DOCKET NUMBER
PETITION RULE PRM 35-9
(54 FR 38239)

ACNP

1101 Connecticut Avenue, N.W. • Suite 700 • Washington, D.C. 20036

202-429-5120

SNM

American College of Nuclear Physicians

The Society of Nuclear Medicine

'89 JUN -8 P5:28

June 5, 1989

Secretary of the Commission
U.S. Nuclear Regulatory Commission
Washington, DC 20555

Dear Mr. Secretary:

On behalf of the over 12,000 members of the American College of Nuclear Physicians and the Society of Nuclear Medicine, we respectfully submit the enclosed Petition for Rulemaking Change to Amend 10 CFR Part 35 to Correct Regulatory Incompatibility and Permit the Traditional Practice of Nuclear Medicine and Nuclear Pharmacy. By letters of May 19, 1989, the College and Society alerted each Commissioner that this petition would be filed in the near future.

Thank you for your prompt consideration of our petition.

Sincerely,

E. William Allen, M.D.
President
American College of Nuclear Physicians

Barbara Y. Croft, Ph.D.
President
Society of Nuclear Medicine

cc: All Commissioners

D S10

8910190002 890605
PDR PRM
35-09 PDR

AMERICAN COLLEGE OF NUCLEAR PHYSICIANS

and

SOCIETY OF NUCLEAR MEDICINE

Petition for Rulemaking Change

June 5, 1989

PETITION FOR RULEMAKING TO AMEND 10 CFR PART 35 TO CORRECT REGULATORY INCOMPATIBILITY AND PERMIT THE TRADITIONAL PRACTICE OF NUCLEAR MEDICINE AND NUCLEAR PHARMACY

Submitted by:

The Society of Nuclear Medicine
136 Madison Avenue
New York, NY 10016-6760

and

The American College of Nuclear Physicians
1101 Connecticut Avenue, N.W.
Suite 700
Washington, DC 20036

For further information contact:

Carol S. Marcus, Ph.D., M.D.
Director, Nuclear Medicine Outpatient Clinic
Building A-13
Harbor - UCLA Medical Center
1000 W. Carson Street
Torrance, CA 90509

(213) 533-2845

I. Grounds for and interest in the action requested.

A. The Society of Nuclear Medicine (SNM) and the American College of Nuclear Physicians (ACNP).

SNM and ACNP are comprised of over 12,000 individuals who participate in the medical use of byproduct material. Physician members supervise the preparation and administration of radiopharmaceuticals to diagnose and treat patients. Technologist members administer radiopharmaceuticals and perform clinical procedures under the direction and supervision of an authorized user physician. Nuclear pharmacist members reconstitute radiopharmaceutical kits, compound radiopharmaceuticals, and dispense radiopharmaceuticals for medical use.

All of our members are interested in the requested action because under current NRC regulations, they cannot appropriately practice their professions. Specifically, authorized user physicians cannot prescribe certain radiopharmaceuticals or routes of administration for optimal patient care, even though they are otherwise permitted to do so by the U.S. Food and Drug Administration (FDA) and by their state medical licenses. Nuclear pharmacists have been disenfranchized as a professional entity. Although their state licenses authorize them to prepare radiopharmaceuticals for patient administration upon receipt of a prescription by an authorized user physician, current NRC regulations severely restrict their activity generally to rigid reconstitution of standard kits and dispensing doses of radiopharmaceuticals distributed by manufacturers. As with nuclear physicians, activities of nuclear pharmacists that are permitted by the FDA and the states are not allowed under NRC regulations. Nuclear medicine technologists reconstitute radiopharmaceuticals and perform clinical procedures under the supervision of an authorized user physician. Their normal professional activities are curtailed by the limitations imposed on nuclear physicians and pharmacists.

II. Statement in support of the petition.

A. Issues involved.

1. <u>NRC's regulations.</u> NRC's regulations in 10 CFR Part 35, "Medical Use of Byproduct Material", restrict authorized user physicians to the use of radiopharmaceuticals for which the FDA has accepted a "Notice of Claimed Investigational Exemption" (IND) or approved a "New Drug Application" (NDA) (10 CFR 35.100 at Add. Ii, 10 CFR 35.200 (a) at Add. Iii, and 10 CFR 35.300 at Add. Iiii). The regulations do not allow medical use licensees to modify methods of reconstituting reagent kits to meet specific clinical needs encountered in the practice of medicine (see 10 CFR 35.200 (b) at Add. Iii). Moreover, licensees are required to elute 99-Mo/99m-Tc generators and prepare reagent kits in accordance with the manufacturer's instructions. The regulations do not allow a physician to use radiopharmaceuticals to treat diseases that are not listed in the package insert (see

10 CFR 35.300 at Add. Iiii). Although NRC's regulations in 10 CFR Part 32, "Specific Domestic Licenses to Manufacture or Transfer Certain Items Containing Byproduct Material" appear to allow nuclear pharmacists to distribute radiopharmaceuticals that are not regulated or approved by FDA (see 10 CFR 32.72 (a)(2)(ii) at Add. Iiv and 10 CFR 32.73 (a)(2)(ii) at Add. Iv), but this allowance is withdrawn in the radiopharmacy license document (see Add. II).

2. Interaction with other regulations.

(a) History. Radiopharmaceuticals for medical use were first made with Ernest Lawrence's cyclotron in Berkeley in 1937. After World War II and the development of nuclear reactors, most radiopharmaceuticals were made from byproduct material. Today, about 75% of nuclear medicine procedures involve byproduct radiopharmaceuticals; the remainder involve accelerator-produced material.

At the time the Atomic Energy Act of 1954 was passed, the FDA did not regulate radioactive drugs (although they had the mandate to do so). FDA began regulating accelerator-produced radiopharmaceuticals in 1968, and began regulating byproduct radiopharmaceuticals in 1974. Until that time, the preparation and use of byproduct radiopharmaceuticals had been regulated solely by the AEC. As years passed, FDA continued to refine its role in reviewing, approving, and regulating radiopharmaceuticals for research and clinical purposes. This regulatory evolution continues to the present.

(b) FDA's regulatory framework today for radiopharmacy. Although the practices of medicine (see Add. IIIi) and pharmacy (see Add. IIIii, Add. IV, and Add. V) are exempt from FDA's manufacturing and distribution regulations by congressional mandate, they are definitely not exempt from FDA's regulations forbidding misbranding and adulteration (see Add. XI). In addition, the FDA is the enforcement arm of the drug quality standards published in the United States Pharmacopoeia (USP). In other respects, FDA now regulates all radiopharmaceuticals, whether made by manufacturers, nuclear pharmacists or their designees in medical institutions or in centralized radiopharmacies, or nuclear physicians or their designees. FDA has the federal authority to regulate all research and clinical use of radioactive drugs directly or indirectly.

Because of the manufacturing and distribution exemption for pharmaceuticals (including radiopharmaceuticals) prepared under state laws regulating the practice of medicine and pharmacy, commercial New Drug Applications (NDA's) are not granted for these drug preparations. Nevertheless, it should be appreciated that these drugs are still recognized and regulated by FDA.

One mechanism of FDA radiopharmaceutical regulation is the Investigational New Drug Application (IND). An IND from a commercial manufacturer is very carefully scrutinized by FDA in terms of all aspects of manufacturing, chemistry, and the details of the clinical trial protocols. There are several well-defined phases of clinical trials designed to minimize risk to human subjects and maximize needed drug information. Physician sponsored IND's are handled with more flexibility because they involve fewer human subjects and are for research purposes. These physicians do not become commercial manufacturers or distributors of the drugs they study. The actual clinical trials of both commercial IND's and physician-sponsored IND's take place in medical institutions which also provide Institutional Review Board (IRB) and Radiation Safety Committee oversight.

When sufficient supporting information is obtained under the various phases of a commercial IND, the manufacturer submits an NDA. When this is approved, the manufacturer may sell his drug to any appropriately licensed user.

The only FDA regulatory mechanisms recognized by NRC are the IND and NDA.

(c) Incompatibility of NRC's regulations with FDA's statute and other standards. Part 35 directly conflicts with FDA's regulatory framework because except for physician sponsored IND's, Part 35 only allows the use of radiopharmaceuticals prepared under the portion of FDA regulations devoted to manufacturers with nationwide distribution. Even in this limited scope, NRC's regulations contort the concept, intent, and application of FDA's designations "accepted" and "approved" (see Add. IIIi).

NRC's regulations also conflict with the laws of 50 States regulating the practices of medicine (see Add. VI) and pharmacy (see Add. VIIi and ii). They also conflict with the Hippocratic Oath (see Add. VIII), which provides the ethical foundation for Western medicine, and the spirit of NRC's organic statute (see Add. IX).

3. Summary of issue. FDA regulates all clinical and research use of radiopharmaceuticals in many ways. Approved IND's and NDA's are only two of them. However, they are the only two avenues recognized in 10 CFR Part 35. Part 35 needs to be amended to recognize all the mechanisms that FDA uses to authorize the use of a radiopharmaceutical. NRC's current regulations that identify which radiopharmaceuticals may be used, how they may be prepared, and for which purposes they may be administered are in conflict with the long-standing regulatory framework established by other Federal and State regulatory agencies.

4. Purpose. The purpose of this petition for rulemaking is to amend NRC's regulations to allow the use of radiopharmaceuticals in accordance with FDA requirements. Acceptance of this petition would, consistent with FDA jurisdiction and regulations and state law: allow nuclear physicians and nuclear pharmacists to reconstitute non-radioactive kits differently from the method recommended by the manufacturer; allow nuclear physicians and nuclear pharmacists to prepare radiopharmaceuticals whose manufacture and distribution are purposefully not regulated by FDA; and permit nuclear physicians to determine appropriate diagnostic and therapeutic applications of radiopharmaceuticals, as is their professional obligation.

III. Petitioner's views and arguments.

A. Patient care.

The delivery of quality patient care often requires that a physician modify an existing clinical procedure, create a new clinical procedure, or use an existing product for an application not described in the package insert. Some examples are provided below.

Example 1. Modification of an existing diagnostic clinical procedure. Tc-99m-albumin colloid is approved by the FDA as a liver and spleen imaging agent. The colloid particles are phagocytized by cells of the reticuloendothelial system which reside in these organs. If the kit is reconstituted using a modification of the manufacturer's instructions, high specific activity particles may be produced. When these are incubated with the patient's white blood cells, the particles are phagocytized, resulting in radiolabeled white blood cells. These labeled cells are then injected into the patient, where sites of infection and inflammation are imaged with a gamma camera. This procedure is useful in diagnosing appendicitis, for example (see Add. Xi). Compared to alternative procedures for its purpose, the Tc-99m-albumin colloid method results in substantially less radiation dose to the patient.

Example 2. Creation of a new clinical procedure: An angiographer uses bits of gelfoam to occlude intractably bleeding varices. Gelfoam is radiolucent, so he cannot use x-rays to locate the particles once they have been introduced into a blood vessel. The radiopharmacist can label the gelfoam with Tc-99m so that the angiographer can use nuclear medicine imaging to verify the final destination of the particles. The radiopharmacist works out a convenient labeling method so that he can prepare the labeled particles quickly on "prescription order" from the physician (see Add. Xii).

Example 3. Creation of a new clinical procedure: A group of patients with a variety of underlying disorders needs frequent red cell transfusions. These patients develop multiple minor group antibodies, and traditional in vitro crossmatch methods to evaluate potential blood transfusions are often unsatisfactory. The immunohematologist requests an in vivo crossmatch using radiolabeled potential donor red cells. (This method is more accurate.) The radiopharmacist makes lyophilized stannous citrate kits to be used

for labeling donor red cells with Tc-99m. These will be injected into the intended recipient and their survival determined by dilution measurements (see Add. Xiii).

Example 4. Use of an existing product for a therapeutic application not described in the package insert. A hematologist asks a nuclear medicine physician to administer P-32 sodium phosphate to a patient with documented thrombocythemia vera. The case is somewhat atypical because it is not associated with any other myeloproliferative disorder. Although P-32 has been used to treat this category of disease since 1937, this particular abnormality is not listed on the package insert (see Add. Xiv).

Under NRC's regulatory framework, example 1 is contrary to 10 CFR 35.200 (b) (see Add. Iii), example 2 is contrary to 10 CFR 35.200 (a) (see Add. Iii), example 3 is contrary to 10 CFR 35.100 (see Add. Ii), and example 4 is contrary to 10 CFR 35.300 (see Add. Iiii) and recently occurred in a hospital under NRC license. The nuclear physician insisted on treating his patient, and an emergency license amendment was requested. As such an amendment would be contrary to the regulations, NRC made a determination that the patient's diagnosis was sometimes observed as an element of an indication listed on the package insert. The rulemaking change discussed in this petition would completely relieve the NRC of its role of providing mandatory medical consultative services in life-threatening cases.

It is essential to point out that all four of the above clinical procedure examples are recognized and purposefully permitted under the Federal Food, Drug, and Cosmetic Act and by the States under the various laws regulating the practices of medicine (see Add. VI) and pharmacy (see Add. IIIi and Add. VIIi). At the Federal level, this broad authorization is not merely a matter of regulatory discretion; the exemption for medicine and pharmacy was directed by Congress in the Food, Drug and Cosmetic Act (see Add. Xi). Thus, we believe the NRC's stringent regulations for the medical use of byproduct material are at odds with Congress' clearly stated mandate to the lead Federal drug regulatory agency. They are also at odds with state laws under which all other aspects of the physician-pharmacist-patient relationship are regulated.

B. Medical Research.

Medical research is often conducted at community hospitals in addition to large, nationally known research centers that hold NRC or Agreement State specific licenses of broad scope. The large research centers typically develop whole new classes of radiopharmaceuticals, quality control and quality assurance procedures to ensure their safe and effective use, and develop and refine procedures and equipment to prepare these radiopharmaceuticals and image their biodistribution in patients with various pathologies. They also participate in research under commercial and physician-sponsored investigational new drug applications (IND's) and other research categories to be described below. Community hospitals may participate in regional or nationwide research programs, use

approved drugs for additional applications that may become established clinical procedure, as described in scientific literature, modify approved drugs to assess their utility in new clinical applications, and conduct basic research that may lead to development of new radiopharmaceuticals and nuclear medicine procedures.

The FDA has established a complete regulatory framework to provide for oversight of all these activities.

Specialized staff at the FDA review physician-sponsored and manufacturer-sponsored clinical trials before they are begun. The review team includes nuclear and other physicians, pharmacists and nuclear pharmacists, dosimetrists, statisticians, pharmacologists, chemists, radiochemists, etc. The purpose of this review is to ensure that the clinical procedure is as safe as possible, and that the clinical trial design is of sufficient quality to allow for scientific evaluation of the results. NRC regulations allow all authorized user physicians to participate in these IND clinical trials (see 10 CFR 35.100 at Add. Ii, 10 CFR 35.200 at Add. Iii, and 10 CFR 35.300 at Add. Iiii).

