U.S. NUCLEAR REGULATORY COMMISSION
OFFICE OF NUCLEAR REGULATORY RESEARCH

DRAFT REGULATORY GUIDE

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Division 10
Task DG-0009

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DRAFT REGULATORY GUIDE DG-0009

PROPOSED SUPPLEMENT

To REGULATORY GUIDE 10.8, REVISION 2,

"GUIDE FOR THE PREPARATION OF APPLICATIONS FOR MEDICAL USE PROGRAMS"

This regulatory guide is being issued in draft form to involve the public in the early stages of the development of a regulatory position in this area. It has not received complete staff review and does not represent an official NRC staff position.

Public comments are being solicited on the draft guide (including any implementation schedule) and its associated regulatory analysis or value/impact statement. Comments should be accompanied by appropriate supporting data. Written comments may be submitted to the Rules Review and Directives Branch, DFIPS, Office of Administration, U.S. Nuclear Regulatory Commission, Washington, DC 20555. Copies of comments received may be examined at the NRC Public Document Room, 2120 L Street NW., Washington, DC. Comments will be most helpful if received by **July 31, 1997.**

Requests for single copies of draft guides (which may be reproduced) or for placement on an automatic distribution list for single copies of future guides in specific divisions should be made in writing to the U.S. Nuclear Regulatory Commission, Washington, DC 20555, Attention: Office of Administration, Distribution and Mail Services Section.

Regulatory Guide 10.8, "Guide for the Preparation of Applications for Medical Use Programs," Revision 2, August 1987, provides directions for completing NRC Form 313 for the preparation of applications for specific medical use byproduct material licenses. The guide is based on major revisions to 10 CFR Part 35 that became effective April 1, 1987. On December 2, 1994, the NRC published new medical use regulations (59 FR 61767) that affect some of the guidance provided in Revision 2 of Regulatory Guide 10.8, which remains the current guidance for the completion of applications for the medical use of byproduct material. This supplement would provide additional guidance in consideration of the new regulations and add Appendix Y, "Provisions for Research Involving Human Subjects," to Revision 2 of Regulatory Guide 10.8.

The changes in the regulations (effective January 1, 1995) include:

- Recognition of pharmacists with specific training and experience in nuclear pharmacy as "authorized nuclear pharmacists,"

- Deletion of previous restrictions on the sources of supply for unsealed byproduct material to be used for medical use,

- Deletion of previous restrictions on the preparation of unsealed byproduct material for medical use,

- Permission for some qualified physician authorized users to work as authorized users without being listed on the license,

- Clarification of circumstances under which holders of specific licenses of broad scope are relieved from submitting amendments, and

- Authorization for the use of byproduct material in the conduct of research involving human subjects as a part of "medical use," as defined in 10 CFR 35.2.

In addition to this supplement, Draft Regulatory Guide DG-0006, "Guide for the Preparation of Applications for Commercial Nuclear Pharmacy Licenses," is being developed to provide guidance to applicants and licensees who intend to prepare unsealed byproduct material for medical use by or under the supervision

of an "authorized nuclear pharmacist" or "authorized user," as defined in 10 CFR 35.2. This supplement should clarify for applicants and licensees the use of the guidance proposed in Draft Regulatory Guide DG-0006 on completing NRC Form 313, "Application for a Material License."

This supplement addresses the effects of the new medical use regulations for each section and appendix in Revision 2 of Regulatory Guide 10.8 as follows:

Section 1. INTRODUCTION -- Not affected.

Section 2. FILING AN APPLICATION -- Not affected.

Section 3. CONTENTS OF AN APPLICATION

ITEM 1 - License Information -- Not affected.

ITEM 2 - Applicant's Name and Mailing Address -- Not affected.

ITEM 3 - Locations of Use -- Not affected.

ITEM 4 - Persons to Be Contacted About Application -- Not affected.

<u>ITEM 5 - Radioactive Material and ITEM 6 - Purpose</u>

The regulations in 10 CFR Part 35 continue to divide byproduct material for medical use into six types of use. The new regulations permit the use of any unsealed byproduct material for the medical uses permitted by 10 CFR 35.100, 200, and 300. Therefore, applicants and licensees are no longer limited to radioisotopes traditionally used in radiopharmaceuticals or the use of radiopharmacuticals for which the U.S. Food and Drug Administration has accepted a "Notice of Claimed Investigational Exemption for a New Drug" (IND) or approved a "New Drug Application" (NDA). Further, the regulations in 10 CFR Part 35 now specifically address research involving human subjects (10 CFR 35.6). Guidance being developed on this type of research is issued for public comment in this draft guide in the proposed Appendix Y.

