; judged as definitely related to TheraSphere® after the patient received an estimated dose of 56 Gy to the lungs as a result of pulmonary shunting).
- *Probable Benefit:* As of February 14, 1997, only two patients remained alive resulting in a median survival of 378 days (95% CI, 209 - 719), with a minimum survival of 49 days and a maximum survival of 1265 days. Based on a stratified Cox survival analysis model; activity ratio, Okuda stage, and liver dose appeared to influence survival by approximately the same magnitude of effect.

2. Pilot HCC [4] and Mixed Neoplasia Studies [3, 11]

- *Objectives:* The objectives of the Pilot HCC study were to define the activity of yttrium-90 microspheres administered by hepatic arterial infusion to patients with HCC and to evaluate the toxicity of yttrium-90 microsphere therapy.
  The objectives of the Mixed Neoplasia study were to evaluate the toxicity of yttrium-90 microsphere therapy and to define, using escalating radiation doses, the maximum tolerated dose of yttrium-90 glass microspheres administered by hepatic arterial infusion

that would be suitable for Phase II-III studies in a similar patient population.

- *Study Design:* Patients in the Pilot HCC study received TheraSphere® in an amount that was determined to deliver a radiation absorbed dose of approximately 50 Gy to the tumor. The Mixed Neoplasia study was designed to treat patients with metastatic colonic carcinoma of the liver, carcinoid tumor metastatic to the liver, or primary hepatobilliary carcinoma. Patients received a single injection of TheraSphere® with an initial group of patients receiving a calculated radiation absorbed dose of 50 Gy to the liver; after determination of acceptable and reversible toxicity, a second group of patients received 75 Gy to the liver followed by a third group of patients who received 100 Gy to the liver.

For both studies, response duration was calculated from the date of treatment with TheraSphere® to the date of documentation of progression of disease. Survival was calculated from the date of treatment with TheraSphere® until the date of death. Toxicities were coded using the SWOG grading system (see above under 100 Gy HCC Study).

- *Study Population and Treatment Administration:* Thirteen patients, nine from the Pilot HCC study and four from the Mixed Neoplasia study, provide safety data. All 13 patients were treated once with TheraSphere®. The median activity administered was 2.6 GBq (range, 2.2 GBq to 6.6 GBq). The median liver dose was 74 Gy (range, 34 Gy to 105 Gy). Because of the dose escalation, seven patients received less than 80 Gy.
- *Safety Results:* All 13 treated patients reported at least one treatment-emergent adverse event; however, the majority (82%) of the adverse events were graded as mild or moderate in severity. The most common serious (i.e., graded as severe, life threatening, or lethal/fatal) adverse events were liver related (43%). Liver toxicities were primarily due to elevated enzymes during the week after treatment. Among the serious adverse events, two patients also experienced gastric ulcers. Two patients died during the follow-up period. The deaths were attributed to elevated bilirubin (elevated before TheraSphere® treatment that increased in severity 2 days after treatment and continued until the patient's death 2 weeks later; judged as possibly related to TheraSphere®), and pneumonitis, (death approximately 6 weeks after TheraSphere® treatment; judged as possibly related to TheraSphere®).

- **Table 2. Therasphere® Median Survival (months)**

	Dose < 80 Gy	Dose ≥ 80 Gy
Adenocarcinoma	**9.1 (n=22)**	**9.7 (n=50)**
Hepatocellular	**3.6 (n=8)**	**11.1 (n=7)**

INDIVIDUALIZATION OF TREATMENT

1. Gastroduodenal ulceration is a potential complication of inadvertent disposition of radioactive microspheres. It is likely that Inadvertent deposition of yttrium-90 microspheres in the terminal gastric vascular bed reflects the backflow of microspheres during administration or shunting through aberrant small vessels within the cirrhotic liver or tumor. Although angiographic occlusion techniques and the use of vasoactive drugs may reduce gastrointestinal shunting, their effectiveness is uncertain.
2. In some patients, part of the hepatic arterial blood supply bypasses the capillary bed and flows directly to the venous system. This may be associated with pathologic abnormalities of the liver. For such patients, a fraction F of spheres injected into the hepatic artery will not be embolized in the liver but will flow to the heart and subsequently be deposited into the lungs. As the product of the bypass fraction, F, and

the injected activity, A, increases the potential for delivering a damaging dose of radiation to the lungs increases. Consequently, it is essential that F be measured before use of this product. This can be done by injecting a tracer dose of Tc-99 MAA and observing with an Anger camera. The observed radiation from the lung field, divided by the total radiation observed by the camera is a measure of F. The product of F and A is then a measure of the activity that will be deposited into the lungs [22]. Based on clinical study experience [15, 16] with radioactive microspheres and TheraSphere® in HCC treatment, an upper limit of F x A of 610 MBq (16.5 mCi) is recommended. The estimated dose (Gy) to the lungs is equal to A (GBq) x F x 50, and assuming the total mass of both lungs to be 1 kg [23]; an upper limit of dose to the lungs from a single TheraSphere® treatment is 30 Gy.