However, certain research protocol categories are exempt from the need to file IND's. Many of these involve the investigation of an approved drug for an unapproved indication and/or by an unapproved route of administration. To provide for regulatory oversight of such research, hospital-based Institutional Review Boards (IRB's) are established under HHS regulations (see 45 CFR 46.107 at Add. XI). Their specific purpose is to "ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice." FDA requires IRB approval of research projects that FDA regulates. As a matter of ethics and civil law, hospitals require that all research projects be authorized and monitored by their IRB's. If radioactive drugs are involved, the IRB will require approval of the institution's Radiation Safety Committee as well. This category of research, that which does not require an approved IND, is nevertheless not permitted by NRC regulations. This impedes the development of improved medical care, and is also a source of great annoyance and frustration to the FDA, which is constantly badgered by investigators demanding IND's they do not even need except to satisfy NRC's requirement. At a recent forum, an FDA spokesman publicly stated that FDA had even granted some unnecessary IND's only to aid investigators who needed to comply with NRC regulations.

A third administrative category of medical research involves the use of radiolabeled compounds for metabolic studies. Generally speaking, these drugs are not destined for diagnostic or therapeutic use except for the radiopharmaceuticals used in positron emission tomography (PET). To provide regulatory oversight of such research projects, FDA charters Radioactive Drug Research Committees (RDRC's) under 21 CFR 361.1 (see Add. XII). The purpose of the RDRC review is to ensure that the radiation absorbed dose to human subjects is ALARA and less than 5 rem (i.e., annual or total dose commitment) to

whole body, active blood-forming organs, lens of the eye, and gonads, and that the quantity of substance to be administered is known not to cause any toxic effects in humans. Approval of appropriate proposals involving more than 30 subjects must be promptly reported to FDA. These proposals must also be approved by the IRB and the Radiation Safety Committee. NRC regulations do not permit this category of research to be carried out, thereby impeding the development of basic science information. Although NRC does provide line-item authorizations for such research on community hospital specific licenses of limited scope, the public health and safety basis for the need of the applicant to specifically request this authorization is not apparent.

An incipient problem exists with biologicals used for research, such as radiolabeled antibodies. Although biologicals, like drugs, have approved IND's for investigational use, when biologicals are eventually approved for general use they do not have approved new drug applications (NDA's), as do drugs. They have product license application approvals (PLA's). NRC regulations do not allow use of PLA's; only IND's and NDA's.

A very serious problem exists with the interpretation of 10 CFR Part 35 as regards medical institutions that possess specific licenses of broad scope (see Add. XVi and vii). Although the Statements of Consideration appear to leave broad licensees relatively unchanged by the revision (see Add. XVi), in practice NRC has sought to significantly limit the necessary activities of these institutions. NRC has removed the traditional and essential power of the Radiation Safety Committee to approve research and clinical uses of radiopharmaceuticals and has denied the traditional rights of the practice of nuclear medicine and nuclear pharmacy to these institutions as well. If this trend continues, the concept of the broad license will end in NRC States and many Agreement States as well because of NRC precedent. At the present time, this situation is occurring in California and appears to be unjustified and inappropriate. Regulations pertaining to broad licensees need to be clarified.

The contents of Addendum XV have been assembled to show a progression of interpretations of Part 35 that led inevitably to crippling restrictions on the broad medical license. An example of such a restricted license appears as Add. XVvi. NRC does not appear to have set a determined course to destroy this license concept. The contrary is probably closer to the truth. What appears to have happened is that a straightforward interpretation of part 35 logically had to lead to this unfortunate state of affairs. The problem is Part 35 itself, not its interpretation.

It is to NRC's credit that when it became aware of the impact of its interpretation of Part 35 on broad medical licensees, the memo of Add. XViv was sent to all regions (and all Agreement States). After thorough consideration of this and related problems, NRC staff determined that the best course of action was to change Part 35. This Petition is the result of that decision.

C. Economy.

Instructions and suggestions for compounding many radiopharmaceuticals are provided in the scientific and professional literature. The actual acts of compounding and administration are authorized under state laws regulating the practices of medicine and pharmacy. However, NRC regulations forbid the act of compounding except for the very limited act of reconstituting reagent kits in accordance with manufacturer's instructions. The only radiopharmaceuticals permitted are those that have accepted IND's and approved NDA's. The act of radiopharmaceutical compounding, as described in state and FDA regulations, is not recognized by NRC; this effectively disenfranchises the key professional practitioners, the nuclear pharmacists. The nuclear pharmacist, who is permitted in 10 CFR 35.900 (a)(5) to be the Radiation Safety Officer, is nevertheless not entitled to practice his primary profession. Certification by the Board of Pharmaceutical Specialties in Nuclear Pharmacy is recognized in all 50 States, but NRC does not recognize the professional practice of nuclear pharmacy. This needs to be rectified.

Many radiopharmaceuticals could be prepared by state-licensed nuclear pharmacists or nuclear physicians or their designees at lower cost or higher quality than for commercially available radiopharmaceuticals. Or, radiopharmaceuticals could be prepared that are not commercially available at any price but may be used for a nuclear medicine procedure which is economically competitive compared with an alternative procedure. This issue has gained in importance over the last few years because of health care cost containment policies and government reimbursement schedules.

The Federal government is responsible for the health care costs of about 30 million patients each year, and most major third party payers incorporate the HCFA fee schedules. Each clinical procedure is reimbursed based on the professional component (the physician's fee) and the technical component (the cost of consumables, equipment amortization, service of technologists, computer scientists, radiological physicists, nuclear pharmacists, secretaries, receptionists, and overhead). In many cases the technical component barely covers the cost of the radiopharmaceutical of choice (see, for example, "thyroid imaging with single determination" at Add. XIII). Thus, the federal reimbursement schedule, coupled with NRC's requirement to use only NDA-approved radiopharmaceuticals, occasionally forces physicians to use radiopharmaceuticals that are not of choice. If NRC permitted the practice of nuclear pharmacy, this would allow for greater radiopharmaceutical flexibility and better and more economical patient care. FDA has specifically approved the manufacture of cold kits by nuclear pharmacists (see Add. IIIii and IV). NRC's refusal to permit this practice is a severe regulatory contradiction.

D. Summary.

Regulatory incompatibility between 10 CFR Part 35 and FDA regulations and state pharmacy and medicine laws is causing serious problems in the optimal delivery of quality nuclear medicine care

and the implementation of nuclear medicine research. The adoption of the amendments described below will rectify this unfortunate situation, and we urge NRC to carefully consider these much-needed changes.

IV. Text of Amendment.

The petitioners recommend that the NRC publish for public comment the following statements of consideration and proposed regulatory text:

A. Definitions.

Statement of Considerations. Certain definitions are needed to clarify the scope and purpose of the regulations. The definition of "medical institution" needs to be amended to permit appropriate flexibility and compatibility with FDA determinations. It is assumed that a clear statement of responsibility will be available for medical institutions composed of more than one entity where separate IRB's, Radiation Safety Committees, and licensing agreements exist.

Regulatory Text. 10 CFR 30.4 is amended by adding:

"Medical Research Use" means the intentional internal or external administration of byproduct material, or the radiation therefrom, to human subjects for research purposes.

Regulatory Text. 10 CFR 35.2 is amended by adding:

"Radiopharmaceutical" means any drug or biologic that contains byproduct material.

"Medical Research Use" means the intentional internal or external administration of byproduct material, or the radiation therefrom, to human subjects for research purposes.

Regulatory Text. 10 CFR 35.2 is amended by changing the definition of "medical institution" to read as follows:

"Medical Institution" means a single health care facility or a health care organization which may physically exist in multiple separate locations but is integrated through economic and/or management agreements. Several medical disciplines may be practiced in a medical institution.

B. Practice of pharmacy, practice of medicine, and medical research.

Statement of Considerations. To avoid unnecessary duplication or conflict with state and other Federal regulations that govern the practice of pharmacy, the practice of medicine, and medical research, the NRC regulations should be modified. The modifications should permit the use of radiopharmaceuticals compounded under state pharmacy and medicine laws. The NRC regulations should also be modified such that the licensee is required to comply with appli-

cable FDA regulations. Because of the fact that state and FDA laws and regulations are subject to change and to new interpretations, and resultant policy changes, NRC should not attempt to itemize these frameworks within its own requirements. It becomes the licensee's responsibility to know and abide by the appropriate state and Federal laws and regulations.

Regulatory Text. 10 CFR 35.100 is amended in its entirety to read:

(a) A licensee may use for medical use any byproduct material in a radiopharmaceutical and for a diagnostic use involving measurements of uptake, dilution, or excretion in which:

(1) The radiopharmaceutical is manufactured and distributed in accordance with the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, or:

(2) The radiopharmaceutical is manufactured, prepared, propagated, compounded, or processed under an exempt category of Section 510(g) of the Federal Food, Drug and Cosmetic Act.

(b) A medical institution licensee may use for medical research use any byproduct material in a radiopharmaceutical and for a use involving measurements of uptake, dilution, or excretion if its use has been approved by the Radiation Safety Committee (RSC) and the Institutional Review Board (IRB) chartered in accordance with 45 CFR Part 46.

Regulatory Text. 10 CFR 35.200 is amended in its entirety to read:

(a) A licensee may use for medical use any byproduct material in a radiopharmaceutical and for a diagnostic use involving imaging in which:

(1) The radiopharmaceutical is manufactured and distributed in accordance with the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, or:

(2) The radiopharmaceutical is manufactured, prepared, propagated, compounded or processed under an exempt category of Section 510(g) of the Federal Food, Drug, and Cosmetic Act.

(b) A medical institution licensee may use for medical research use any byproduct material in a radiopharmaceutical and for a use involving imaging if its use has been approved by the RSC and the IRB chartered in accordance with 45 CFR Part 46.

Regulatory Text. 10 CFR 35.300 is amended in its entirety to read:

(a) A licensee may use for medical use any byproduct material in a radiopharmaceutical and for a therapeutic use in which:

(1) The radiopharmaceutical is manufactured and distributed in accordance with the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, or:

(2) The radiopharmaceutical is manufactured, prepared, propagated, compounded, or processed under an exempt category of Section 510(g) of the Federal Food, Drug, and Cosmetic Act.

(b) A medical institution licensee may use for medical research use any byproduct material in a radiopharmaceutical for a therapeutic use if its use has been approved by the RSC and the IRB chartered in accordance with 45 CFR Part 46.

C. NRC licenses.

Statement of Considerations. Licenses issued to date under 10 CFR Part 35 only authorize medical use. To eliminate the administrative burden of amending all those licenses to allow for medical research use, the NRC will allow any medical institution licensee to also use byproduct material for medical research use.

Regulatory Text. 10 CFR 35.11 is amended by adding a new paragraph (c):

(c) Any medical institution licensed to use byproduct material for medical use as described in sections 35.100, 35.200 or 35.300 may also use byproduct material for medical research use described in the sections for which it is licensed. This authorization supersedes any license condition issued before (insert effective date).

D. Suppliers.

Statement of Considerations. To allow the practice of institutional nuclear pharmacy, the section that describes permissible sources of radiopharmaceuticals must be expanded.

Regulatory Text. 10 CFR 35.49 is amended by changing the current paragraph (c) regarding teletherapy sources to paragraph (d), and inserting a new paragraph (c):

(c) Byproduct material in radiopharmaceuticals compounded by or under the supervision of a state-licensed nuclear pharmacist or nuclear medicine physician if such radiopharmaceuticals are manufactured, prepared, propagated, compounded, or processed under an exempt category of Section 510(g) of the Federal Food, Drug, and Cosmetic Act.

E. Free-standing Radiopharmacies.

Statement of Considerations. The NRC licenses free-standing radiopharmacies to distribute radiopharmaceuticals, but typically requires that they only distribute FDA-approved radiopharmaceuticals

that have been reconstituted in accordance with the manufacturer's instructions. The NRC must amend these licenses to allow free-standing radiopharmacies licensed under 10 CFR 32.72 and 10 CFR 32.73 to also compound radiopharmaceuticals. This must be accomplished by licensing action because those licenses have a clause that states that if the license document is more restrictive than the regulation, the license document takes precedence. Those licenses will be amended by NRC, without charge to the licensee, to: remove the requirement to reconstitute radiopharmaceuticals in accordance with the manufacturer's instructions, and allow the compounding of radiopharmaceuticals under the practice of pharmacy regulations in accordance with requirements of the Food and Drug Administration and applicable State requirements. In the event of any disciplinary action by NRC, the applicable State Board of Pharmacy will be alerted.

F. Specific Licenses of Broad Scope for Medical Research Use.

Statement of Considerations. In order to eliminate confusion regarding the conduct of medical research use under a specific license of broad scope, it is advisable to amend portions of Part 33.

Regulatory Text. 10 CFR 33.11 (a) is amended to read as follows:

10 CFR 33.11 Types of specific licenses of broad scope.

(a) A "Type A specific license of broad scope" is a specific license authorizing receipt, acquisition, ownership, possession, use, and transfer of any chemical or physical form of the byproduct material specified in the license, but not exceeding quantities specified in the license, for purposes authorized by the Act. The quantities specified are usually in the multicurie range. Applicants that are medical institutions may conduct medical research use in addition to conducting research and development as defined in 10 CFR 30.4.

* * * * *

Regulatory Text. 10 CFR 33.13 (c)(3) is amended by adding a new paragraph (iv) as follows:

10 CFR 33.13 Requirements for the issuance of a Type A specific license of broad scope.

An application for the issuance of a Type A specific license of broad scope will be approved if:

* * * * *

(c) * * *

(3) The establishment of appropriate administrative procedure to assure:

(i) * * *

(ii) * * *

(iii) * * *

(iv) Review, approval, and recording by the Radiation Safety Committee and the Institutional Review Board of the safety and ethics of proposed uses involving medical research use prepared in accordance with paragraph (c)(3)(ii) of this section prior to use of the byproduct material.

Regulatory Text. 10 CFR 33.17 (a)(4) is amended to read as follows:

10 CFR 33.17 Conditions of specific licenses of broad scope.

(a) Unless specifically authorized pursuant to other parts of this chapter, persons licensed under this part shall not:

(1) * * *

(2) * * *

(3) * * *

(4) Add or cause the addition of byproduct material to any food, beverage, cosmetic, drug, or other product designed for ingestion or inhalation by, or application to, a human being unless permitted by the license document to conduct medical research use.

* * * * *

ADDENDA

I. NRC regulations.

i. 10 CFR 35.100 - - - Uptake, Dilution, Excretion
ii. 10 CFR 35.200 - - - Imaging
iii. 10 CFR 35.300 - - - Therapy
iv. 10 CFR 32.72 - - - Radiopharmacy
v. 10 CFR 35.73 - - - Distribution
vi. 10 CFR 35.11 - - - License required
vii. 10 CFR 35.49 - - - Suppliers

II. Sample free-standing radiopharmacy license (NRC) that only allows FDA products reconstituted in accordance with the manufacturer's instructions. NRC Task FC 410-4, August 1985, pp. 53-57.

III. Letter from Paula Botstein of FDA dated 10 June 88 to Carol Marcus explaining FDA's regulatory framework emphasizing that:

i. FDA permits the research and clinical uses of NDA-approved radiopharmaceuticals for unapproved indications, by unapproved routes of administration, and using kit reconstitution methods other than as described in the package insert. No IND is required. The FDA does not distinguish between diagnostic and therapeutic radiopharmaceuticals.
ii. FDA permits the practice of pharmacy.