Table 1 on page 7 of Revision 2 of Regulatory Guide 10.8 has been used as guidance to respond to Item 5 of NRC Form 313 for the uses described in 10 CFR 35.100, 35.200, and 35.300. This supplement would provide two new tables. Table 1a would replace the first three entries in Table 1 of Revision 2 of Regulatory Guide 10.8 for licensees who have either an authorized nuclear pharmacist or a physician who is an authorized user and who meets the requirements specified in 10 CFR 35.920. Table 1b would replace the same first

three entries of Table 1 for licensees who do not have an authorized nuclear pharmacist and the authorized user physician's training and experience is limited to that specified in 10 CFR 35.910 or 35.930. Applicants and licensees would use the matrix format provided in Tables 1a and 1b to respond to Item 5 of NRC Form 313 for unsealed radioactive material. For Item 5a, you may state "Any byproduct material" or "Any byproduct material initially distributed pursuant to 10 CFR 32.72 or equivalent Agreement State requirements" (depending on whether you follow Table 1a or 1b). For Item 5b, you may state "Unsealed"; and for Item 5c, you should state the maximum activity you would like to possess for each requested use (i.e., under 10 CFR 35.100, 35.200, or 35.300). The maximum activities requested should be representative of current uses and projected waste storage needs. For Item 6, the purpose for which the licensed material will be used, you should state "Any use described in 35.100," "Any use described in 35.200," or "Any use described in 35.300."

Table 1a

Item 5a, Elements and mass number	Item 5b, Chemical and/or physical form	Item 5c, Maximum amount that will be possessed at any one time	Item 6, Purpose for which licensed material will be used
Any byproduct material	Unsealed	_____ Activity	Any use described in § 35.100
Any byproduct material	Unsealed	_____ Activity	Any use described in § 35.200
Any byproduct material	Unsealed	_____ Activity	Any use described in § 35.300

Table 1b

Item 5a, Elements and mass number	Item 5b, Chemical and/or physical form	Item 5c, Maximum amount that will be possessed at any one time	Item 6, Purpose for which licensed material will be used
Any byproduct material initially distributed pursuant to 10 CFR 32.72 or equivalent Agreement State requirements	Unsealed	_____ Activity	Any use described in § 35.100
Any byproduct material initially distributed pursuant to 10 CFR 32.72 or equivalent Agreement State requirements	Unsealed	_____ Activity	Any use described in § 35.300

Items 5.d, 5.e, 5.f, 6.d, 6.e, and 6.f in Table 1 of Revision 2 of Regulatory Guide 10.8 would continue to be the format to be used in responding to Item 5 of NRC Form 313 for the uses described in 10 CFR 35.400 and 10 CFR 35.500.

ITEM 7 -- Individuals Responsible for Radiation Safety Programs -- Their Training and Experience

The regulations in 10 CFR 35.2, "Definitions," have been amended to add the term "authorized nuclear pharmacist." In addition to the authorized user, RSO, or teletherapy physicist, the authorized nuclear pharmacist may be responsible for the radiation safety program.

The regulations in 10 CFR 30.33(a) state: "An application for a specific license will be approved if: ... (3) The applicant is qualified by training and experience to use the material for the purpose requested in such manner as to protect health and minimize danger to life or property." Therefore, for new license applications and license renewals, applicants and licensees should identify all authorized users, authorized nuclear pharmacists, the radiation safety officer, and teletherapy physicists as well as provide documentation of their training and experience. If documentation of an individual's training or experience was provided in an earlier notification, it does not have to be resubmitted.

The regulations in 10 CFR 35.13(b) permit certain pharmacists and physicians to work as authorized nuclear pharmacists or authorized users, respectively, without requiring the licensee to apply for and receive a license amendment to identify them on the license. The regulations in 10 CFR 35.13(b) require that these physicians and pharmacists are (1) certified by an organization specified in 10 CFR 35.910(a), 35.920(a), 35.930(a), 35.940(a), 35.950(a), 35.960(a), or 35.980(a); (2) identified as an authorized user or an authorized nuclear pharmacist on a Commission or Agreement State medical use or commercial nuclear pharmacy license; or (3) identified as an authorized user or an authorized nuclear pharmacist on a permit issued by a Commission or Agreement State medical use license of broad scope. Licensees using this provision, in accordance with 35.14(a), must provide NRC with a copy of each individual's certification, the NRC or Agreement State license identifying the individual as an authorized user or authorized nuclear pharmacist, or a permit issued by a broad scope licensee identifying the individual as an authorized user or authorized nuclear pharmacist. The regulations in 10 CFR 35.14(a) require that this documentation be submitted to the NRC no later than 30 days from the date the licensee allows the individual to work as an authorized user or authorized nuclear pharmacist.