INSTRUCTIONS FOR USE

Dosage and Administration

To correct for the physical decay of yttrium-90, the fractions that remain at selected time intervals from calibration are shown in Table 3.

Table 2
Yttrium-90 Physical Decay Table
Half-Life 64.2 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-4	1.044	26	0.755	56	0.546
-2	1.022	28	0.739	58	0.534
0*	1.000	30	0.723	60	0.523
2	0.979	32	0.708	62	0.511
4	0.958	34	0.692	64	0.500
6	0.937	36	0.677	66	0.489
8	0.917	38	0.663	68	0.479
10	0.897	40	0.649	70	0.469
12	0.878	42	0.635	72 (Day 3)	0.459
14	0.859	44	0.622	96 (Day 4)	0.354
16	0.841	46	0.609	120 (Day 5)	0.273
18	0.823	48 (Day 2)	0.596	144 (Day 6)	0.210
20	0.806	50	0.583	168 (Day 7)	0.162
22	0.789	52	0.570		
24 (Day 1)	0.772	54	0.558		

*Calibration Time

Preliminary Patient Evaluation

Prior to the administration of TheraSphere® the patient should undergo hepatic arterial catheterization using balloon catheterization or other appropriate angiographic techniques to prevent extrahepatic shunting [21]. Following the placement of the hepatic catheter 75 MBq to 150 MBq (2 mCi to 4 mCi) of Tc-99 MAA is administered into the hepatic artery to determine the extent of A-V shunting to the lungs. Air contrast scintigraphic views of the stomach are also obtained to confirm the absence of gastric and duodenal flow. If such flow is present and cannot be corrected using established angiographic techniques the patient is disqualified from treatment. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheraSphere® can be administered.

Calculation of Dose

The recommended dose to the liver is between 80 Gy to 150 Gy (8,000 rad to 15,000 rad). The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{Liver Mass (Kg)}]}{50\,[1-F]},$$

where F is the fraction of injected activity deposited into the lungs as measured by Tc-99 MAA.

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans.

If F is unknown, assume the upper limit of activity, which is 0.61 GBq, will be delivered to the lungs for the purpose of requisitioning TheraSphere®, and then using the Yttrium-90 Physical Decay Table (Table 3) to determine the appropriate time of injection. For determining the actual liver dose (Gy) delivered to the liver after injection, the following formula is used:

$$\text{Dose (Gy)} = 50 \frac{[\text{Injected Activity (GBq)}]\,[1 - F]}{\text{Liver Mass (Kg)}}$$

The upper limit of injected activity shunted to the lungs is F x A = 0.61 GBq.

TheraSphere® Administration Set

The TheraSphere® Administration Set (Table 4 and Diagram 1) consists of one dose vial inlet set, one dose vial outlet set and one empty vial. Both the inlet set and the outlet set are made up of preassembled sterile, apyrogenic components as shown in the schematic diagram.

The dose vial inlet set, used to connect the fluid source to the TheraSphere® dose vial, consists of a fluid line (3), an inlet line (7) and a 5 mL pumping syringe (6), joined together via a red 3-way stopcock (4). The red stopcock is used to switch from the fluid line to the inlet line, so that fluid may be drawn into the syringe, then pumped through the inlet line and into the TheraSphere® dose vial.

The piercing pin (2) at the free end of the fluid line is used to connect the inlet set to the fluid source (1), usually a heparinized (100 U/mL) saline solution. The 20-gauge needle (9) at the free end of the inlet line is used to connect the inlet set to the TheraSphere® dose vial (10). A check valve (8) prevents spheres from flowing back into the inlet line. Consequently, the inlet set should not contain any radioactivity during a normal procedure.

The dose vial outlet set, used to connect the TheraSphere® dose vial to the patient catheter, consists of an outlet line (13) and a vent line (17) joined together via a blue 3-way stopcock (14). The patient catheter is connected to the free port (15) on the blue stopcock. The blue stopcock is used to switch from the vent line to the catheter (16), so that the system's lines can be properly vented before the TheraSphere® dose is administered. The 20-gauge needle (12) at the free end of the outlet line is used to connect the outlet set to the TheraSphere® dose vial. The dispensing pin and filter vent assembly (18) at the end of the vent line is used to connect the outlet set to the sterile empty vial (19). The empty vial is used to collect fluid and any spheres that may flush through during air venting. The filter vent in the dispensing pin prevents pressure buildup in the empty vial and also blocks any spheres from escaping. The dose vial outlet set, including the empty vial, may contain radioactivity at the end of the administration procedure. For added safety, the lead pot (20) used for shipping may be used to hold the empty vial during the procedure.

Throughout the administration procedure, the TheraSphere® dose vial (10) remains sealed within the clear acrylic vial shield (11) in which it was supplied. A removable plug at the top of the vial shield provides access to the septum of the TheraSphere® dose vial.

Administration Instructions

The entire contents of the TheraSphere® dose vial are administered to the patient.