IV. Letter from Robert West of FDA dated 16 March 87 to Arun Sukerkar stating that FDA permits the in-house manufacture of cold kits.

V. FDA Nuclear Pharmacy Guideline: Criteria for determining when to register as a drug establishment. May, 1984. (Also known as the "Lavender Report".)

VI. Sample definition of the practice of medicine and related definitions. Corpus Juris Secundum 70:377-379; 393-394; 411-412, 1987.

VII. Pharmacy

i. Sample description of the practice of pharmacy.
ii. Sample state radiopharmacy license.

VIII. Hippocratic oath.

IX. Atomic Energy Act of 1954: Caution against intrusion into medicine.

X. Documentation of Clinical Examples

i. Marcus CS, Kuperus JH, Butler JA et al.: Phagocytic labeling of leukocytes with Tc-99m-albumin colloid for nuclear imaging. Nuc. Med. Biol. 15:673-682, 1988.

Henneman PL, Marcus CS, Butler JA et al.: Appendicitis: Evaluation by Tc-99m-leukocyte scan. Ann. Emerg. Med. 17:111-116, 1988.

ii. Conroy RM, Lyons KP, Kuperus JH et al.: New technique for localization of therapeutic emboli using radionuclide labeling. Am. J. Roentgenol. 130:523-528, 1978.

iii. Marcus CS, Myhre BA, Angulo MC et al.: Radiolabeled red cell viability I. Comparison of Cr-51, Tc-99m, and In-111 for measuring the viability of autologous stored red cells. Transfusion 27:415-419, 1987.

Marcus CS, Myhre BA, Angulo MC et al.: Radiolabeled red cell viability II. Tc-99m and In-111 for measuring the viability of homologous red cells in vivo. Transfusion 27:420-424, 1987.

iv. Hollander L: Treatment of malignant blood disease with radioactive phosphorus. Chapter 29 of Blahd WH: Nuclear Medicine, Mcgraw-Hill, NY, NY, pp. 760-774, 1971.

XI. Federal Food, Drug, and Cosmetic Act, as amended.

i. Exemptions for pharmacy and medicine.
ii. Definition of a drug.

XII. Department of Health and Human Services Regulations for research involving human subjects.

XIII. Food and Drug Administration Regulations for Radioactive Drug Research Committees: 21 CFR 361.1.

XIV. Marcus CS,: Radiopharmaceutical cost, procedure reimbursement, and radiation absorbed dose: the cost of quality nuclear medicine in America. Feb. 1989.

XV. NRC Limitation of Broad Licensees

i. Statements of Consideration
ii. NRC correspondence prompted by Gerard C. Wong, Ph.D., of the Radiologic Health Branch, California.
iii. Letter from the President of the American Pharmaceutical Association to VADM Lando W. Zech, Jr., and the NRC reply.
iv. Memo from NRC to all regions (and also to Agreement States): Notice of intent to reassess NRC regulations and policy on byproduct radiopharmaceuticals.
v. Letter from Paula Botstein, M.D., FDA, to Richard E. Cunningham, NRC.
vi. The first of a series of new "broad licenses" issued in California pursuant to XIVi.
vii. NRC correspondence prompted by Raymond C. Barrall, Director of Radiation Protection, Illinois.

I i.

I ii.

Subpart D—Uptake, Dilution, and Excretion

§ 35.100 Use of radiopharmaceuticals for uptake, dilution and excretion studies.

A licensee may use any byproduct material in a radiopharmaceutical and for a diagnostic use involving measurements of uptake, dilution, or excretion for which the Food and Drug Administration (FDA) has accepted a "Notice of Claimed Investigational Exemption for a New Drug" (IND) or approved a "New Drug Application" (NDA).

§ 35.120 Possession of survey instrument.

A licensee authorized to use byproduct material for uptake, dilution, and excretion studies shall have in its possession a portable radiation detection survey instrument capable of detecting dose rates over the range 0.1 millirem per hour to 100 millirem per hour.

Subpart E—Imaging and Localization

§ 35.200 Use of radiopharmaceuticals, generators, and reagent kits for imaging and localization studies.

(a) A licensee may use any byproduct material in a diagnostic radiopharmaceutical or any generator or reagent kit for preparation and diagnostic use of a radiopharmaceutical containing byproduct material for which the Food and Drug Administration has accepted a "Notice of Claimed Investigational Exemption for a New Drug" (IND) or approved a "New Drug Application" (NDA).

(b) A licensee shall elute generators and prepare reagent kits in accordance with the manufacturer's instructions.

§ 35.204 Permissible molybdenum-99 concentration.

(a) A licensee may not administer to humans a radiopharmaceutical containing more than 0.15 microcurie of molybdenum-99 per millicurie of technetium-99m.

(b) A licensee that uses molybdenum-99/technetium-99m generators for preparing a technetium-99m radiopharmaceutical shall measure the molybdenum-99 concentration in each eluate or extract.

(c) A licensee that must measure molybdenum concentration shall retain a record of each measurement for two years. The record must include, for each elution or extraction of technetium-99m, the measured activity of the technetium expressed in millicuries, the measured activity of the molybdenum expressed in microcuries, the ratio of the measures expressed as microcuries of molybdenum per millicurie of technetium, the time and date of the measurement, and the initials of the individual who made the measurement.

§ 35.205 Control of aerosols and gases.

(a) A licensee that administers radioactive aerosols or gases shall do so in a room with a system that will keep airborne concentrations within the limits prescribed by §§ 20.103 and 20.106 of this chapter. The system must either be directly vented to the atmosphere through an air exhaust or provide for collection and decay or disposal of the aerosol or gas in a shielded container.

(b) A licensee shall administer radioactive aerosols and gases in rooms that are at negative pressure compared to surrounding rooms.

(c) Before receiving, using, or storing a radioactive gas, the licensee shall calculate the amount of time needed after a spill to reduce the concentration in the room to the occupational limit listed in Appendix B to Part 20 of this chapter. The calculation must be based on the highest activity of gas handled in a single container, the air volume of the room, and the measured available air exhaust rate.

(d) A licensee shall make a record of the calculations required in paragraph (c) of this section that includes the assumptions, measurements, and calculations made and shall retain the record for the duration of use of the area. A licensee shall also post the calculated time and safety measures to be instituted in case of a spill at the area of use.

(e) A licensee shall check the operation of collection systems each month, and measure the ventilation rates available in areas of use each six months.

§ 35.220 Possession of survey instrume

A licensee authorized to use byp uct material for imaging and local tion studies shall have in its posse a portable radiation detection sur instrument capable of detecting c rates over the range of 0.1 milli per hour to 100 millirem per hour, a portable radiation measurem survey instrument capable of mea ing dose rates over the range 1 lirem per hour to 1000 millirem hour.

Subpart F—Radiopharmaceuticals Therapy

§ 35.300 Use of radiopharmaceuticals therapy.

A licensee may use any byproc material in a radiopharmaceutical for a therapeutic use for which Food and Drug Administration has cepted a "Notice of Claimed Invest tional Exemption for a New Dr (IND), or approved a "New Drug plication" (NDA). The licensee s comply with the package insert structions regarding indications method of administration.

§ 35.310 Safety instruction.

(a) A licensee shall provide radiat safety instruction for all person caring for the patient receiving ra pharmaceutical therapy and hospi ized for compliance with § 35.75 of t chapter. To satisfy this requirem the instruction must describe the censee's procedures for:

(1) Patient control;

(2) Visitor control;

(3) Contamination control;

(4) Waste control; and

(5) Notification of the Radia Safety Officer in case of the patie death or medical emergency.

(b) A licensee shall keep for years a list of individuals receivin struction required by paragraph (a this section, a description of the struction, the date of instruction, the name of the individual who the instruction.

§ 35.315 Safety precautions.

(a) For each patient receiving ra pharmaceutical therapy and hosp

I iii.

(c) A licensee that must measure molybdenum concentration shall retain a record of each measurement for two years. The record must include, for each solution or extraction of technetium, the measured activity of the technetium expressed in millicuries, the measured activity of the molybdenum expressed in microcuries, the ratio of the measures expressed as microcuries of molybdenum per millicurie of technetium, the time and date of the measurement, and the initials of the individual who made the measurement.

§ 35.205 Control of aerosols and gases.

(a) A licensee that administers radioactive aerosols or gases shall do so in a room with a system that will keep airborne concentrations within the limits prescribed by §§ 20.103 and 20.106 of this chapter. The system must either be directly vented to the atmosphere through an air exhaust or provide for collection and decay or disposal of the aerosol or gas in a shielded container.

(b) A licensee shall administer radioactive aerosols and gases in rooms that are at negative pressure compared to surrounding rooms.

(c) Before receiving, using, or storing radioactive gas, the licensee shall calculate the amount of time needed after a spill to reduce the concentration in the room to the occupational limit listed in Appendix B to Part 20 of this chapter. The calculation must be based on the highest activity of gas planned in a single container, the air volume of the room, and the measured available air exhaust rate.

(d) A licensee shall make a record of the calculations required in paragraph (c) of this section that includes the assumptions, measurements, and calculations made and shall retain the record for the duration of use of the area. A licensee shall also post the calculated time and safety measures to be instituted in case of a spill at the area of use.

(e) A licensee shall check the operation of collection systems each month, and measure the ventilation rates available in areas of use each six months.

§ 35.220 Possession of survey instruments.

A licensee authorized to use byproduct material for imaging and localization studies shall have in its possession a portable radiation detection survey instrument capable of detecting dose rates over the range of 0.1 millirem per hour to 100 millirem per hour, and a portable radiation measurement survey instrument capable of measuring dose rates over the range 1 millirem per hour to 1000 millirem per hour.

Subpart F—Radiopharmaceuticals for Therapy

§ 35.300 Use of radiopharmaceuticals for therapy.

A licensee may use any byproduct material in a radiopharmaceutical and for a therapeutic use for which the Food and Drug Administration has accepted a "Notice of Claimed Investigational Exemption for a New Drug" (IND), or approved a "New Drug Application" (NDA). The licensee shall comply with the package insert instructions regarding indications and method of administration.

§ 35.310 Safety instruction.

(a) A licensee shall provide radiation safety instruction for all personnel caring for the patient receiving radiopharmaceutical therapy and hospitalized for compliance with § 35.75 of this chapter. To satisfy this requirement, the instruction must describe the licensee's procedures for:

(1) Patient control;

(2) Visitor control;

(3) Contamination control;

(4) Waste control; and

(5) Notification of the Radiation Safety Officer in case of the patient's death or medical emergency.

(b) A licensee shall keep for two years a list of individuals receiving instruction required by paragraph (a) of this section, a description of the instruction, the date of instruction, and the name of the individual who gave the instruction.

§ 35.315 Safety precautions.

(a) For each patient receiving radiopharmaceutical therapy and hospitalized for compliance with § 35.75 of this chapter, a licensee shall:

(1) Provide a private room with a private sanitary facility;

(2) Post the patient's door with a "Radioactive Materials" sign and note on the door or in the patient's chart where and how long visitors may stay in the patient's room;

(3) Authorize visits by individuals under age 18 only on a patient-by-patient basis with the approval of the authorized user after consultation with the Radiation Safety Officer;

(4) Promptly after administration of the dosage, measure the dose rates in contiguous restricted and unrestricted areas with a radiation measurement survey instrument to demonstrate compliance with the requirements of Part 20 of this chapter, and retain for two years a record of each survey that includes the time and date of the survey, a plan of the area or list of points surveyed, the measured dose rate at several points expressed in millirem per hour, the instrument used to make the survey, and the initials of the individual who made the survey;

(5) Either monitor material and items removed from the patient's room to determine that their radioactivity cannot be distinguished from the natural background radiation level with a radiation detection survey instrument set on its most sensitive scale and with no interposed shielding, or handle them as radioactive;

(6) Provide the patient radiation safety guidance that will help to keep radiation dose to household members and the public as reasonably achievable before authorizing release of the patient.

(7) Survey the patient and private sanitary facility for removable contamination with a radiation detection survey instrument before assigning another patient to the room. The room must not be released until removable contamination is less than 200 disintegrations per minute per 100 square centimeters; and

(8) Measure the thyroid burden of each individual who helps care for or administer a dosage of iodine-131 within three days after administering the dosage, and retain a record required by § 20.401(c) for the period of

odine-129 and 0.005 microcurie of icium-241 each; and

Displaying the radiation caution ol described in § 20.203(a)(1) of r ter and the words, "Caution, ve Material", and "Not for nal or External Use in Humans or als."

The following statement, or a antially similar statement which ains the information called for in ollowing statement, appears on a affixed to each prepackaged unit ppears in a leaflet or brochure h accompanies the package: [1]

radioactive material may be received, ed, possessed, and used only by physi- veterinarians in the practice of veteri- medicine, clinical laboratories or hospi- nd only for in vitro clinical or labora- ests not involving internal or external nistration of the material, or the radi- therefrom, to human beings or ani- Its receipt, acquisition, possession, use, ransfer are subject to the regulations general license of the U.S. Nuclear latory Commission or of a State with the Commission has entered into an ment for the exercise of regulatory au- y.

(Name of Manufacturer)

The label affixed to the unit, or eaflet or brochure which accom- s the package, contains adequate nation as to the precautions to served in handling and storing b product material. In the case e ck Iodine-125 reference or at on source, the information ac- anying the source must also con- irections to the licensee regard- ne waste disposal requirements it in § 20.301 of Part 20 of this er.

16553, Nov. 14, 1968, as amended at 34110, Dec. 11, 1973; 39 FR 26168, 7, 1974; 40 FR 8786, Mar. 3, 1975; 42 104, Apr. 28, 1977; 42 FR 26867, May 7; 44 FR 50325, Aug. 28, 1979]

is authorized by the regulations in n September 26, 1979, may be used e year from September 27, 1979.

§ 32.72 Manufacture and distribution of radiopharmaceuticals containing byproduct material for medical use under Part 35.

(a) An application for a specific license to manufacture and distribute radiopharmaceuticals containing byproduct material for use by persons authorized pursuant to Part 35 of this chapter will be approved if:

(1) The applicant satisfies the general requirements specified in § 30.33 of this chapter;

(2) The applicant submits evidence that:

(i) The radiopharmaceutical containing byproduct material will be manufactured, labeled, and packaged in accordance with the Federal Food, Drug and Cosmetic Act or the Public Health Service Act, such as a new drug application (NDA) approved by the Food and Drug Administration (FDA), a biologic product license issued by FDA, or a "Notice of Claimed Investigational Exemption for a New Drug" (IND) accepted by FDA; or

(ii) The manufacture and distribution of the radiopharmaceutical containing byproduct material is not subject to the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act;

(3) The applicant submits information on the radionuclide, chemical and physical form, packaging including maximum activity per package, and shielding provided by the packaging of the byproduct material that is appropriate for safe handling and storage of radiopharmaceuticals by group licensees; and

(4)(i) The label affixed to each package of the radiopharmaceutical contains information on the radionuclide, quantity, and date of assay, and the label, or the leaflet or brochure that accompanies each package, contains a statement that the U.S. Nuclear Regulatory Commission has approved distribution of the radiopharmaceutical to persons licensed to use byproduct material listed in §§ 35.100, 35.200, or 35.300, as appropriate, and to persons who hold an equivalent license issued by an Agreement State. However, labels worded in accordance with requirements that were in place on March 30, 1987 may be used until March 30, 1989.