NOTE: You are still required to amend your license when adding a new radiation safety officer or teletherapy physicist. Even though amendment requests are not needed for some individuals to be listed on a license as authorized users or authorized nuclear pharmacists prior to their working in that capacity, it may be advantageous when updating the license for other purposes to include these individuals for the following reasons: (1) authorized nuclear pharmacists who are currently board certified will no longer be recognized as authorized nuclear pharmacists when their certification expires

unless they are listed on a license and (2) an authorized user or an authorized nuclear pharmacist may use this publicly available document to demonstrate continuing experience to meet the criteria in 10 CFR 35.972, "Recentness of Training."

The guidance that applicants and licensees should use regarding training and experience for individuals identified on a license as "authorized users" is on pages 8 and 9 of Revision 2 of Regulatory Guide 10.8.

Applicants and licensees may use guidance that is proposed in Item 7 and Appendix A in Draft Regulatory Guide DG-0006 regarding the training and experience of individuals who must be identified on a license as "authorized nuclear pharmacists." Applicants and licensees may find it convenient to document the training and experience of these individuals using the format in Figures A-1 and A-2 of Draft Regulatory Guide DG-0006.

ITEM 8 - Training for Individuals Working in or Frequenting Restricted Areas

The regulations in 10 CFR 35.25 regarding supervision and instruction must be followed if the applicant or licensee permits the preparation of unsealed byproduct material for medical use under the supervision of an authorized nuclear pharmacist or authorized user as permitted by 10 CFR 35.11(c). Item 8 of Draft Regulatory Guide DG-0006 provides information, based on 10 CFR 35.25, on the instruction, supervision, and review that would meet these supervision and instruction requirements.

ITEM 9 - Facilities and Equipment, and ITEM 10 - Radiation Safety Program

The new regulations no longer restrict licensees to only the use of specific isotopes or to the formulation and reformulation procedures for the preparation of unsealed byproduct material for the uses described in 10 CFR 35.100, 35.200, and 35.300. Also, the new regulations no longer restrict medical uses to diagnosis and therapy, but permit research involving human subjects provided the research meets the criteria in 10 CFR 35.6.

On pages 11-13, Regulatory Guide 10.8 provides guidance for an acceptable radiation safety program for the uses of isotopes approved prior to January 1, 1995. However, with the increased flexibility provided by the new regulations,

the applicant or licensee is now responsible for determining whether (1) the guidance in Revision 2 of Regulatory Guide 10.8 provides an adequate radiation safety program for its operations or (2) additional facilities, equipment, personnel, and radiation safety procedures are necessary.

If the applicant or licensee determines that the scope of its operations is within the guidance provided in Revision 2 of Regulatory Guide 10.8, it should continue to use that guidance in responding to Items 9, Facilities and Equipment, and 10, Radiation Safety Program, of NRC Form 313.

An applicant or licensee who determines that the guidance provided in Revision 2 of Regulatory Guide 10.8 is not adequate for the scope of its operations (including radiation safety programs necessitated by or associated with research or the use of alpha-, low-energy photon-, or low-energy beta-emitters) should supplement the application with additional information to demonstrate that its facilities, equipment, personnel, and radiation safety program meet the requirements in 10 CFR Part 20 as well as the requirements in 10 CFR Part 35.

Licensees who will use only unit dosages of alpha- or beta-emitting radionuclides obtained from a manufacturer or preparer licensed pursuant to 10 CFR Part 32 are not required to have instruments to measure the alpha- or beta-emitter dosages (10 CFR 35.52). This does not relieve such licensees from applicable requirements to assay or measure effluent releases, fixed or removable contamination, and doses to workers or the general public.

The guidance being developed in Draft Regulatory Guide DG-0006 (in Items 9 and 10) may be helpful in describing the scope of your operations, facilities, equipment, and associated radiation safety programs to handle uses of unsealed alpha-, beta-, and low-energy photon-emitting radionuclides for medical use or in the preparation of unsealed byproduct material for medical use.

Appendices B, C, D, I, J, M, N, O, and R of Regulatory Guide 10.8 were developed primarily for photon-emitting radionuclides. Generally, high-energy beta-emitters can be measured or assayed with the same instruments, and these appendices can be used provided energy dependence and geometric considerations are taken in to account. Applicants and licensees should continue to use these appendices for photon- and high-energy beta-emitting radionuclides. Some of the information in these appendices may not be appropriate and additional changes may be needed to the model programs provided in these appendices to

reflect the decrease in prescriptive requirements and the removal of some requirements from the regulations.