The directions for administration should be followed to ensure accurate delivery of the calculated dose. Approximately 96% of the radioactivity in the TheraSphere® dose vial will be delivered to the patient using the recommended technique.

Assembly of Dose Vial Inlet Set (Table 4 and Diagram 1)

1. The fluid line (3) is connected to the fluid source (1) via the white piercing pin (2).
2. The 5 mL syringe (6) is connected to the free port (5) on the red 3-way stopcock (4).
3. The red stopcock is switched to the fluid line.
4. 5 mL of solution is drawn into the syringe from the fluid source.
5. The tamper-evident seal is removed from the top of the clear acrylic vial shield (11) exposing the top shielding plug which the seal had secured in place. The plug is now free and is removed by turning the vial shield over adhering to appropriate radiation safety procedures.
6. Once the plug has been removed, the vial shield is returned to its upright position and the septum of the TheraSphere® dose vial (10) is swabbed with alcohol.
7. The 20-gauge needle (9) at the free end of the inlet line (7) is carefully inserted through the center of the TheraSphere® dose vial septum and pushed to the bottom of the vee at the base of the vial.

Assembly of Dose Vial Outlet Set (Table 4 and Diagram 1)

8. The flip-off seal is removed from the empty vial (19).
9. The dispensing pin and filter vent assembly (18) on the free end of the vent line (17) is inserted through the septum of the empty vial.
10. The empty vial is placed in the lead pot used for shipping (20).
11. The 20-gauge needle (12) at the free end of the outlet line (13) is carefully pushed through the septum of the TheraSphere® dose vial until it is just visible below the level of the seal.

System Evacuation (Table 3 and Diagram 1)

12. The red stopcock is switched to the inlet line.
13. The blue stopcock (14) is switched to the vent line.
14. Fluid from the syringe is slowly forced through the inlet line, into the TheraSphere® dose vial, and out through the outlet and vent lines until all air is exhausted from the system and fluid has entered the empty vial.
    NOTE: A low flow rate and gentle tapping of the TheraSphere® dose vial will reduce the possibility of premature introduction of spheres into the outlet line.

15. The outlet needle is pushed half way into the TheraSphere® dose vial. The purpose of this step is to eliminate the possibility of sweeping air that may be trapped near the top of the TheraSphere® dose vial into the catheter.

16. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.

17. The red stopcock is switched back to the inlet line.

TheraSphere® Administration (Table 4 and Diagram 1)

18. The patient catheter (16) is attached to the free port (15) on the blue stopcock.

19. The blue stopcock is switched to the catheter.

20. After verifying that both stopcocks are correctly positioned, the fluid in the syringe is expressed at a rate of approximately 1 mL per second. This flow rate will carry the spheres out of the TheraSphere® dose vial, through the outlet line, and into the catheter.

21. The red stopcock is switched to the fluid line and the syringe is refilled with 5 mL of solution.

22. The red stopcock is switched back to the inlet line and another 5 mL of solution is administered as in step 19.

Disassembly (Table 4 and Diagram 1)

23. The blue stopcock is switched to the vent line.

24. The catheter is disconnected from the blue stopcock.

25. The rest of the administration set is disassembled. The empty TheraSphere® dose vial, the dose vial outlet set and the catheter should be stored for decay or disposed of as radioactive waste.

RADIATION DOSIMETRY

The yttrium-90 in TheraSphere® is a constituent of an insoluble matrix thereby limiting irradiation to the immediate vicinity of the spheres. The average range of the radiation in tissue is 2.5 mm. One GBq (27 mCi) of yttrium-90 per kg of tissue gives an initial radiation dose of 13 Gy (1,297 rad) per day. The mean life of yttrium-90 is 3.85 days; thus, the radiation dose delivered by yttrium-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5,000 rad).

HOW SUPPLIED

TheraSphere® is available in three dose sizes: 5 GBq (135 mCi), 10 GBq (270 mCi), and 20 GBq (540 mCi). The dose is supplied in 0.05 mL of sterile, pyrogen-free water in a vee-bottom vial sealed within a 12 mm clear acrylic vial shield. Each dose is supplied with all the components required for administration, exclusive of items utilized in catheterization. The TheraSphere® dose and Administration Set should be stored at room temperature.

DISTRIBUTION

TheraSphere® is manufactured and distributed by MDS Nordion Inc., Kanata, Ontario, Canada.