(ii) The labels, leaflets or brochures required by this paragraph are in addition to the labeling required by the Food and Drug Administration (FDA) and they may be separate from or, with the approval of FDA, may be combined with the labeling required by FDA.

(b) If an application is filed pursuant to paragraph (a) of this section on or before October 15, 1974, for a license to manufacturer and distribute a radiopharmaceutical that was distributed commercially on or before August 16, 1974, the applicant may continue the distribution of such radiopharmaceutical to group licensees until the Commission issues the license or notifies the applicant otherwise.

[39 FR 36140, July 17, 1974, as amended at 51 FR 36937, Oct. 16, 1986]

§ 32.73 Manufacture and distribution of generators or reagent kits for preparation of radiopharmaceuticals containing byproduct material.

(a) An application for a specific license to manufacture and distribute generators or reagent kits containing byproduct material for preparation of radiopharmaceuticals by persons licensed pursuant to § 35.14 of this chapter for the uses listed in Group III of Schedule A, § 35.100 of this chapter will be approved if (See Note 1):

(1) The applicant satisfies the general requirements specified in § 30.33 of this chapter;

(2) The applicant submits evidence that:

(i) The generator or reagent kit is to be manufactured, labeled, and packaged in accordance with the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, such as new drug application (NDA) approved by the Food and Drug Administration (FDA), a biologic product license issued by FDA, or a "Notice of Claimed Investigational Exemption for a New Drug" (IND) accepted by FDA; or

(ii) The manufacture and distribution of the generator or reagent kit are not subject to the Federal Food,

Drug, and Cosmetic Act and the Public Health Service Act.

NOTE 1: Although the Commission does not regulate the manufacture and distribution of reagent kits that do not contain byproduct material, it does regulate the use of such reagent kits for the preparation of radiopharmaceuticals containing byproduct material as part of its licensing and regulation of the users of byproduct material. Any manufacturer of reagent kits that do not contain byproduct material who desires to have his reagent kits approved by the Commission for use by persons licensed pursuant to § 35.14 and Group III of Schedule A, § 35.100 of this chapter may submit the pertinent information specified in this § 32.73.

(3) The applicant submits information on the radionuclide, chemical and physical form, packaging including maximum activity per package, and shielding provided by the packaging of the byproduct material contained in the generator or reagent kit;

(4) The label affixed to the generator or reagent kit contains information on the radionuclide, quantity, and date of assay; and

(5) The label affixed to the generator or reagent kit, or the leaflet or brochure which accompanies the generator or reagent kit, contains:

(i) Adequate information, from a radiation safety standpoint, on the procedures to be followed and the equipment and shielding to be used in eluting the generator or processing radioactive material with the reagent kit, and

(ii) A statement that this generator or reagent kit (as appropriate) is approved for distribution to persons licensed by the U.S. Nuclear Regulatory Commission to use byproduct material identified in § 35.200 or under an equivalent license of an Agreement State. However, labels worded in accordance with requirements that were in place on March 30, 1987 may be used until March 30, 1989.

The labels, leaflets or brochures required by this paragraph are in addition to the labeling required by FDA and they may be separate from or, with the approval of FDA, may be combined with the labeling required by FDA.

(b) If an application is filed pursuant to paragraph (a) of this section on or before October 15, 1974, for a license to manufacture and distribute a generator or reagent kit that was distributed commercially on or before August 16, 1974, the applicant may continue the distribution of such generator or reagent kit until the Commission issues the license or notifies the applicant otherwise.

[39 FR 26148, July 17, 1974, as amended at 51 FR 36937, Oct. 16, 1986]

§ 32.74 Manufacture and distribution of sources or devices containing byproduct material for medical use.

(a) An application for a specific license to manufacture and distribute sources and devices containing byproduct material to persons licensed pursuant to Part 35 of this chapter for use as a calibration or reference source or for the uses listed in §§ 35.400 and 35.500 of this chapter will be approved if:

(1) The applicant satisfies the general requirements in § 30.33 of this chapter;

(2) The applicant submits sufficient information regarding each type of source or device pertinent to an evaluation of its radiation safety, including:

(i) The byproduct material contained, its chemical and physical form, and amount;

(ii) Details of design and construction of the source or device;

(iii) Procedures for, and results of, prototype tests to demonstrate that the source or device will maintain its integrity under stresses likely to be encountered in normal use and accidents;

(iv) For devices containing byproduct material, the radiation profile of a prototype device;

(v) Details of quality control procedures to assure that production sources and devices meet the standards of the design and prototype tests;

(vi) Procedures and standards for calibrating sources and devices;

(vii) Legend and methods for labeling sources and devices as to their radioactive content;

(viii) Instructions for handling and storing the source or device from the radiation safety standpoint; these instructions are to be included on a durable label attached to the source device or attached to a permanent storage container for the source device: *Provided*, That instructions which are too lengthy for such labels may be summarized on the label and printed in detail on a brochure which is referenced on the label;

(3) The label affixed to the source device, or to the permanent storage container for the source or device, contains information on the radionuclide, quantity and date of assay, and a statement that the U.S. Nuclear Regulatory Commission has approved distribution of the (name of source or device) to persons licensed to use byproduct material identified in §§ 35.400, or 35.500, as appropriate, or to persons who hold an equivalent license issued by an Agreement State. However, labels worded in accordance with requirements that were in place on March 30, 1987 may be used until March 30, 1989.

(b)(1) In the event the applicant desires that the source or device be required to be tested for leakage of radioactive material at intervals longer than six months, he shall include in his application sufficient information to demonstrate that such longer interval is justified by performance characteristics of the source or device or similar sources or devices and other design features that have a significant bearing on the probability or consequences of leakage of radioactive material from the source.

(2) In determining the acceptable interval for test of leakage of radioactive material, the Commission will consider information that includes, but is not limited to:

(i) Primary containment (source capsule);

(ii) Protection of primary containment;

(iii) Method of sealing containment;

(iv) Containment construction materials;

(v) Form of contained radioactive material;

(vi) Maximum temperature withstood during prototype tests;

(vii) Maximum pressure withstood during prototype tests;

(viii) Maximum quantity of contained radioactive material;

I vi.

(b) The approved information collection requirements contained in this part appear in §§ 35.13, 35.13, 35.14, 35.21, 35.22, 35.23, 35.27, 35.29, 35.31, 35.33, 35.50, 35.51, 35.53, 35.59, 35.60, 35.61, 35.70, 35.80, 35.92, 35.204, 35.205, 35.310, 35.315, 35.404, 35.605, 35.610, 35.615, 35.630, 35.633, 35.634, 35.636, 35.641, 35.643, 35.645, and 35.647.

(c) This part contains information collection requirements in addition to those approved under the control number specified in paragraph (a) of this section. These information collection requirements and the control numbers under which they are approved as follows:

(1) In § 35.12, Form NRC-313 is approved under control number 3150-0120.

§ 35.11 License required.

(a) A person shall not manufacture, produce, acquire, receive, possess, use, or transfer byproduct material for medical use except in accordance with a specific license issued by the Commission or an Agreement State, or as allowed in paragraph (b) of this section.

(b) An individual may receive, possess, use, or transfer byproduct material in accordance with the regulations in this chapter under the supervision of an authorized user as provided in § 35.25, unless prohibited by license condition.

§ 35.12 Application for license, amendment, or renewal.

(a) If the application is for medical use sited in a medical institution, only the institution's management may apply. If the application is for medical use not sited in a medical institution, any person may apply.

(b) An application for a license for medical use of byproduct material as described in §§ 35.100, 35.200, 35.300, 35.400, and 35.500 of this part must be made by filing an original and one copy of Form NRC-313, "Application for Material License." For guidance in completing the form, refer to the instructions in the most current versions of the appropriate Regulatory Guides. A request for a license amendment or renewal may be submitted as an original and one copy in letter format.

(c) An application for a license for medical use of byproduct material as described in § 35.600 of this part must be made by filing an original and one copy of Form NRC-313. For guidance in completing the form, refer to the instructions in the most current version of the appropriate Regulatory Guide. A request for a license amendment or renewal may be submitted as an original and one copy in letter format.

(d) For copies of regulatory guides, application forms, or to submit an application or an amendment request, refer to § 30.6 of this chapter.

§ 35.13 License amendments.

A licensee shall apply for and must receive a license amendment:

(a) Before it receives or uses byproduct material for a clinical procedure permitted under this Part but not permitted by the license issued pursuant to this part;

(b) Before it permits anyone, except a visiting authorized user described in § 35.27, to work as an authorized user under the license;

(c) Before it changes Radiation Safety Officers or Teletherapy Physicists;

(d) Before it orders byproduct material in excess of the amount, or radionuclide or form different than authorized on the license; and

(e) Before it adds to or changes the areas of use or address or addresses of use identified in the application or on the license.

§ 35.14 Notifications.

A licensee shall notify the Commission by letter within thirty days when an authorized user, Radiation Safety Officer, or Teletherapy Physicist permanently discontinues performance of duties under the license or has a name change, or when the licensee's mailing address changes. The licensee shall mail the report to the appropriate address identified in § 30.6 of this chapter.

§ 35.18 License issuance.

The Commission shall issue a lic for the medical use of byproduct m rial for a term of five years if:

(a) The applicant has filed F NRC-313 "Application for Mate License" in accordance with the structions in § 35.12;

(b) The applicant has paid any a cable fee as provided in Part 17 this chapter;

(c) The Commission finds the a cant equipped and committed to serve the safety standards establi by the Commission in this Chapte the protection of the public he and safety; and

(d) The applicant meets the req ments of Part 30 of this chapter.

§ 35.19 Specific exemptions.

The Commission may, upon apt tion of any interested person or its own initiative, grant such ex tions from the regulations in this as it determines are authorized b and will not endanger life or pro or the common defense and sec and are otherwise in the public i est. The Commission will revie quests for exemptions from tra and experience requirements wit assistance of its Advisory Comm on the Medical Uses of Isotopes.

Subpart B—General Administrat Requirements

§ 35.20 ALARA program.

(a) Each licensee shall develop implement a written radiation p tion program that includes prov for keeping doses ALARA.

(b) To satisfy the requireme paragraph (a) of this section:

(1) At a medical institution, ma ment, the Radiation Safety O and all authorized users must p pate in the program as request the Radiation Safety Committee.

(2) For licensees that are not cal institutions, management a authorized users must particip the program as requested by the ation Safety Officer.

(c) The program must include to workers of the program's ex and workers' responsibility to

I vii.

other, respectively. These notifica- is must be made within 24 hours er the licensee discovers the misad- inistration. If the referring physi- 'ent, or the patient's responsi- ..ive or guardian cannot be ched within 24 hours, the licensee ll notify them as soon as practica- The licensee is not required to ify the patient or the patient's re- nsible relative or guardian without consulting the referring physi- ; however, the licensee shall not y medical care for the patient be- se of this.

) Within 15 days after an initial apy misadministration report to , the licensee shall report, in writ- to the NRC Regional Office ini- y telephoned and to the referring sician, and furnish a copy of the rt to the patient or the patient's onsible relative (or guardian) if er was previously notified by the ısee under paragraph (a) of this on. The written report must in- e the licensee's name; the refer- physician's name; a brief descrip- of the event; the effect on the pa- ; the action taken to prevent re- ence; whether the licensee in- ed the patient or the patient's re- sible relative (or guardian), and if why not. The report must not in- the patient's name or other in- ation that could lead to identifi- n of the patient.

When a misadministration in- s agnostic procedure, the Ra- ı. ..fety Officer shall promptly tigate its cause, make a record for review, and retain the record as ed in § 35.33(d). The licensee also notify the referring physi- and the appropriate NRC Office ied in § 30.6 of this part in writ- n Form NRC——[1] within 15 if the misadministration involved se of byproduct material not in- d for medical use, administration dosage five-fold different from tended dosage, or administration product material such that the patient is likely to receive an organ dose greater than 2 rem or a whole body dose greater than 500 millirem. Licensees may use dosimetry tables in package inserts, corrected only for amount of radioactivity administered, to determine whether a report is required.

(d) Each licensee shall retain a record of each misadministration for ten years. The record must contain the names of all individuals involved in the event (including the physician, allied health personnel, the patient, and the patient's referring physician), the patient's social security number or identification number if one has been assigned, a brief description of the event, the effect on the patient, and the action taken, if any, to prevent recurrence.

(e) Aside from the notification requirement, nothing in this section affects any rights or duties of licensees and physicians in relation to each other, patients, or responsible relatives (or guardians).

§ 35.49 Suppliers.

A licensee may use for medical use only:

(a) Byproduct material manufactured, labeled, packaged, and distributed in accordance with a license issued pursuant to the regulations in Part 30 and §§ 32.72, 32.73, or 32.74 of this chapter or the equivalent regulations of an Agreement State;

(b) Reagent kits that have been manufactured, labeled, packaged, and distributed in accordance with an approval by the Commission pursuant to § 32.73 or an Agreement State under equivalent regulations for the preparation of radiopharmaceuticals for medical use; and

(c) Teletherapy sources manufactured and distributed in accordance with a license issued pursuant to Part 30 of this chapter or the equivalent regulations of an Agreement State.

Subpart C—General Technical Requirements

§ 35.50 Possession, use, calibration, and check of dose calibrators.

(a) A medical use licensee authorized to administer radiopharmaceuticals shall have in its possession a dose calibrator and use it to measure the amount of activity administered to each patient.

(b) A licensee shall:

(1) Check each dose calibrator for constancy with a dedicated check source at the beginning of each day of use. To satisfy the requirement of this paragraph, the check must be done on a frequently used setting with a sealed source of not less than 10 microcuries of radium-226 or 50 microcuries of any other photon-emitting radionuclide;

(2) Test each dose calibrator for accuracy upon installation and at least annually thereafter by assaying at least two sealed sources containing different radionuclides whose activity the manufacturer has determined within 5 percent of its stated activity, whose activity is at least 10 microcuries for radium-226 and 50 microcuries for any other photon-emitting radionuclide, and at least one of which has a principal photon energy between 100 keV and 500 keV;

(3) Test each dose calibrator for linearity upon installation and at least quarterly thereafter over the range of its use between the highest dosage that will be administered to a patient and 10 microcuries; and

(4) Test each dose calibrator for geometry dependence upon installation over the range of volumes and volume configurations for which it will be used. The licensee shall keep a record of this test for the duration of the use of the dose calibrator.

(c) A licensee shall also perform appropriate checks and tests required by this section following adjustment or repair of the dose calibrator.

(d) A licensee shall mathematically correct dosage readings for any geometry or linearity error that exceeds 10 percent if the dosage is greater than 10 microcuries and shall repair or replace the dose calibrator if the accuracy or constancy error exceeds 10 percent.

(e) A licensee shall retain a record of each check and test required by this section for two years unless directed otherwise. The records required in paragraphs (b)(1) through (b)(4) of this section must include:

[1] staff is developing this form and will t available before the effective date regulation. A notice of its availability published in the FEDERAL REGISTER.

II.