Therefore, if you use alpha-, low-energy photon-, or low-energy beta-emitters, you should describe your program to demonstrate the safe use of these radionuclides. Regulatory Guide 10.8 was not specifically developed for the use of alpha-, low-energy photon-, or low-energy beta-emitters.

ITEM 11 - Waste Management -- Not affected.
ITEM 12 - License Fees -- Not affected.
ITEM 13 - Certification -- Not affected.
ITEM 14 - Voluntary Economic Data -- Not affected.

Section 4. AMENDMENTS TO LICENSE

The regulations in 10 CFR 35.13, 35.14, and 35.15 are either new or revised. Licensees should review the regulations regarding the need for amendments, the regulations that now permit notification instead of amendments, and the amendment and notification exemptions granted to holders of medical use Type A Specific Licenses of Broad Scope.

Section 5. RENEWAL OF LICENSE -- Not affected.
Section 6. IMPLEMENTATION -- Not affected.

APPENDICES

Appendices A, E, G, H, K, P, Q, S, W, and X are not affected.

Appendices B, C, D, F, I, J, L, M, N, O, R, T, U, and V may be affected as described in Item 9.

Appendix Y is proposed in this Draft Regulatory Guide DG-0009 as a new appendix to Revision 2 of Regulatory Guide 10.8.

If the applicant or licensee determines that its scope of operations is within the guidance provided in the above appendices to Revision 2 of Regulatory Guide 10.8, it should continue to use that guidance in responding to NRC Form 313.

All licensees and applicants may want to modify or remove certain commitments in the appendices in response to regulatory changes to less prescriptive requirements.

If the applicant or licensee determines that the guidance provided in these appendices is not adequate for the scope of its operations, it should supplement the application with additional information.

The appendices should be supplemented, as appropriate, to include:

(1) Information on alpha-, beta-, and low-energy photon-emitting radionuclides,

(2) Additional responsibilities of the radiation safety committee to review and approve or disapprove of individuals to work as or be listed as authorized users, authorized nuclear pharmacists, teletherapy physicists, or radiation safety officers in accordance with 10 CFR 35.22(b)(2);

(3) Additional radiation safety precautions, facilities, and equipment, if any, associated with preparing unsealed byproduct material by or under the supervision of an authorized nuclear pharmacist or appropriately trained authorized user, and

(4) Radiation safety program changes that may be necessitated by or associated with research involving human subjects.

EXHIBITS

EXHIBITS 1, 2, 3, 4, 5, 15, 17, 18, 19, 20, 21 are not affected.

EXHIBITS 6, 7, 8, 9, 10, 11, 12, 13, 14, 16 may be affected.

The applicant or licensee who determines that its scope of operation is within the guidance provided in the above exhibits to Revision 2 to Regulatory Guide 10.8 should continue to use that guidance in responding to NRC Form 313.

All licensees and applicants may also want to modify or remove certain commitments in the exhibits in response to regulatory changes to less prescriptive requirements.

If an applicant or licensee determines that the guidance provided in these exhibits is not adequate for the scope of the operations, the application should be supplemented with additional information.

The exhibits may have to be supplemented, as appropriate, to include information on alpha-, beta-, and low-energy photon-emitting radionuclides and radiation safety programs associated with preparing unsealed byproduct material by or under the supervision of an authorized nuclear pharmacist or appropriately trained authorized user.

APPENDIX Y
PROVISIONS FOR RESEARCH INVOLVING HUMAN SUBJECTS

The amendment to 10 CFR Part 35 (published December 2, 1994, 59 FR 61767) changed a number of requirements for medical use programs. Among other things, the term "medical use" was amended and a new section was added to address human research. "Medical use" means the intentional internal or external administration of byproduct material or the radiation therefrom to patients or human research subjects under the supervision of an authorized user. Section 35.6, "Provisions for Research Involving Human Subjects," specifically addresses research and places research involving human subjects into the following two categories:

- Research covered by the Federal Policy for the Protection of Human Subjects (Federal Policy) (published in the Federal Register on June 18, 1991, 56 FR 28003) and

- Research not covered by the Federal Policy.

Table 1 provides a chart to assist applicants and licensees in categorizing research projects.

1. Research Covered by the Federal Policy

The provisions in 10 CFR 35.6 state that licensees may conduct research involving human subjects provided the research is conducted, funded, supported, or regulated by another Federal Agency that has implemented the Federal Policy. Therefore, a specific licensing authorization or amendment is not required if the applicant or licensee meets this criterion. The applicant or licensee must obtain informed consent from the human subject and obtain, as a minimum, prior review and approval of the research activities by an "Institutional Review Board" in accordance with the meaning of these terms as defined and described in the "Federal Policy for the Protection of Human Subjects."