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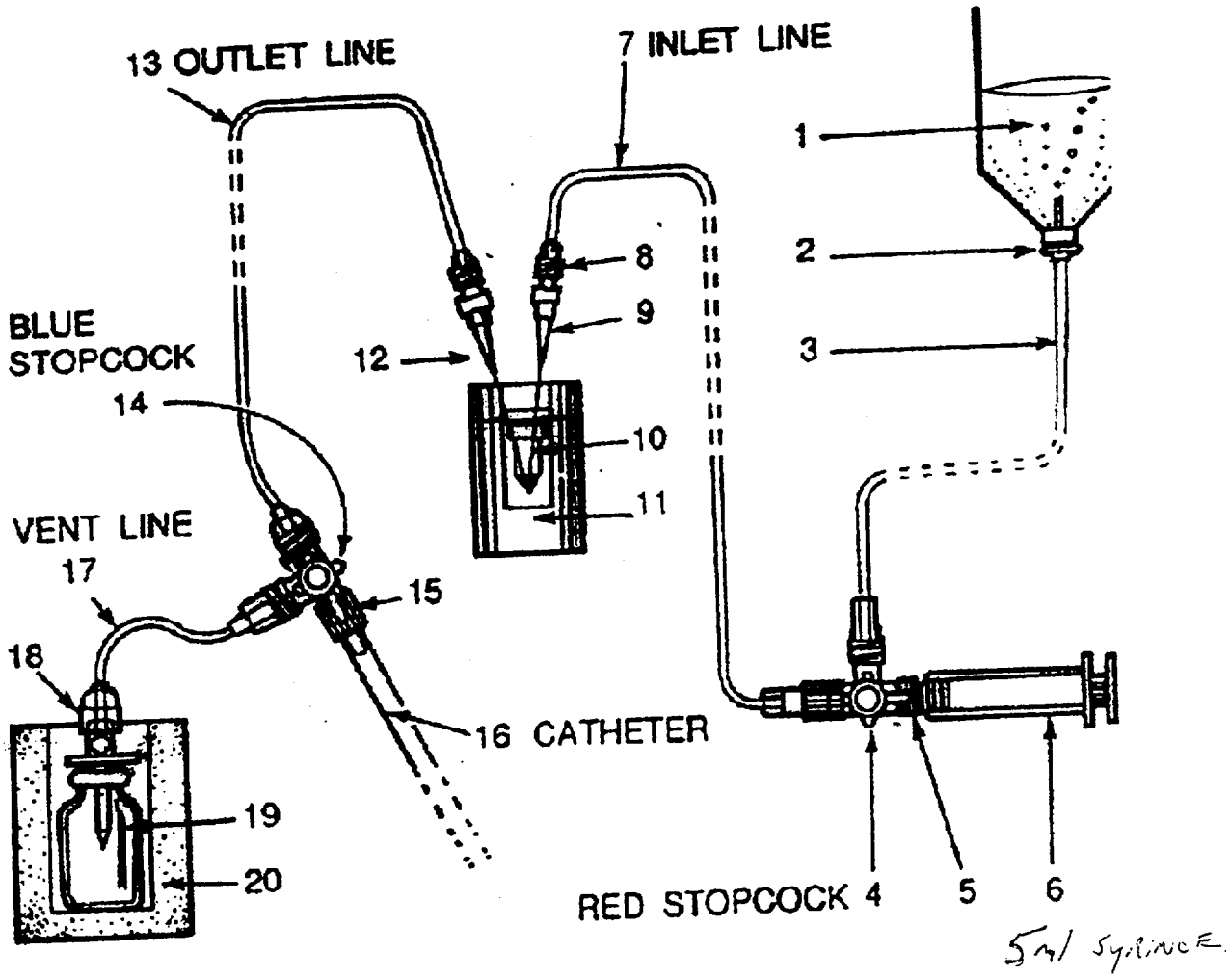
Table 4
TheraSphere® Administration Set Configuration

Drawing Number	Item
1	Fluid source
2	Piercing pin
3	Fluid line
4	Red 3-way stopcock
5	Free port on the red 3-way stopcock
6	5 mL syringe
7	Inlet line
8	Check valve
9	20-gauge needle at the free end of the inlet line
10	TheraSphere® dose vial
11	Acrylic vial shield
12	20 gauge needle at the free end of the outlet line
13	Outlet line
14	Blue 3-way stopcock
15	Free port on the blue stopcock
16	Catheter
17	Vent line
18	Filter vent assembly
19	Sterile empty vial
20	Lead pot

Diagram 1
TheraSphere® Administration Set Configuration



UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

October 5, 2000

MEMORANDUM TO: Cynthia D. Pederson, Chair
Mallinckrodt Lessons Learned Task Group

FROM: William F. Kane, Director
Office of Nuclear Material Safety
and Safeguards

SUBJECT: MALLINCKRODT LESSONS LEARNED CHARTER

As we have discussed, I have asked you to form a team to examine specific aspects of our experience with the recent Mallinckrodt overexposure events. This effort is part of a more comprehensive, multi phase review of the materials program. Attached is the charter for you and your team.

Assessment and feedback are important pieces of our PBPM process and our desire for continuous improvement. This effort is a significant part of that process and I look forward to the team's conclusions and recommendations.