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

DRAFT REGULATORY GUIDE AND VALUE/IMPACT STATEMENT

August 1985
Division 10
Task FC 410-4

Contact: P. Vacca (301) 427-4002

GUIDE FOR THE PREPARATION OF APPLICATIONS FOR NUCLEAR PHARMACY LICENSES

This regulatory guide and the associated value/impact statement are being issued in draft form to involve the public in the early stages of the development of a regulatory position in this area. They have not received complete staff review and do not represent an official NRC staff position.

Public comments are being solicited on both drafts, the guide (including any implementation schedule) and the value/impact statement. Comments on the value/impact statement should be accompanied by supporting data. Comments on both drafts should be sent to the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Docketing and Service Branch, by October 31, 1985.

Requests for single copies of draft guides (which may be reproduced) or for placement on an automatic distribution list for single copies of future draft guides in specific divisions should be made in writing to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Technical Information and Document Control.

CONDITIONS

14. continued

C. If the test reveals the presence of 0.005 microcurie or more of removable contamination, the licensee shall immediately withdraw the sealed source from use and shall cause it to be decontaminated and repaired or to be disposed of in accordance with Commission regulations. A report shall be filed within 5 days of the test with the U. S. Nuclear Regulatory Commission, Region I, 631 Park Avenue, King of Prussia, Pennsylvania 19406, describing the equipment involved, the test results, and the corrective action taken.

D. Tests for leakage and/or contamination shall be performed by the licensee or by other persons specifically authorized by the Commission or an Agreement State to perform such services.

15. The licensee shall conduct a physical inventory every 6 months to account for all sealed sources received and possessed under the license. The records of the inventories shall be maintained for 2 years from the date of the inventory for inspection by the Commission, and shall include the quantities and kinds of byproduct material, manufacturer's name and model numbers, location of sealed sources and the date of the inventory.

16. The licensee may transport licensed material or deliver licensed material to a carrier for transport in accordance with the provisions of Title 10, Code of Federal Regulations, Part 71, "Packaging and Transportation of Radioactive Material."

17. Radioactive waste may be picked up from the licensee's customers and disposed of in accordance with the procedures, statements, and representations in its application dated April 1, 1985.

18. A. Radiopharmaceuticals dispensed and/or distributed for human use shall be either:

(i) Repackaged from prepared radiopharmaceuticals that are the subject of an FDA-approved "New Drug Application" (NDA) or for which FDA has accepted a "Notice of Claimed Investigational Exemption for a New Drug" (IND), or

(ii) Prepared from generators and reagent kits that are the subject of an FDA-approved NDA or for which FDA has accepted an IND.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number
XX-XXXXX-XXMD

Docket or Reference number
030-XXXXX

CONDITIONS

18. Continued

B. Prepared radiopharmaceuticals for which FDA has accepted an IND and radiopharmaceuticals prepared from generators or reagent kits for which FDA has accepted an IND shall be dispensed and/or distributed:

(i) In accordance with the directions provided by the sponsor of the IND, and

(ii) Only to physicians who have been accepted by the sponsor of the IND to participate in clinical evaluation of the drug.

The licensee shall inform in writing each physician who participates in an IND evaluation that the physician is responsible to the sponsor of the IND for use of the drug in accordance with protocols established by the sponsor and for reporting to the sponsor the clinical information obtained through use of the drug.

19. The licensee shall elute generators and prepare radioactive material with reagent kits in accordance with instructions furnished by the manufacturer on the label attached to or in the leaflet or brochure that accompanies the generator or reagent kit.

20. Any proposed changes in packaging, shielding, or labeling shall be submitted for review to the Material Licensing Branch, Division of Fuel Cycle and Material Safety, U.S. Nuclear Regulatory Commission, Washington, D. C. 20555.

21. Except as specifically provided otherwise by this license, the licensee shall possess, use, package, label, and distribute licensed material described in Items 6, 7, and 8 of this license in accordance with statements, representations, and procedures contained in application dated April 1, 1985; and letter dated June 1, 1985. The Nuclear Regulatory Commission's regulations shall govern the licensee's statements in applications or letters, unless the statements are more restrictive than the regulations.

FOR THE U.S. NUCLEAR REGULATORY COMMISSION

DATE June 15, 1985

BY VOID
Material Licensing Branch
Division of Fuel Cycle and
Material Safety
Washington, D. C. 20555

III.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 10 1988

University of California, Los Angeles
UCLA School of Medicine
Harbor-UCLA Medical Center
1000 Carson Street, Building A-13
Torrance, California 90509

Attention: Carol S. Marcus, Ph.D., M.D.
Director, Nuclear Medicine Outpatient Clinic

Dear Dr. Marcus:

Dr. Temple has requested that I reply to your letter dated July 20, 1987 regarding particular issues which affect the radiopharmaceutical community.

Because our response may have a significant impact on this promising modality, we have attempted to approach these complex regulatory issues in a thoughtful and measured manner. We hope you will understand our delay in providing this response.

I will address each point in your letter sequentially.

Radiochemicals and Chemicals vs. Radiopharmaceuticals and Pharmaceuticals

The Food, Drug, and Cosmetic Act (hereafter referred to as the Act) establishes extensive controls to assure that finished pharmaceuticals and components are safe and effective for their intended uses. A shipper or supplier may be liable to injunction and/or criminal prosecution if a new drug is distributed contrary to the provisions of the Act. This is not a new position.

FDA has for many years regarded suppliers of chemicals for prescription compounding, or for other drug uses, as fully subject to regulation under the Act's drug labeling and preclearance requirements. Suppliers must register pursuant to section 510, submit to inspection under Section 704 and meet the current good manufacturing practice requirements of Section 501(a)(2)(B). In addition, in the case of new drugs, the manufacturer of such chemicals must be approved in an NDA. These are legal requirements which we believe to be in the public interest.

As you have stated, for many years radiopharmacists have obtained radiochemicals to prepare unapproved radiopharmaceuticals for human administration. FDA has not sought to regulate under the new drug provisions of the Act this limited aspect of the practice of pharmacy, where a radiopharmacist, acting pursuant to a prescription order from a physician, compounds a radiopharmaceutical for clinical use within the institution with which he or she is affiliated.

The agency takes a different view with regard to sale of unapproved non-radioactive kits or similar ligands (not synthesized from components) for purposes of being labeled by radiopharmacists with radiochemicals. In this case, the radiopharmacist labels a commercially prepared "cold" kit or ligand, which was in all probability shipped in interstate commerce from the supplier with the intent of ultimately being used for diagnosis or treatment. An example of this is the labeling of cold mIBG with radioactive iodine I 131 for adrenal scanning. The mIBG is a drug (a component for a finished product) that has not been compounded from its individual components by the radiopharmacist, but usually has been purchased from an outside source. Similarly, the iodine I 131 being used for the labeling procedure is often supplied as a radiochemical. If the safety and effectiveness of such drugs have not been established in an approved NDA, an IND should be submitted to the FDA to provide for the clinical use of the drug. I have enclosed for your information FDA's "Nuclear Pharmacy Guideline", which discusses in detail the agency's approach to the practice of nuclear pharmacy.

Similarly, a kit or ligand for PET imaging, because of its intended use, is not an intermediate but is rather a drug that is fully subject to FDA regulation. As you probably are aware, non-radioactive reagent kits or nuclide generators are regulated as drugs under the Act when used in the preparation of a radiopharmaceutical. See 21 C.F.R. 310.3(n).

At this time, let me address some additional concerns you have raised regarding the FDA policy.

With respect to your belief that the Agency is "trespassing on the territory of other regulatory agencies", it is the FDA's ultimate responsibility to assure that any new drug, prepared for either diagnostic or therapeutic purposes, has been determined to be safe and effective for its stated purpose and is the subject of an approved NDA or an abbreviated NDA. Alternatively, the drug should be under active investigation (IND) involving controlled clinical trials to establish its safety and effectiveness. No other agency performs this task.

Regarding your remarks concerning National Laboratories, FDA does not set policy for the National Laboratories. Nothing in FDA's regulations would prohibit National Laboratories, or any one else, from submitting an IND or NDA in compliance with the requirements of the Act. Submissions have been made and are being made by National Laboratories under the new drug section of the Act.

Moreover, we do not believe that patients are being deprived of optimal care. As previously stated, the FDA has not sought to apply the new drug provision of the Act to the compounding of a radiopharmaceutical under limited circumstances consistent with the practice of pharmacy and medicine and we are aware that this practice has led to the initial development of new products and new uses of existing products. However, with regard to the distribution of kits or ligands for medical use, we have applied the new drug provisions of the Act. See FDA's "Nuclear Pharmacy Guideline," enclosed. Better quality safety and effectiveness data will be derived from studies conducted under the IND regulations and patient safety will be safeguarded. I am certain you will agree, that patients receive optimal care when they receive drugs which have been approved on the basis of data generated from adequate and well-controlled scientific studies and they have adequate prescribing information in their labeling. In addition, we welcome suppliers of unapproved radionuclides to work with the Agency so that these agents may become the subject of NDA approvals and thus be more readily available to the entire community.

For your information, the FDA has recently explicitly relaxed its regulations regarding investigations of additional unlabeled uses of approved drugs including radiopharmaceuticals. Please be advised that no IND need be submitted for such uses, if the following conditions [see final rule published in the Federal Register of March 19, 1987 (52 FR 8748-8847)] and codified at 21 CFR 312.2(b) are met:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

2. the investigation is not intended to support a significant change in the advertising for the product; and,

3. the investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product.

4. The investigation is conducted in compliance with the requirements for institutional review, informed consent and promotion and sale of investigational drugs.

In addition, an IND is not required when a physician uses an already approved drug for an unlabeled indication within the practice of medicine, which the Agency has consistently viewed as including the use of marketed drugs for unlabeled indications in the "day to day" treatment of patients. 21 CFR 312.2(a).

Radiopharmaceuticals for PET Imaging

Many of the staff at FDA, particularly those in our Division of Oncology and Radiopharmaceutical Drug Products, have spent substantial effort in exploring the various aspects of the regulation of radiopharmaceuticals for PET imaging. The clinical use of PET imaging carries a great potential for the radiopharmaceutical community and for the patients served. It also raises complex medical, legal, regulatory, compliance and management issues.

For example, although PET centers are customarily located in clinical institution settings, these centers are similar in many respects to drug manufacturing sites. Reconciling the implications that emerge just from this situation alone makes it apparent that serious consideration must be given to devising, within the Act and regulations, means of regulation that assure safe and effective PET imaging agents without placing an undue burden on either the PET centers or the FDA.

PET is not a new modality, but sufficient assurance of individual product uniformity from site to site and over time at the same site appears lacking. However it is achieved, such assurance is, of course, important in consistently obtaining the anticipated effect of PET radiopharmaceuticals in patients. Were such a goal obtainable it would be reasonable to expect, within regulatory limitations, that the amount of clinical safety and effectiveness data for each drug product among PET centers would necessarily be reduced substantially.

We are approaching the regulation of PET with an open mind and with due regard for its special nature and role in the development of new products. We intend to be flexible and creative in our approach.

Physician Sponsored INDs and Outside Review of INDs

The most efficient mechanism to get a drug through the NDA approval process is for the commercial sponsor to conduct an appropriate number of adequate and well-controlled clinical studies which are of proper design to yield data upon which the Agency may base an approval. As newer radiopharmaceutical agents have evolved, we have urged the sponsors to proceed in this more focused direction.

An important aspect of this approach includes a commitment on the part of the sponsor to limit the number of certain kinds of physician-sponsored INDs beyond those for studies deemed adequate and necessary for NDA approval. Sponsors of individual INDs may want the drug for various reasons. These principally include (1) using the drug in clinical practice without really evaluating the drug or collecting safety and effectiveness data, (2) using the drug as a specific research tool typically in a funded research investigation in an area of interest which is different from that of the commercial sponsor, and (3) evaluating the performance of the drug in a manner substantially different from the approach and setting chosen by the commercial sponsor. The last two types of INDs will collect important data, although these data may not be directly or readily applicable for use by the sponsor in the original NDA submission.

The first type of physician-sponsored IND mentioned above is less useful with regard to drug approval. Such an IND expends resources, usually does not provide usable data and may contribute to delayed approval. Thus, in an attempt to hasten the approval process we have discouraged commercial IND sponsors from freely providing a drug which is under clinical trials to additional practitioners, particularly for use under such individual physician-sponsored INDs.

The American College of Nuclear Physicians and the Society of Nuclear Medicine also expressed themselves on this matter by recommending that widespread distribution of drugs under INDs with cost recovery be avoided. The societies stated their concern on this issue and on a related issue to Dr. Frank Young, Commissioner of Food and Drugs, when they met with the FDA in August 1986:

> "Prohibit Commercialization of an IND - The widespread distribution of an IND pharmaceutical, with cost recovery, should be eliminated. This widespread distribution decreases the incentive to obtain an NDA approval. A limit on IND studies would also stimulate the timely performance of adequate and well controlled studies, and thus lead to a more rapid response during the review process." (ACNP/Scanner, Volume XII, No. 7 September 1986).

Additionally, FDA has sometimes suggested for firms, as a further means of increasing the focus and hastening approval, that they limit the number of initial indications for use of the drug. Firms are encouraged to plan and implement studies on additional indications to be submitted for supplemental approval after the drug is approved for marketing.

It should be understood that we are restricting our remarks regarding physician-sponsored INDs to cases in which a commercial sponsor is actively seeking approval for marketing the drug. FDA is certainly supportive of the concept of physician-sponsored INDs in general.

Development of a new drug can be made more burdensome by submission of a large number of INDs, the number being more of a problem than the amount of clinical data contained in the INDs. This is because in most of the INDs submitted, the physician sponsor is simply using the drug in the clinical practice of medicine. In those INDs, the amount of medical data to review is minimal and is not a significant burden on the FDA medical reviewer. I cannot agree with your suggestion that the review of such INDs is an appropriate task to share with an outside peer review group. The types of physician-sponsored INDs that would be candidates for an outside peer review group generally are not numerous enough to constitute a significant burden on the FDA medical review staff.

I thank you for your interest and concern for the nuclear medicine community. Please excuse our delay in responding, but our intent was to provide as comprehensive a response as possible to your concerns. We believe that the Agency and the community can continue to work together to resolve differences and solve problems.

Sincerely yours,

Paula Botstein MD

Paula Botstein, M.D.
Deputy Director (Medical Affairs)
Office of Drug Research and Review
Center for Drug Evaluation and Review

Enclosure

IV.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 1 6 1987

Arun Sukerkar, M.D.
Director, Department of Nuclear Medicine
Illinois Masonic Hospital
836 West Wellington Avenue
Chicago, Illinois 60657

Dear Dr. Sukerkar:

This is in response to a written request from Stephen M. Karesh, Ph.D., Consultant in Radiopharmacy, for clarification of the Agency's current policy regarding the in-house manufacture of radiopharmaceutical cold kits for use within the institution's nuclear medicine department.

The Agency considers the in-house manufacture of approved radiopharmaceutical cold kits intended for use solely within the institution as permissible and clearly within the pharmacy exemption provided for under section 510(g)(1) of the Federal Food, Drug, and Cosmetic Act. Implicit in this exemption is the need for the dispensing pharmacy to maintain adequate manufacturing records for each lot of each product manufactured, to perform appropriate quality control testing, to maintain a hard copy of the prescription or physician's order and to comply with all other aspects of pharmacy practice as required by local authorities. A publication titled Nuclear Pharmacy Guideline - Criteria for Determining When to Register as a Drug Establishment discusses this policy in greater detail. A copy may be obtained from the FDA's Office of Compliance (HFN-310).