NOTE: Fifteen Federal Agencies have adopted the "Federal Policy for the Protection of Human Subjects": United States Department of Agriculture;

Department of Energy; National Aeronautics and Space Administration; Department of Commerce; Consumer Product Safety Commission; International Development Cooperation Agency, Agency for International Development; Department of Housing and Urban Development; Department of Justice; Department of Defense; Department of Education; Department of Veterans Affairs; Environmental Protection Agency; Department of Health and Human Services; National Science Foundation; and Department of Transportation.

2. Research Not Covered by the Federal Policy

If the research involving human subjects is not conducted, funded, supported, or regulated by a Federal Agency that has adopted the Federal Policy, the applicant or licensee must apply, in accordance with 10 CFR 35.6, for a specific amendment before conducting research involving human subjects.

When applying for this specific amendment, the applicant should submit an affirmation (or other evidence) that:

(1) An Institutional Review Board (as defined and described in the Federal Policy) will review and approve the research prior to the conduct of the research, and

(2) Prior to the conduct of the research, the licensee will obtain informed consent (as defined and described in the Federal Policy) from the human subject.

If the licensee does not provide the affirmation described above or other evidence, the amendment will not be approved.

If the radiation safety program necessitated by or associated with the research goes beyond the applicant's previously described radiation safety program, a revised radiation safety program should be submitted in the amendment request.

NOTE: In the past, the NRC has authorized a few medical use licensees with limited specific licenses and most medical use licensees with specific licenses of broad scope to do research involving human subjects. Prior to renewal of such licenses, these licensees may continue research that is not conducted, funded, supported, or regulated by a Federal Agency that has adopted the Federal Policy, provided (as required in 10 CFR 35.6) their internal procedures (1) require prior review and approval of the research by an Institutional Review Board (IRB), (2) require informed consent by each research

subject, and (3) use the terms "informed consent" and "Institutional Review Board" as defined and described in the Federal Policy for the Protection of Human Subjects. If the internal procedures of a limited specific licensee or a specific licensee of broad scope do not meet all three criteria, the licensee must revise its internal procedures prior to continuation of the research involving human subjects to ensure that the research conforms to all three criteria as required by 10 CFR 35.6. If the licensee does not revise its internal procedures to meet all three criteria, the licensee may no longer conduct research involving human subjects and must apply for an amendment to remove this authority from its license.

TABLE 1

Is the licensee one of the 15 Federal Agencies that adopted the Federal Policy?	→ →Yes → →	Research <u>is</u> covered by Federal Policy. No further information is needed.*
↓ ↓ No ↓ ↓		
Is <u>all</u> human research conducted, funded, supported, or regulated by one of the 15 Federal Agencies that adopted the Federal Policy?	→ →Yes→ →	Research <u>is</u> covered by Federal Policy. No further information is needed.*
↓ ↓ No or not sure ↓ ↓		
Does the licensee have a valid "Multiple Project Assurance" with the Department of Health and Human Services (or other equivalent assurance with one of the other 14 Federal Agencies that adopted the Federal Policy)?	→ →No→ →	Research <u>not specifically</u> conducted, funded, supported, or regulated by one of these Federal agencies requires an amendment request.*
↓ ↓ Yes ↓ ↓		
Did the licensee voluntarily state in the "Multiple Project Assurance" (or other equivalent assurance with one of the other 14 Federal Agencies that adopted the Federal Policy) that all human research would be performed in accordance with the assurance?	→ →No→ →	Research not specifically under the assurance <u>is not</u> covered by Federal Policy. An amendment request is necessary for this research.*
↓ ↓ Yes ↓ ↓		
Research <u>is</u> covered by the Department of Health and Human Services or one of the other 14 agencies that adopted the Federal Policy, and no further information is needed.*		

*If the radiation safety program necessitated by or associated with the research goes beyond the applicant's previously described radiation safety program, a revised radiation safety program should be submitted in an amendment request.

DRAFT VALUE/IMPACT STATEMENT

A draft value/impact statement was published with the proposed Revision 2 to Regulatory Guide 10.8 (Task FC 415-4) when the draft guide was published for public comment in August 1985. No changes were necessary, so a separate value/impact statement for the final guide, or for this proposed supplement, has not been prepared. A copy of the draft value/impact statement is available for inspection and copying for a fee at the NRC's Public Document Room at 2120 L Street NW., Washington, DC; the PDR's mailing address is Mail Stop LL-6, Washington, DC 20555; telephone (202)634-3273; fax (202)634-3343.

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