Attachment: As Stated

cc: C. Paperiello, OEDO
H. Miller, RI
L. Reyes, RII
J. Dyer, RIII
E. Merschoff, RIV
P. Lohaus, OSTP
S. Collins, NRR
W. Borchardt, OE
D. Cool, NMSS
S. Treby, OGC
A. Thadani, RES

MALLINCKRODT LESSONS LEARNED INITIATIVE

Region III initiated an Augmented Inspection Team (AIT) inspection at the Mallinckrodt, Inc., Maryland Heights, MO, manufacturing facility on May 3, 2000, to review multiple occupational extremity exposures in excess of the NRC annual limit of 0.5 sievert (50 rem). The exposures originated from Mallinckrodt's activities involving byproduct material and radioactive materials regulated by the State of Missouri. As such, the AIT included a representative from the State agency having jurisdiction. The team's findings were issued in a special inspection report on July 14, 2000. Enforcement action is pending on the regulatory issues associated with the AIT's findings. The apparent violations are described in Inspection Report No. 030-00001/2000-002(DNMS).

On July 5, 2000, Region I conducted a special inspection at the Harrisburg, PA, Mallinckrodt nuclear pharmacy to review a reported exposure to the extremities of a pharmacist in excess of the NRC annual limit. The results of the Region's inspection are documented in Inspection Report No. 030-32995/2000-001(DNMS). Enforcement action is pending on apparent violations identified as a result of that inspection.

Based on the root causes of the problems associated with each licensee's exposure events, and common issues associated with Mallinckrodt's corporate oversight, NMSS established a task group to develop a lessons learned to include issues associated with NRC licensing and inspection, regulations, and NRC/State jurisdiction. To focus the group's efforts, a Charter has been developed and is attached.

The team is composed of the following individuals:

Chair:	Cynthia D. Pederson, Director, DNMS, Region III
Member:	Penny Lansizera, DNMS, Region I
Member:	Jamnes L. Cameron, DNMS, Region III
Member:	Randy Erickson, DNMS, Region IV
Member:	Joe DeCicco, IMNS, NMSS
Member:	Jim Smith, Risk Task Group, NMSS
Member:	Candice Drummond, Risk Task Group, NMSS
Member:	Marjorie Rothschild, OGC
Member:	Richard Blanton, OSTP
Member:	Joel Kramer, RES
Member:	Julius Persensky, RES
Member:	Paul Feeser, Commonwealth of Pennsylvania

The working group is scheduled to meet between September 20 and October 20, 2000.

At the conclusion, the group will discuss its recommendations with William Kane, Director, NMSS. The group will document its recommendations.

CHARTER
MALLINCKRODT LESSONS LEARNED TASK GROUP

The task group is to examine the regulatory issues surrounding NRC's licensing, inspection, and rulemaking, and the jurisdiction of the NRC and other regulatory programs, associated with the overexposure events that occurred at Mallinckrodt's Maryland Heights, MO, and Harrisburg, PA, facilities. The examination should include, but is not limited to the following:

1. Evaluate whether changes are needed to NRC's regulatory requirements limiting dose to workers, which must account for exposure from sources licensed by the NRC and those not licensed by NRC.

2. Evaluate whether changes are needed to NRC's licensing program and guidance for radiochemical and radiopharmaceutical manufacturers, and radiopharmacies.

3. Evaluate whether changes are needed to NRC's routine inspection program and guidance specific to radiochemical and radiopharmaceutical manufacturers, and radiopharmacies.

4. Evaluate whether changes are needed to NRC's generic inspection guidance for the review of materials licensee radiation safety programs, occupational radiation exposure control programs, and ALARA programs as they pertain to radiochemical and radiopharmaceutical manufacturers, and radiopharmacies. Particular attention should be given to guidance concerning the review of total dose (as defined in Part 20).

5. Evaluate the adequacy of NRC's interactions with other regulatory agencies and jurisdictions during the licensing and inspection of the Maryland Heights, Missouri, and Harrisburg, Pennsylvania facilities.

6. Evaluate whether changes are needed to NRC's inspection program and guidance for reactive inspections resulting from events involving licensed material as it relates to the Maryland Heights, Missouri, and Harrisburg, Pennsylvania events.

7. Evaluate whether there are areas in the implementation of NRC's activities for the licensing and inspection of these facilities that could be improved.

8. Evaluate whether there are changes needed to the Strategic Plan strategies and measures as they relate to the Maryland Heights, Missouri, and Harrisburg, Pennsylvania events.

9. Develop recommendations to resolve identified weaknesses and be considered in the context of the agency Performance Goals. Recommendations to be categorized into:

   a) actions involving short/long term changes to NRC programs and guidance
   b) actions involving other regulatory changes (i.e., rulemaking)
   c) issues involving further interactions with other agencies/jurisdictions,
   d) issues to be referred to and considered by the event evaluation working group
   e) actions to be considered in subsequent program reviews

10. Document findings and recommendations, along with a discussion of the basis (criteria) used in reaching these conclusions.