Sincerely yours,

Robert L. West

Robert L. West
Consumer Safety Officer
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

NUCLEAR PHARMACY GUIDELINE

CRITERIA FOR DETERMINING WHEN TO REGISTER AS A DRUG ESTABLISHMENT

Date: May 1984

Office Responsible
for Guideline: Division of Drug Labeling Comliance
Office of Compliance (HFN-310)
Center for Drugs and Biologics
Food and Drug Administration
301-443-7281

MAY, 1984

NUCLEAR PHARMACY GUIDELINE
CRITERIA FOR DETERMINING WHEN TO REGISTER AS A DRUG ESTABLISHMENT

This guideline prepared by the Food and Drug Administration's Center for Drugs and Biologics states the criteria for determining when a nuclear pharmacy is required to register as a drug establishment

REGULATORY HISTORY

In the FEDERAL REGISTER of July 25, 1975 (40 FR 31298), the Food and Drug Administration (FDA) published regulations which terminated a then-existing exemption for radioactive drugs from the investigational new drug requirements of the Federal Food, Drug, and Cosmetic Act (the act). The exemption was originally published in the FEDERAL REGISTER of January 8, 1963 (28 FR 183). The effect of the termination was to require manufacturers and distributors of radioactive drug products to comply with the act and applicable regulations, including requirements for registration, drug listing, current good manufacturing practice, new drug applications, investigational new drugs, labeling, and advertising. With the publication of the termination, the FDA replaced the Nuclear Regulatory Commission (NRC) as the agency responsible for regulating the safety and effectiveness of radioactive drugs as they affect patients. Certain residual authority to control the use of radioactive materials, discussed in greater detail below, remained with the NRC.

The FDA has legislative authority under the Federal Food, Drug, and Cosmetic Act to regulate drugs for human use. Section 510 of the act (21 U.S.C. 360) requires drug establishments to register with FDA. Other provisions of the act provide the authority for FDA to regulate the manufacture, sale, and distribution in interstate commerce of new drugs, to assure that they are safe and effective for their intended use (Secs. 501, 502, 505 of the act; 21 U.S.C. 351, 352, 355). Section 201(p) of the act defines the term "new drug" generally to mean a drug not generally recognized by qualified experts to be safe and effective. It has been the agency's position that all radioactive drugs, including radioactive biological products, are new drugs except for those generally recognized as safe and effective when administered for research under the conditions set forth in § 361.1(b) of the act (21 CFR 361.1(b)).

Under section 510(g)(1) of the act, a pharmacy, including a nuclear pharmacy, is exempt from complying with the need to register as a drug establishment if (1) it operates in conformance with any applicable local laws regulating the practice of pharmacy and medicine, (2) it is regularly engaged in dispensing prescription drugs upon the prescription of practitioners licensed to administer prescription drugs to patients under their care in the course of their professional practice, and (3) it does not manufacture, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling at retail. Thus, to the extent these requirements are met, a nuclear pharmacy may prepare a radioactive drug without being required to register with FDA

as a drug establishment under section 510. Under other circumstances, however, registration of a nuclear pharmacy will be required.

As a matter of practice, in addition to nuclear pharmacies, nuclear medicine laboratories under the control of a physician may also prepare radioactive drugs. Section 510(g)(2) of the act specifically permits licensed practitioners to manufacture drugs without having to register as drug manufacturers provided the drugs are solely for use in the course of the practioner's professional practice.

Because the NRC has legislative authority to license and regulate all aspects of the possession and use of radioactive by-product (i.e., reactor-produced) materials in order to protect health and minimize danger to life or property, it also has certain regulatory authority over radioactive drugs. Both radioactive drug manufacturers and nuclear pharmacies are required, therefore, to comply with applicable regulations of the NRC as well as those of FDA.

In a separate notice also published in the FEDERAL REGISTER of July 25, 1975 (40 FR 31314), FDA announced its intention to clarify the responsibilities of nuclear pharmacies under the act. The notice contained an interim enforcement policy pertaining to nuclear pharmacies. It stated that FDA would not take regulatory action against a nuclear pharmacy that did not comply with the requirements of the act, except when regulatory action was necessary to protect the public health, provided the pharmacy (1) complied with applicable local laws regulating the practice of pharmacy, and (2) was licensed, when applicable, by the NRC or an Agreement

State to possess, use, or transfer radioactive drugs. (An Agreement State is one that, under formal agreement with the NRC, is authorized to license, under Federal law, persons engaged in the possession, use, or transfer of source, by-product or special nuclear materials in that State). FDA adopted this interim enforcement policy in 1975 to avoid any disruption in the practice of nuclear pharmacy and nuclear medicine throughout the United States. FDA concluded that, although radioactive drug manufacturers would be subject to the act, it would not take regulatory action for the failure of nuclear pharmacies to comply with the requirements of the act, under the conditions specified, until the status of nuclear pharmacies was further clarified.

DEVELOPMENT OF NUCLEAR PHARMACIES

Since 1946, when artificially produced radioisotopes became available in quantity, there has been a rapid growth in the medical use of radioactive drugs, including radioactive biological products, to diagnose and treat disease. Radioactive drugs are administered for two different purposes: as a radiation source, and as a radioactive tracer. As a radiation source their principal role is in therapy; as a radioactive tracer they are used primarily for diagnostic purposes.

When radioactive drugs first became generally available, they were usually prepared by commercial drug manufacturers under approved new drug applications (NDA's) and shipped to users in a form suitable for direct

administration to patients. As the use of radioactive drugs increased within hospitals, units within hospitals were often created to receive and store all incoming radioactive drugs. In most hospitals--where, in fact, most radioactive drugs are administered--those units often became part of the pharmacy department. Pharmacies employing registered pharmacists and other personnel having specialized training and experience in compounding, preparing, storing, and dispensing radioactive drugs became known specifically as "nuclear pharmacies."

Initially, the activities of a nuclear pharmacy included (1) purchasing a commercially prepared radioactive drug from a drug manufacturer who held an approved NDA and dispensing the drug in its original unopened container, (2) dispensing a single dose from a multiple-dose container of a commercially prepared radioactive drug, and (3) diluting (including adjustments of buffers, bacteriostatic agents, and stabilizers) and repackaging a commercially prepared radioactive drug for subsequent use or distribution. As the training and experience of nuclear pharmacists increased, some nuclear pharmacies began preparing their own radioactive drugs.

One method used by nuclear pharmacies to prepare radioactive drugs was to add a radionuclide to a nonradioactive substance, usually a drug product, resulting in what is referred to as a "labeled compound." In nuclear medicine the term "labeling" refers to the process of adding a radioisotope to a suitable nonradioactive substance. In this document, this process is referred to as "radiolabeling" to avoid confusion with the term "labeling" as defined in section 201(m) of the act.

As technology developed, and in order to reduce the radiation dose to patients, radioactive drugs with shorter-lived radionuclides were introduced. Because of their short half-lives, many of these drugs must be prepared in a final dosage form shortly before they are to be administered to patients. Thus, these drugs had to be prepared at a facility close to where they would be administered. Otherwise the delivery time could be so long that significant radioactive decay would take place before the drug was administered. The ability to prepare radioactive drugs with short half-lives became possible, in part, through the use of a radionuclide generator. A radionuclide generator contains a glass or plastic column filled with an adsorbant, such as a resin or alumina, in which the long-lived "parent" radionuclide is retained. Radioactive decay of the long-lived parent radionuclide results in the production of a short-lived "daughter" radionuclide which is eluted by passing an appropriate liquid or gas through the column. These radionuclides are then used by a nuclear pharmacy to prepare short-lived radioactive drugs, often by using a nonradioactive kit. A "nonradioactive kit" or "reagent kit" contains all the necessary ingredients, except the radionuclide, for making a radioactive drug product. By adding the radionuclide to the nonradioactive kit according to the directions accompanying the kit, a radioactive drug product of specified purity can be produced, often just prior to administration. Most nonradioactive kits are prepared by a commercial manufacturer under an approved NDA, but some nuclear pharmacies are now preparing their own kits.

Another aspect in the development of nuclear pharmacies has been their physical location and extent of activities. Most nuclear pharmacies are located in hospitals and dispense radioactive drugs only within the institution in which they are located. As the practice of nuclear pharmacies has matured, some nuclear pharmacies, although located in a particular institution, may supply radioactive drugs to other institutions that do not have nuclear pharmacies. In other instances, some nuclear pharmacies may be completely independent of any institution and may supply radioactive drugs to a number of institutions and practitioners. Distribution of radioactive drugs by a nuclear pharmacy may thus be limited to (1) one institution, (2) a few institutions and practitioners in the vicinity of the nuclear pharmacy, or (3) a large number of institutions and practitioners in a large metropolitan or geographic area, which may be located in more than one State.

ACTIVITIES OF NUCLEAR PHARMACIES

Activities of a nuclear pharmacy may include:

- Purchasing a commercially prepared radioactive drug product which is marketed under an approved NDA and dispensing the drug in its original unopened container.

- Repacking a radioactive drug product which is the subject of an approved NDA for subsequent use or distribution.

- Dispensing a single dose, or series of single doses, from a multiple-dose container of an approved radioactive drug product. For example, dispensing single capsules of radioactive sodium iodide, drawing a single dose of a radioactive drug into a syringe, or drawing a number of single doses of a radioactive drug into syringes.

- Diluting and repackaging an approved radioactive drug product, such as adding water for injection to reduce the concentration of the active components, and adjustment of buffers, bacteriostatic agents and stabilizers.

- Eluting an approved radionuclide generator and using the eluate to radiolabel a nonradioactive kit to prepare a radioactive drug product.

- Manufacturing a nonradioactive kit for subsequent use in preparing a radioactive drug product.

- Preparing a radioactive drug product by using a commercially prepared radionuclide or a radionuclide obtained from a nuclear reactor or particle accelerator to which the nuclear pharmacy has access.

Some activities of a nuclear pharmacy clearly involve pharmacy practice that qualify for the statutory exemption available to pharmacies. Other activities, however, are operations that would require the establishment to

register under section 510 of the act. Nuclear pharmacies that are required to register under the act will also be subject to the drug listing provisions of section 510 of the act and FDA's regulations under 21 Part 207, the current good manufacturing practice requirements of section 501 of the act and FDA's regulations under 21 CFR Parts 210 and 211, and the factory inspection provisions of section 704 of the act. A nuclear pharmacy, particularly one that is required to register, may also be subject to the new drug provisions of section 505 of the act and FDA's regulations under 21 CFR Parts 310, 312, and 314.

All pharmacies, including nuclear pharmacies that qualify for the statutory exemption, are subject to section 501 of the act. Section 501(a)(2)(B) of the act deems a drug to be adulterated if the facilities or controls used for its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices. Although nuclear pharmacies are required to comply with section 501(a)(2)(B) of the act, it has not been the policy of FDA to apply the current good manufacturing practice regulations under 21 CFR Parts 210 and 211 to pharmacies as these regulations are not specifically applicable to many pharmacy operations.

All pharmacies, including nuclear pharmacies, are also subject to the factory inspection provisions of section 704 of the act. This section authorizes, among other things, the inspection of any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held for introduction into interstate

commerce or after such introduction into interstate commerce. Thus, as establishments holding drugs after their introduction into interstate commerce, all pharmacies, including nuclear pharmacies, are subject to inspection under this provision. In addition, nuclear pharmacies that are required to register as drug establishments under section 510 of the act are subject to more extensive provisions of the inspectional authority of section 704. Although subject to inspection, the agency is not required to inspect, and except for reasonable cause normally does not inspect pharmacies, including nuclear pharmacies, operating entirely under the pharmacy exemptions in the act. However, the agency will be required, under section 510(b) of the act (21 U.S.C. 360(b)), to inspect pharmacies, including nuclear pharmacies, that are registered as drug establishments under section § 510(b) of the act.

DEVELOPMENT OF GUIDELINE

To better understand the nature of the practice of nuclear pharmacy, including the types of activities and organizational settings in which these activities are performed, FDA has met with a number of professionals, professional organizations, and Federal and State agencies having an interest in nuclear medicine and pharmacy. A meeting, jointly sponsored by the State of Washington Radiation Control Unit and FDA's regional office in Seattle, was held in Seattle on November 12 and 13, 1975. Representatives of a number of State radiation control agencies,

two State boards of pharmacy, the American Pharmaceutical Association, and several practicing nuclear pharmacists and others attended this meeting. Issues discussed at this meeting were: (1) What is a nuclear pharmacist, and what kind of qualifications should he/she have for preparing and dispensing radioactive drugs? (2) What credentialing requirements are appropriate for nonpharmacist dispensers of radioactive drugs? (3) What is the definition of radiopharmacy or nuclear pharmacy, and what constitutes a prescription for a radioactive drug? (4) What are the requirements for the preparation and supply of radioactive new drugs including those for investigational purposes? A summary of this meeting is available for inspection at FDA's Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD, 20857, under Docket No. 80D-0069.

FDA believes the first three questions involve primarily State and local laws regulating the practice of pharmacy. However, under the act the answers to these questions may determine, in a given situation, whether a pharmacy is exempt from the registration provisions of the act. Thus the licensure procedures that designate a person as being a pharmacist, the extent that a pharmacist may delegate authority, and the type of order that qualifies as a prescription are all matters that are determined under State laws, but they may also affect the application of the act to pharmacies.

To aid the agency in establishing criteria to determine what activities of a nuclear pharmacy require registration, a subcommittee of FDA's Radiopharmaceuticals Advisory Committee was appointed in October

1975 to consider and report on issues relating to nuclear pharmacy. Specifically, the subcommittee was requested to consider the following two questions: What types of operations engaged in by nuclear pharmacies should be regulated to some degree by FDA? What is the relative urgency for issuing new regulations or statements of policy, if they are needed?

The subcommittee reported to the Radiopharmaceuticals Advisory Committee on April 15, 1976. In preparing its report the subcommittee received suggestions and recommendations from numerous individuals and organizations. In addition, it considered the public testimony presented on these two questions before the full committee in April 1975, and the statements and discussions at a meeting of the subcommittee in January 1976. A copy of this report is also available for inspection at FDA's Dockets Management Branch (address above) under Docket No. 80D-0069.

In considering which nuclear pharmacy operations should be regulated by FDA, the subcommittee concluded that if the radioactive drug was prepared and dispensed under a prescription, the laws and regulations governing the practice of pharmacy and medicine at the State level should apply and the nuclear pharmacy should be considered as engaging in the practice of pharmacy. On the other hand, the subcommittee stated that the presence of a third party in the distribution of a prescription drug, between the location where the product is formulated, compounded, or manufactured and the point where it is administered to patients, changes the practice to one of manufacturing. Examples of this type of situation that were cited by the subcommittee included one in which a nuclear

pharmacy sells radioactive drugs to a second pharmacy for dispensing by the second pharmacy under a prescription, and one in which a nuclear pharmacy sells to other pharmacies bulk quantities of nonradioactive kits that it develops. In each case the first pharmacy would be a manufacturer under the act and be required to register under Section 510 of the act.