May 11, 2000

MEMORANDUM TO: William Kane, Director
Office of Nuclear Material Safety
and Safeguards

Paul H. Lohaus, Director
Office of State and Tribal Programs

FROM: Donald Cool, Director **/RA/**
Division of Industrial and
Medical Nuclear Safety, NMSS

SUBJECT: CHARTER FOR NRC/STATE WORKING GROUP
ON EVENT REPORTING

The charter for the NRC/State Working Group on Event Reporting is provided in Attachment 1 for your approval in accordance with Management Directive 5.3 "NRC and Agreement State Working Groups." The working group met at NRC Headquarters on April 4-5, 2000. The charter was reviewed and comments were incorporated. A meeting summary provided in Attachment 2.

Attachments:
1. Working Group Charter
2. April Meeting Summary

Contact: Kevin Ramsey, NMSS/IMNS
(301) 415-7887

W Kane **/RA by**
Charter approved: **M Virgilio For/** 9/6/00
Director, NMSS

Charter approved: P Lohaus **/RA/** 9/6/00
Director, STP

CHARTER FOR THE NRC / AGREEMENT STATE WORKING GROUP ON EVENT REPORTING

The NRC Office of Nuclear Material Safety and Safeguards (NMSS) has formed a working group to provide NRC management with recommendations for making the reporting and assessment of material events more effective, efficient and realistic. Agreement States and NRC Regions have raised concerns that the resources required to submit event reports and respond to requests for additional information are having a significant impact on their programs. In addition, NRC management has a growing perception that certain parts (i.e., briefings, etc.) of the materials event program are inefficient. Although NRC Headquarters conducted a self-assessment last year (see SECY-99-005, Self-Assessment of Operational Safety Data Review Processes), a review by the internal stakeholders is needed to address these concerns. The quality of materials event data is important because it is used to measure outcomes and determine if the performance measures in the NRC Strategic Plan (NUREG-1614) have been met. The working group is composed of representatives of State governments and NRC. The working group will coordinate its efforts with the Steering Committee for the National Materials Program Working Group and produce a draft and a final report with findings and recommendations for the Steering Committee and NRC management's consideration.

The Mission:

The mission is to develop recommendations for making the materials event program more effective, efficient and realistic. The program should implement the following philosophy:

To create a true partnership of the NRC and the States that will ensure protection of public health, safety, and the environment while:

optimizing resources of federal, state, professional and industrial organizations;

accounting for individual agency needs and abilities;

promoting consensus on regulatory priorities;

promoting consistent exchange of information; and

harmonizing regulatory approaches while recognizing state and federal needs for flexibility.

To accomplish the mission, the working group will undertake the following tasks to prepare a report on the event information collected:

1. The working group will review the NRC Strategic Plan and identify what event information related to safety and environmental protection is needed to implement the plan and the activities derived from the Materials and Waste Safety portions of the Plan. Then, the group will review current NRC reporting requirements (and associated Agreement State compatibility assignments) and determine whether the information required supports implementation of the plan. The group will recommend how to resolve any discrepancies between the information needed and the information required by regulation. The review should consider the health and safety significance of the information. The group may use

this as an opportunity to recommend changes to the Strategic Plan. The purpose of this is to determine if the NRC and the Agreement States are collecting the right safety information across the nation, and at the right level of detail.

2. The working group will examine guidance to licensees on event reporting. NMSS believes that existing event reporting guidance may contribute to the inconsistent quality of event reports submitted by licensees. The group is expected to consider whether the quality of event data could be improved by providing improved guidance to licensees. The working group should determine whether guidance is available, whether it is adequate, and whether licensees are aware of it. In addition, the group should note any changes that would require rulemaking.

To accomplish the mission, the working group will undertake the following additional tasks to prepare a report on the use of event information after it is received:

3. The group is expected to review the event information provided to NMED, and recommend how the quantity, quality, and consistency of event information can be improved. The information NMED receives on events has improved greatly in recent years and NRC staff believes that events with significant safety issues are being captured (i.e., overexposures, major misadministrations, loss of sealed sources). However, some less-significant events (i.e., loss of control of low levels of unsealed radioactive material) may be under-reported, and, if so, these less-significant events are not captured in NMED. In addition, important initial and follow up information is missing for some events. Several performance measures in the NRC Strategic Plan are based on NMED data, and missing or incomplete NMED data are a concern for NRC. The working group will assess whether necessary event information (as determined under Task 1) is under-reported, and, if needed, recommend improvements to the reporting process.

4. The working group will review the NMSS Generic Issues Program to identify opportunities to improve the program. NRC staff has noted that the program is labor intensive and is concerned that significant issues may be missed in the large volume of reports reviewed. NRC believes that the materials event assessment program has not been explained well and many stakeholders do not understand why materials event data are required, or how they are processed and analyzed. Internal stakeholders have expressed concerns about duplicative efforts, lack of coordination, and participation on the part of the Agreement States. The Generic Assessment Panel (GAP) has experienced problems where information has been lost or misdirected. The group should address the need to assess each event for 1) its significance for the affected licensee, 2) its significance for other licensees, and 3) its significance for regulators and the adequacy of their programs. The group is expected to review the program and offer recommendations in the following areas: 1) Describe what analyses should be conducted, who should conduct the analyses, when should the analyses be conducted, and how the results of the analyses should be utilized and shared nationally; and 2) identify where internal stakeholder communication and participation, and effectiveness and efficiency can be improved, especially with respect to analyzing events meeting the thresholds in the Strategic Plan, trends and precursor events.