The subcommittee also recognized that radioactive drugs are often administered by a nuclear medicine unit in a single institution. Such a nuclear medicine unit may operate a nuclear pharmacy and maintain control over any radioactive drug manufactured or compounded within the pharmacy until it is dispensed. Here, the subcommittee concluded that the high level of control exercised over the drug precluded any need for registration.

The subcommittee recommended to FDA that substantive changes in FDA regulations, as they pertain to true nuclear pharmacies, were not needed. The subcommittee recommended that individual State boards of pharmacy rather than FDA should regulate nuclear pharmacies in the same manner as they now regulate traditional pharmacies which do not compound or dispense radioactive drugs.

At the same time, the subcommittee recommended that FDA clarify "the issue of nuclear pharmacy manufacturing versus traditional pharmacy compounding with a policy statement; this statement should indicate that the same criteria will be used in making this determination for radioactive drugs as those which are used for nonradioactive drugs. This statement will also affirm that certain of the operational procedures in which some nuclear pharmacies engage are, in fact, manufacturing, and must be regulated as such."

CRITERIA FOR DETERMINING WHEN A NUCLEAR PHARMACY MUST REGISTER AS A DRUG ESTABLISHMENT

FDA agrees with the subcommittee's recommendation that, to the extent practicable, the criteria for registration as a drug establishment for nuclear pharmacies should be the same as those for traditional pharmacies. The agency further agrees with the subcommittee that regulations applicable to nuclear pharmacies contemplated in the July 25, 1975 notice are not needed at this time and that FDA can fulfill its regulatory responsibilities in this area by issuing a guideline on the subject. This guideline also responds to the subcommittee recommendation that FDA notify State boards of pharmacy and other State and Federal agencies of FDA's policy in the area of nuclear pharmacies.

Section 510(g)(1) of the act (21 U.S.C. 360(g)(1)) states that pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine are exempt from the drug registration provisions of the act. For the exemption to apply they must be regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and they must not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail. Because many States do

not appear to have laws that apply specifically to the practice of nuclear pharmacy, and may not have mechanisms specifically designed for certifying nuclear pharmacists, and because many nuclear pharmacies require specially trained personnel whose activities resemble those of drug manufacturers more than those of traditional pharmacy practice, FDA does not believe that the "pharmacy" exemption of the drug registration provisions of section 510(g)(1) of the act (21 U.S.C. 360(g)(1)) applies to all so-called "nuclear pharmacies." FDA's regulation of nuclear pharmacies will be based on a reasonable application of the provisions of section 510(g)(1) of the act to nuclear pharmacies and it will treat these nuclear pharmacies as other pharmacies have been traditionally treated under this section. Therefore, a pharmacy, including a nuclear pharmacy, whose activities are consistent with section 510(g)(1) of the act will be exempt from registering as a drug establishment and from complying with other requirements that flow from registration. Conversely, a pharmacy, including a nuclear pharmacy, whose activities are outside the provisions of section 510(g)(1) of the act will be subject to the registration provisions of the act and to those requirements that are concomitant to registration.

To operate under applicable local laws regulating the practice of pharmacy and medicine may mean that a nuclear pharmacy must be operated under the supervision of a pharmacist, registered in the State to practice pharmacy. In States with such requirements, nuclear medical laboratories operated by chemists or physicists who are not also registered pharmacists will not qualify for the exemption from registration under section 510(g)(1) of the act regardless of the activity in which the facility engages.

Certain activities of nuclear pharmacies are clearly within the pharmacy exemption of section 510(g)(1) of the act. For example, in a situation where the nuclear pharmacy is operating within applicable local laws regulating the practice of pharmacy and only prepares and dispenses a radioactive drug upon receipt of a "valid prescription," the pharmacy exemption clearly applies. FDA views the term "valid prescription" to mean an order that qualifies as a prescription under State law for a prescription drug, from a practitioner licensed to administer the drug to a patient under the care of the practitioner in the course of his or her professional practice. Further, although the act does not define the term "prescription," section 503(b)(2) of the act states that any drug dispensed by filling a prescription of a practitioner licensed by law to administer the drug is exempt from certain of the misbranding provisions of the act if it bears a label containing the name and address of the dispenser, the serial number and date of the prescription or its filling and, if stated in the prescription, the name of the patient and directions for use and cautionary statements, if any, contained in the prescription. Thus, except for prescriptions for controlled drugs, Federal law requires the name of the patient to appear on the label of the prescribed drug only when this information is stated in the prescription by the physician. However, without stating the precise format of a prescription, the act contemplates that certain information will ordinarily be supplied by the licensed practitioner to the pharmacist. Further, the act implies that a prescription is written with a particular patient in mind. In addition, many States, as part of their pharmacy practice statutes, require the patient's full name.

In the traditional practice of pharmacy, prescriptions are usually handled differently depending upon whether the prescriber and patient are in an institutional setting or in a private setting. In the institutional setting, the patient's prescription is usually forwarded to the pharmacy by the nursing staff and the prescribed drug is then sent back to the nursing staff for storage without the institutionalized patient ever obtaining possession of the prescription or of the prescribed drug. In the private setting, the prescriber usually hands the prescription to the patient, who takes it to their pharmacy of choice and receives the prescribed drug from the pharmacist. In either situation, however, the prescription is normally written for a specific patient. Rarely, in the private setting, is a prescription written for more than one patient. One example of such a situation would be when all members of a single family are being treated for the same condition with the same drug, e.g., pinworms. In such a situation it is considered appropriate to write and dispense one prescription for the entire family rather than write and dispense separate prescriptions for each family member. However, in such a situation, a member of the family normally obtains possession of the prescription and takes it to a pharmacy to be filled.

The agency believes that, although traditional pharmacy practice concepts should apply to nuclear pharmacies to the extent possible, the unique nature involved in the preparation, handling and administration of radioactive drugs might require some departures from the traditional pharmacy practice. For example, when dealing with radioactive drugs the

patient, whether or not in an institution, normally does not obtain possession of the prescription or of the prescribed drug. Usually, the physician orders the drug from a nuclear pharmacy which dispenses it directly to the physician for administration to the patient under the physician's supervision. Further, because most radioactive drugs are intended for diagnostic purposes, they must be administered to the patient at a facility having the specialized equipment necessary for the diagnostic procedure to be performed.

The agency is also aware that in nuclear pharmacy there are instances where physicians in private practice specializing in nuclear medicine, as well as physicians specializing in nuclear medicine connected with a private clinic, will schedule several patients to undergo the same diagnostic procedure using the same injectable radioactive drug on a particular day. Rather than order a separate container of the drug for each patient, a multiple dose container of the radioactive drug to be administered to all the patients undergoing the same procedure is ordered. In addition, the physician or clinic may have a standing order with the nuclear pharmacy to supply a multiple-dose container of a particular radioactive drug on a certain day of the week to be administered to patients scheduled to undergo a common diagnostic procedure. The practice of having one order cover several unrelated, but scheduled patients and supplying a multiple-dose container for such patients is not normally considered to be the traditional pharmacy practice. However, the agency has evaluated this practice with respect to the dispensing of

radiopharmaceuticals and concludes that, while it is a departure from traditional pharmacy practice, it is, given the unique circumstances of nuclear medicine, a reasonable variant of it, and thus appropriately considered accepted pharmacy practice. Accordingly, FDA will not require a nuclear pharmacy engaging in such activities to register as a drug establishment provided the dispensing pharmacy maintains a hard copy of the prescription or physician's order as required by section 503(b)(2) of the act and the pharmacy otherwise complies with all aspects of traditional pharmacy practice. Although the above referenced practices will not subject a nuclear pharmacy to registration with the FDA as a drug establishment, a nuclear pharmacy should also determine that such practices are consistent with applicable State pharmacy laws.

In certain situations, the fact that the preparation of the radioactive drug results in the preparation of a new drug or requires more technical equipment and expertise than that of a nonradioactive prescription drug does not nullify the pharmacy exemption. Likewise, neither the location of the patient nor the location or ownership of the nuclear pharmacy would nullify the pharmacy exemption. Several different situations involving a nuclear pharmacy operating under applicable State pharmacy laws and preparing and dispensing a radioactive drug upon receipt of a valid prescription are set forth in the examples given below.

In other situations, the activities of a nuclear pharmacy will be clearly outside the pharmacy exemption. For example, if a nuclear pharmacy prepares a nonradioactive kit for sale to other nuclear pharmacies which add the radionuclide for dispensing under prescription,

the activity of the first pharmacy clearly falls outside the pharmacy exemption. The examples below give several situations in which the pharmacy exemption does not apply because there is no prescription.

Nonetheless, in some situations, it will not be clear whether the activities of a nuclear pharmacy will fall within the pharmacy exemption. Many involve nuclear pharmacies that are located within a hospital. To determine if the pharmacy exemption applies, FDA believes it will be helpful to compare the activities of a hospital nuclear pharmacy with the activities of a traditional hospital pharmacy. In addition to filling and dispensing valid prescriptions for both inpatients and outpatients, a traditional hospital pharmacy may also send prescription drugs to a ward or clinic within the hospital upon the order of an authorized person. The drug, when sent to the ward or clinic, is not intended for any specific patient, but is intended to be used by the ward or clinic as needed when a licensed practitioner orders the drug in a patient's medical record. The term "ward or floor stock" has been applied to drugs made available in this manner. Because these drugs are under the control of the pharmacy and the institution within which the ward or clinic is located and the drug is prescribed by a licensed practitioner for a particular patient, this activity will be considered to fall within the pharmacy exemption. Under the same rationale, if a hospital nuclear pharmacy prepares a radioactive drug and dispenses it to a nuclear medicine clinic or department located within the hospital upon an order for the drug by an authorized person, even though the drug were

in a multiple-dose container, the pharmacy exemption would apply. Of course, because of their short half-life, it would not be expected that radioactive drugs would be maintained as ward or floor stock in the same manner as other drugs.

On occasion, a traditional hospital pharmacy may, upon request of another pharmacy, send a drug product in its original unopened container to another pharmacy. This situation may arise when the second pharmacy finds that it is out of stock of a particular drug product. Provided the first pharmacy did not manufacture the drug product, it would not be required to register for such an activity. Likewise, a nuclear pharmacy can send a radioactive drug product marketed under an approved NDA in its original unopened container to another nuclear pharmacy upon request without being subject to the registration provision of the act.

The agency is aware that some nuclear pharmacies have been instrumental in the development of new radioactive drugs or new uses for existing radioactive drugs. Nuclear pharmacies may also prepare new radioactive drugs that are not commercially available, but whose use and preparation have been described in the medical literature. Physicians that write a prescription for a drug that must be compounded by a pharmacist bear the professional responsibility to base its use on sound scientific rationale or medical evidence. The agency believes that as long as the pharmacist does not engage in activities that fall outside the normal practice of pharmacy, such use of a drug in the practice of medicine does not require

an Investigational New Drug Application (IND) or NDA. However, if a pharmacist does engage in activities that fall outside the normal practice of pharmacy, the pharmacy would legally have to be registered notwithstanding that it may be filling physician's orders. Therefore, depending upon how such a drug is prepared, promoted, and distributed, its preparation may fall outside the normal practice of pharmacy and not qualify for the pharmacy exemption. In such cases, even if the drug were dispensed on prescription, the nuclear pharmacy would have to comply with the new drug provisions of the act even though it may not be required to register under section 510 of the act (though it may be required to do both). Because the particular circumstances surrounding the operation of the nuclear pharmacy would have to be examined in detail to determine whether the pharmacy is operating within the practice of pharmacy, such situations will have to be decided on a case-by-case basis. An example where a nuclear pharmacy would have to comply with the new drug provisions is where the nuclear pharmacy has developed a rechargeable generator, such as a generator used in preparing Technetium Tc 99^{m} by being charged with Molybdenum Mo 99. Each recharging of the generator is considered the manufacturing of a new drug by the agency. An NDA would be required to cover all phases in the development and use of this type of generator, from its construction to the finished product, including how many times it could be recharged.

It is obvious from this discussion that certain types of nuclear pharmacy activities may be conducted under the pharmacy exemption while others conducted by the same nuclear pharmacy may not. The nuclear

pharmacy must register with FDA for activities that are not within the pharmacy exemption, irrespective of how small a portion they are of the pharmacy's total activities. Under this policy some nuclear pharmacies not now registered will be required to register. Nonetheless, this guideline does not impose new requirements on these establishments. Rather, it applies existing requirements to facilities whose functions have for the first time been examined and quantified. Pharmacies, including nuclear pharmacies, are considered as drug establishments and are subject to the provisions of the Federal Food, Drug, and Cosmetic Act to the extent they are not specifically exempt, including the provisions of sections 501, 502, 503 and the applicable part of the factory inspection provision in section 704. Establishments that are required to register are also subject to the current good manufacturing practice requirements of section 501 of the act and FDA's regulations under 21 CFR Parts 210 and 211, and the factory inspection provisions of section 704 of the act. In addition, an establishment manufacturing a "new drug", or a pharmacy that has itself developed a new drug, will also be subject to the provisions of section 505 of the act and applicable FDA regulations under 21 CFR Parts 310, 312, and 314. Nuclear pharmacies may obtain information and appropriate forms for registering as a drug establishment from FDA Regional or District Offices or by writing directly to the Center for Drugs and Biologics, Drug Listing Branch (HFN-315), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

The examples that follow cover most activities of nuclear pharmacies. Obviously, they cannot represent all possible situations. In addition, it must be remembered that in many situations the particular circumstances surrounding the operation of a nuclear pharmacy may have to be examined in detail to determine whether the pharmacy is operating within the practice of pharmacy, and such situations will have to be decided on a case-by-case basis. Anyone may seek an opinion whether a particular activity qualifies for the pharmacy exemption by writing to the person responsible for maintaining the guideline named above.

Therefore, the agency makes available the following examples reflecting the agency's policy for examining functions of a nuclear pharmacy to determine if they are required to register.