5. The working group will examine the use of computer systems that support the event reporting and assessment process. NMSS believes there is room for improvement in the computer systems that support the materials event program. The group is expected to review the various systems used to create event reports, archive event data, and track followup actions. The group should recommend improvements that would make the

systems more comprehensive, easier to use, or would reduce duplication of effort. In addition, the following specific issues should be addressed:

a. Should NRC delay the posting of event reports on the external NRC website? Recommendation no. 22 from the Incident Response Function Self Assessment Report states that IRO and STP should work with OCIO to identify approaches to allow for a reasonable time delay (24 hours minimum) in posting 24-hour material event reports on the NRC external website.

b. Should NRC continue the use of separate event tracking systems in each office, or should one tracking system be used by NMSS and the Regions? This issue was raised during the 1999 Region IV IMPEP Review.

c. Should NMED be made available to the public, and if so, what conditions and restrictions should be applied?

d. Should NRC and the Agreement States participate in the IAEA materials event database, and what information would we share with IAEA?

Schedule:

The working group will complete the project by March 2001.

- First working group meeting in Rockville, Maryland (April 4 - 5, 2000).
- Conference call status report (May 23, 2000)
- Second working group meeting in Austin, Texas (June 21-22, 2000)
- Conference call status report (July 26, 2000)
- Third working group meeting in Rockville, Maryland (September 6-7, 2000)
- Brief Steering Committee on actions to date and plans for future (late Sept. 2000).
- Working Group conference call to discuss Steering Committee comments and status of efforts (early October 2000)
- Prepare rough draft of report and provide to Steering Committee for review (Nov. 2000)
- Brief Steering Committee on draft report (early December 2000)

- Working Group conference call to discuss Steering Committee comments and actions to complete final report (mid December 2000).
- Prepare draft final report and provide to Steering Committee for final review (late January 2001)
- Brief Steering Committee on final report (February 2001)
- Make final changes and issue report (March 2001)

Update on Other Rulemaking

10 CFR 31: General Domestic Licenses for Byproduct Material

10 CFR 40: Domestic Licensing of Source Material

10 CFR 71: Packaging and Transportation of Radioactive Material

ACMUI Self-evaluation Criteria

1. Does the staff and the ACMUI interact in such a manner as to satisfactorily address issues before the Committee?

2. Do the Committee members clearly define issues for the staff and provide timely, useful, objective information to the staff when requested?

3. Does the Committee provide critical review and oversight of issues?

4. Does the committee provide expertise/advice which is not available from within the Agency?

5. Does the Committee meet frequently enough to address issues in a timely manner?

6. Do committee members bring issues from all elements of the medical community to the attention of NRC staff?

7. Does the committee facilitate/foster communication between the public/medical community and NRC?

8. Does the Committee consider resource constraints of the NRC when recommending new or enhanced regulatory programs?

9. Does the Committee make effective use of subcommittees to assist the staff on specific tasks or projects?

10. Does the scope and size of the Committee meet the current needs of NRC?

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C 20555-0001

MEMORANDUM TO: Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety
Office of Nuclear Material Safety
and Safeguards

FROM: Manuel D. Cerqueira, M.D., Chairman
Advisory Committee on the
Medical Uses of Isotopes

SUBJECT: SELF-EVALUATION OF THE ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES

The Advisory Committee on the Medical Uses of Isotopes (ACMUI) initiated a self evaluation at the October, 1999, committee meeting. The draft evaluation was provided to Committee members for review and comment. Attached is the completed self-evaluation of the ACMUI for your use.

Manuel D. Cerqueira, M.D., Chairman

9/12/00
Date

Attachment: ACMUI self-evaluation

ADVISORY COMMITTEE ON THE MEDICAL USES OF ISOTOPES (ACMUI)

SELF-EVALUATION

1. **Does the staff and the ACMUI interact in such a manner as to satisfactorily address issues before the Committee?**

Yes — Staff and ACMUI members communicate openly and effectively. The ACMUI typically conducts a Spring and Fall meeting. The NRC ACMUI Coordinator or the Designated Federal Official (DFO) for the ACMUI contacts the members to keep them informed of issues that will be brought to the Committee's attention. The Committee is provided with background information on issues that will be discussed at the meetings in advance of scheduled meetings. ACMUI members have also identified issues for Commission consideration. In this situation, the members contact either the ACMUI Coordinator or the DFO and request that the issue be placed on the meeting agendas.

The ACMUI and staff have developed a process that provides for open discussion between staff and ACMUI members. During ACMUI meetings, staff typically opens discussion on a specific issue with a formal presentation. Staff will focus the Committee on the key issues for discussion. The topic is then opened for discussion by ACMUI members. Members of the public attending the meeting are frequently given the opportunity to make a statement on the issue. Following these discussions, an ACMUI member will make a formal recommendation which is then voted on by committee members. This recommendation is placed in the meeting minutes. Staff will then provide ACMUI members with updates on how the recommendation is incorporated into the NRC regulatory program.

2. **Do the Committee members clearly define issues for the staff and provide timely, useful, objective information to the staff when requested?**

Yes — Committee members clearly define issues for the staff and provide timely, useful, and objective recommendation. The Committee is comprised of individuals representing the various uses of byproduct material in medicine - clinical use, radiation safety, health care administration, and patients rights. This diversity allows the Committee to discuss each issue from many different perspectives. As a result, the Committee is able to clearly define issues and to identify the implications of their recommendations. Communicating not only through committee and subcommittee meetings, but also through the use of alternative methods of communication, such as telephone, email and facsimile, the Committee provides timely, useful information to the requests made by the staff.

3. **Does the Committee provide critical review and oversight of issues?**

Yes — The primary focus of the Committee is the safe use of medical byproduct material. The diversity of the medical disciplines represented by the Committee enhances the Committee's ability to recognize issues that need to be addressed, and ensures that each issue is critically reviewed, thus providing better oversight.

4. Does the Committee provide expertise/advice which is not available from within the Agency?

Yes — Committee members provide expertise that is not always available from the NRC staff. Committee members are able to provide staff with first-hand information on the clinical and research use and handling of byproduct material. Committee members provide staff advice on the clinical uses of byproduct material; use and preparation of radiopharmaceuticals; interests and rights of patients and human research subjects; radiation safety issues associated with use of byproduct material in academic and clinical settings; Agreement State issues; and health care administration.

5. Does the Committee meet frequently enough to address issues in a timely manner?

Yes — The ACMUI typically meets twice a year. This allows for timely discussion on issues relating to the use of byproduct material in medicine. More frequent meetings of the full Committee and ad hoc subcommittees are scheduled when issues arise that warrant face-to-face interaction between the Committee and NRC staff. This flexibility afforded staff is beneficial in allowing for timely discussions on regulatory issues, such as the revision of 10 CFR Part 35, "Medical Use of Byproduct Material".

6. Do Committee members bring issues from all elements of the medical community to the attention of NRC staff?

Yes — Committee members frequently bring issues raised by their colleagues to NRC's attention. In addition, members are involved in routine activities involving use of radioactive material in medicine and as such, are able to bring "real-life" issues to NRC's attention. Given the expertise of the Committee members, NRC is presented with many different types of issues involving the use of radioactive material in medicine.

7. Does the Committee facilitate/foster communication between the public/medical community and NRC?

Yes — The Committee encourages communication among the public, medical, and regulatory communities. All meetings are announced in the Federal Register. Members of the public and professional organizations frequently attend the meetings and present information for Committee consideration. In addition, Committee members typically bring issues from their respective professional organization to the NRC for information and consideration. Also, when appropriate, Committee members are able to provide status reports on the NRC regulatory program to their professional organizations. This "two-way" communication provides the opportunity for the NRC and the stakeholders to exchange information in an open forum.

8. Does the Committee consider resource constraints of the NRC when recommending new or enhanced regulatory programs?

Yes — The Committee does consider resource constraints of the NRC when recommending new or enhanced regulatory programs. It also considers resource implications of new or revised regulatory programs on the regulated community. For example, the ACMUI discussed the implications of requiring an examination as one element of the training and experience criteria for authorized users, Radiation Safety Officers, authorized medical physicists, and authorized nuclear pharmacists. One of the reasons that the Committee withdrew the proposal was an understanding that a review of exam programs would have been resource-intensive for the NRC.

9. Does the Committee make effective use of subcommittees to assist the staff on specific tasks or projects?

Yes — On several occasions, subcommittees have been used to assist staff. Most recently, two subcommittees were formed to assist with the revision of Part 35. One subcommittee focused on issues associated with use of unsealed byproduct material while the other focused on use of sealed sources. It has been our experience that at subcommittee meetings both the ACMUI members and NRC staff are able to discuss issues in more detail and to identify those issues that should be discussed by the full Committee. The Committee encourages further use of subcommittees.

10. Does the scope and size of the Committee meet the current needs of NRC?

Yes — The current positions on the ACMUI are as follows:

1. Nuclear medicine physician
2. Nuclear cardiologist
3. Nuclear pharmacist
4. Radiation oncologist (two positions to represent diverse high-risk modalities)
5. Medical physicist (nuclear medicine)
6. Medical physicist (therapy physics)
7. Radiation safety officer
8. Health care administrator
9. Patients' rights and care advocate
10. State or local government representative
11. Food and Drug Administration representative

It is very important that all these disciplines be represented on the Committee because of the diverse use of byproduct material in medicine. As new uses of byproduct material evolve, it is recommended that NRC consider revising the Committee composition to allow for representation by individuals who are familiar with the new technology. Also, it is important that vacancies be filled in a timely manner. Committee members recommend that vacancies be announced well in advance, giving a more effective lead time for filling the positions.