EXAMPLES OF WHEN A NUCLEAR PHARMACY MUST REGISTER AS A DRUG ESTABLISHMENT

Source of drug	Activities of the nuclear pharmacy	Registration required
A. Radioactive drug is supplied by a manufacturer. (Product is subject of an approved NDA or IND)	1. Dispenses the drug under a prescription in the manufacturer's original container.	1. No
	2. After storing the drug, ships the drug in the manufacturer's original container to another nuclear pharmacy or to a physician with or without having received a prescription.	2. No

	3. Fills the drug into single or multiple-dose containers in anticipation of a future need and its subsequent dispensing under a prescription.	3. No
	4. Dispenses a drug that was diluted or filled into single or multiple dose containers upon receipt of a prescription.	4. No
	5. Dilutes or fills the drug into single- or multiple-dose containers and dispenses the drug without a prescription but upon receipt of an appropriate order, for use within the same institution.	5. No
	6. Upon an order from a physician, dilutes or fills the drug into multiple-dose containers and ships the drug to the physician as part of accepted pharmacy practice.	6. No
	7. Dilutes or fills the drug into single- or multiple-dose containers and ships it without a prescription to another nuclear pharmacy or institution that, irrespective of its location or ownership, is recognized as a separate entity by FDA.	7. Yes
B. Radioactive drug (not involving use of a nonradioactive kit) prepared by the nuclear pharmacy.	1. Upon receipt of a prescription, prepares a radioactive drug and dispenses it.	1. No

	2. Prepares a radioactive drug in anticipation of a future need and its subsequent dispensing under a prescription.	2. No
	3. Prepares a radioactive drug and dispenses it without a prescription, but upon receipt of an appropriate order for use within the same institution.	3. No
	4. Operates an accelerator or nuclear reactor to produce radionuclides and radiochemicals to manufacture radioactive drugs to be dispensed under a prescription.	4. No
	5. Upon a request from a physician, prepares a drug in multiple-dose containers and ships the drug to the physician as part of accepted pharmacy practice.	5. No
	6. Prepares a radioactive drug and ships it without a prescription to another pharmacy or institution that, irrespective of its location or ownership, is recognized as a separate entity by FDA.	6. Yes
	7. Prepares radiochemicals and ships them to other nuclear pharmacies or institutions as drug components.	7. Yes
C. A reagent kit and generator are supplied by a manufacturer. (The kit and generator are subject to an approved NDA or IND).	1. Radiolabels the reagent kit according to the manufacturer's directions and dispenses the drug under a prescription.	1. No

	2. Radiolabels a reagent kit in anticipation of a future need and its subsequent dispensing under a prescription.	3. No
	3. Upon request from a physician, radiolabels a reagent kit and ships the drug to the physician as part of accepted pharmacy practice.	3. No
	4. Radiolabels a reagent kit and ships it without a prescription to another pharmacy or institution that, irrespective of its location or ownership, is recognized as a separate entity by FDA.	4. Yes
D. A reagent kit is prepared by the nuclear pharmacy.	1. Upon receipt of a prescription, prepares and radiolabels the reagent kit and dispenses it.	1. No
	2. Prepares a reagent kit in anticipation of a future need. Upon receipt of a prescription, radiolabels and dispenses it.	2. No
	3. Upon a request from a physician, prepares reagent kits and ships them (either before or after radiolabeling) to the physician as part of accepted pharmacy practice.	3. No
	4. Prepares a reagent kit and ships it without a prescription, either before or after radiolabeling, to another pharmacy or institution that, irrespective of its location or ownership, is recognized as a separate entity by FDA.	4. Yes

E. Radioactive drug or reagent kit obtained from another nuclear pharmacy, institution, or practitioner.	1. Uses the radioactive drug or reagent kit to perform one or more steps in the manufacture of a radioactive drug as a service for the nuclear pharmacy or institution that supplied the radioactive drug or kit, i.e., custom manufacturing.	1. Yes

Attachment: Summary of Comments on Proposed Guideline for Nuclear Pharmacies Describing Activities that Require Registration as a Drug Establishment and Agency Responses.

Attachment

SUMMARY OF COMMENTS ON PROPOSED GUIDELINE FOR NUCLEAR PHARMACIES DESCRIBING ACTIVITIES THAT REQUIRE REGISTRATION AS A DRUG ESTABLISHMENT AND AGENCY RESPONSES

[Docket No. 80D-0069, 75N-0069]

In the FEDERAL REGISTER of April 11, 1980, (45 FR 24920) the agency announced the availability of a proposed guideline that would assist nuclear pharmacies in determining if they are required to register as drug establishments under section 510 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360). Twelve comments were received in response to the proposed guideline. A summary of the comments and the agency's response to each are as follows:

1. Several comments cited specific fact situations and asked if registration was necessary. The specific questions were as follows:

(a) One comment asked if registration is necessary if a nuclear pharmacist purchases raw materials, prepares a radioactive drug product and then dispenses the drug product upon receipt of a prescription.

(b) One comment asked if registration is required if a nuclear pharmacist prepares a radioactive drug in bulk at one location, transfers the bulk drug to a second pharmacy where the same nuclear pharmacist also works and uses the material in filling a prescription.

(c) Several comments asked if registration is required if a pharmacist prepares a prescription using a commercial reagent kit, but deviates from the instructions accompanying the reagent kit, such as by adding ascorbic acid.

(d) One comment asked if registration is required when a technician prepares radioactive drugs under either direct or indirect supervision of a physician and then delivers the drug to the physician at multiple sites.

Certain activities of nuclear pharmacies are clearly within the pharmacy exemption of section 510(g)(1)of the Act (21 U.S.C. 360(g)(1)). Likewise, certain other activities of nuclear pharmacies will be clearly outside the pharmacy exemption. However, in many situations, the particular circumstances surrounding the operation of a nuclear pharmacy may have to be examined in detail to determine whether the pharmacy is operating within the practice of pharmacy and such situations will have to be decided on a case-by-case basis. Therefore, the following responses to the question posed by the comments are generalized and are not intended to resolve individual fact situations. Persons seeking guidance on individual situations should contact Division of Drug Labeling Compliance (HFN-310), Office of Compliance, Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, (301)443-7281.

(a) Normally, a nuclear pharmacy that prepares a drug product from raw materials and dispenses it under a prescription is not required to register. (See B. 1. of the guideline).

(b) The fact that the same nuclear pharmacist is involved with the drug at two pharmacies is not relevant to the need to register, nor is necessarily the fact that both pharmacies have common ownership. The agency would have to examine such an arrangment as a whole. However, FDA would consider one relevant factor to be whether the local State Board of Pharmacy recognized the two pharmacies as a single entity and issued them

a single license. In such a case transfer would likely not require registration. However, if a state board considered the pharmacies as two distinct entities, and required separate licensure, then the pharmacy that planned to ship the bulk material would likely be required to register as a drug establishment. Because state pharmacy boards may differ on their treatment of such arrangements, other factors would normally also be considered.

(c) The guideline did not discuss modifications that might be made to an approved reagent kit because issues apart from registration are primarily involved. The agency reviews considerable data before approving an NDA for a reagent kit and concludes that if the manufacturer's instructions are followed, a safe and effective radioactive drug will be produced from the reagent kit. Thus, if the instructions are followed, a physician can be assured that the product prescribed has the properties it purports to possess. If a pharmacist deviates from the manufacturers instruction, apart from as a prescriber may have directed, the possibility of misbranding or adulterating the drug product must be considered. The addition of ascorbic acid as cited here or other uses of a pharmaceutical necessity in compounding a prescription does not subject the pharmacy to registration, but pharmacists are not exempt from the misbranding and adulteration provisions of the act and must rely to a large degree on their professional judgment as to when and the extent to which modifications to an approved new drug are appropriate.

(d) Registration would not be required if a technician prepares radioactive drugs under the supervision of a physician solely for use by

that physician in the course of his or her professional practice. However, registration would be required if the drugs are used by other physicians, or if the drugs are sold to the multiple sites mentioned in the comment.

2. Several comments asked if practices such as modifying a reagent kit would make the resulting product a new drug.

If the nuclear pharmacist modifies a kit as directed by prescription, and dispenses it under the prescription, an NDA would not normally be needed. (See, however, the response to comment 3 for factors to be considered). If distributed without a prescription, however, the NDA requirements would apply. Whenever an NDA is not required, however, the pharmacy must keep in mind the adulteration and misbranding concerns expressed in the response to 1.(c) above.

3. Some comments requested the agency to give examples of specific situations in which a new drug application (NDA) or exemption for investigational use of a new drug (IND) would be required. One comment stated it was not conceivable that an NDA or IND would ever be required if an order from a physician for a radioactive drug is dispensed by a nuclear pharmacy for the physician's own use (examples B7 and D4 of the draft guideline) or in response to a prescription order of a physician.

Although the primary intent of this guideline is to describe activities of nuclear pharmacies that require registration as drug establishments, the draft guideline did indicate that in some situations an IND or NDA may be required. These situations would be unusual and for this reason, the parenthetical statements that an IND or NDA may be required included in the draft have been omitted from the examples of

when a nuclear pharmacy must register as a drug establishment. Such situations, nevertheless, could occur. As stated in the text portion of the guideline, concerning the development of new radioactive drugs or new uses of a radioactive drug, ". . . depending upon how such a drug is prepared, promoted, and distributed, its preparation may fall outside the normal practice of pharmacy and not qualify for the pharmacy exemption. In such cases, even if the drug were dispensed on prescription, the nuclear pharmacy would have to comply, with respect to the products it produced, with the new drug provisions of the act, even though it may not be required to register under section 510 of the act." Such circumstances are commonly found when an individual physician is the sponsor of an IND for a radiopharmaceutical. Thus, application of the new drug provisions requires evidence that the pharmacy is performing activities not normally associated with the normal practice of pharmacy and is operating in a manner that subjects it to the new drug provisions of section 505 of the act.

4. One comment was uncertain of the provisions of section 704 of the act and asked about its application to the nuclear pharmacist.

Section 704 of the act authorizes, among other things, the inspection of any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held for introduction into interstate commerce or after such introduction into interstate commerce. Thus, as establishments holding drugs after their introduction into interstate commerce, all pharmacies, including nuclear pharmacies, are subject to inspection under this provision. In addition, nuclear pharmacies that are required to register as drug establishments under section 510 of the act are subject to more extensive provisions of

the inspectional authority of section 704. Although subject to inspection, the agency is not required to inspect, and except for reasonable cause normally does not inspect pharmacies, including nuclear pharmacies, operating entirely under the pharmacy exemptions in the act. However, the agency will be required, under section 510(b) of the Act (21 U.S.C. 360(b)), to inspect pharmacies, including nuclear pharmacies, that are registered as drug establishments under this section. The revocation of the interim enforcement policy, published in the FEDERAL REGISTER concurrently with the issuance of this guideline, will mean that nuclear pharmacies qualifying for the pharmacy exemptions will be regulated in the same manner as pharmacies generally and that nuclear pharmacies required to register under section 510 will be regulated like drug manufacturers. The guideline has been expanded (see page 9) to clarify the agency's inspectional authority under section 704 of the act.

5. One comment recommended that the agency develop good manufacturing practice regulations specific to nuclear pharmacies.

The agency does not believe that current good manufacturing practice (CGMP) regulations specific for nuclear pharmacies subject to regulation as drug establishments are necessary at this time. The CGMP regulations (21 CFR Part 211) provide sufficient detail for drug manufacturers generally and are reasonably applicable to nuclear pharmacies registered as drug establishments. Although some requirements in the regulations are not specific to all types of manufacturing, the agency believes that nuclear pharmacies will be able to initiate additional good manufacturing practices to insure their products meet appropriate standards. With the revocation of the interim enforcement policy and the issuance of these

guidelines, it is expected that many more nuclear pharmacies will register and be inspected by the agency. If these inspections reveal a problem the agency will take appropriate action, including providing further guidance through additional guidelines or proposing additional regulatory requirements. In the meantime, nuclear pharmacists should, on the basis of their professional training and experience as well as their knowledge of the principles of drug manufacturing, be able to apply reasonable control procedures to insure the integrity of their products.

The agency notes that at the 1980 American Pharmaceutical Association's (APhA) Annual Meeting, the APhA House of Delegates adopted two policy statements regarding nuclear pharmacy. These were: "The American Pharmaceutical Association supports the concept of state boards of pharmacy retaining their authority to regulate all aspects of professional pharmacy practice including nuclear pharmacy practice," and "The American Pharmaceutical Association urges state boards of pharmacy to promptly adopt appropriate rules and regulations for the practice of nuclear pharmacy using the National Association of Boards of Pharmacy Model Regulations for the Licensure of Nuclear Pharmacies as a model".

The FDA supports these policy statements and encourages States to take appropriate action. Implementation of these policies along with appropriate action by nuclear pharmacy organizations may obviate the need for the agency to develop any additional regulations specific for radioactive drugs.

6. One comment recommended that all nuclear pharmacies be required to perform stability and compatability studies on their containers.

A nuclear pharmacy that performs activities that cause it to be a drug establishment is required to follow the CGMP regulations. These regulations include requirements for containers and closures (21 CFR 211.94) and requirements for stability (21 CFR 211.166). Although these requirements do not apply to nuclear pharmacy operations that fall within the pharmacy exemption, it is still necessary that a nuclear pharmacy, like any other pharmacy, observe standards for containers that assure the stability of the final product.

7. One comment stated that nuclear pharmacists who make their own cold kits should be required to register and suggested that FDA require nuclear pharmacies to manufacture final products from FDA approved kits and prohibit pharmacies from compounding from basic ingredients because stability of radioactive drugs is of utmost importance.

The agency advises that as part of the practice of pharmacy, pharmacists have traditionally been considered free to make use of commercially available materials to practice their profession of compounding and dispensing prescription drug products. Nuclear pharmacists that operate within the pharmacy exemption have this same freedom. However, nuclear pharmacies that routinely prepare a particular type of reagent kit and ship it without a prescription are no longer acting as pharmacies and would be required to register. As noted in the response to comment 6, nuclear pharmacists, as well as other pharmacists, are responsible for assuring that drug products prepared under a prescription meet all standards for that product including proper stability requirements as dispensed.

8. One comment referred to a 1978 opinion handed down by the Attorney General of California, which stated that a pharmacist may compound and dispense an individual prescription for an individual's needs if the components have not been banned even though the product might be a new drug if not dispensed under a prescription. The opinion was that the pharmacist is not creating a market for a new drug but rather acting on the decision of a physician who has exercised independent judgement as to the safety and effectiveness of a particular drug in the treatment of a patient. The comment stated that the proposed guideline indicated that in certain circumstances a nuclear pharmacy may be required to sponsor an IND for a product even though it is dispensed under a prescription. The comment indicated that there may be a conflict between the Attorney General's opinion and the guideline and requested clarification.

The agency does not believe there is any conflict between the California opinion and the guideline. The agency recognizes that medical practice dictates that physicians remain free to use drugs according to their best knowledge and judgement. This may include the request for a drug product to be prepared under a prescription that would be a new drug if prepared by a drug establishment without a prescription. Physicians that write a prescription for a drug that must be compounded by a pharmacist bear the professional responsibility to base its use on sound scientific rationale or medical evidence. The agency agrees that as long as the pharmacist does not engage in activities that fall outside the normal practice of pharmacy, such use of a drug in the practice of medicine does not require an IND or

NDA. However, if a pharmacist does engage in activities outside the normal practice of pharmacy, the pharmacy would legally have to be registered notwithstanding that it may be filling physician's orders. The guideline has been modified in order to clarify this point (see page 21).

9. One comment stated that the example in the last sentence on page 20 of the draft guideline stated that a multi-dose vial filled by a nuclear pharmacist to be administered to several unknown patients may not be recognized as a prescription, but also stated on page 29 that a physician's order for a bulk drug for use in the physician's own practice is not cause for registration. The comment stated that this appeared to be a conflict.

The agency has reevaluated these two examples and has concluded that the need for registration under circumstances involving supplying multiple dose containers of a radioactive drug intended for administration to several patients needs clarification. Because of their short half-life, most radioactive drugs must be administered very promptly. Thus, the example of having a physician order a pharmacist to prepare a radioactive drug in bulk for the physician to store in the office as "office stock" for use in the physician's practice on appropriate patients as they are seen by the physician was not a realistic example. Therefore, it has been deleted from the guideline. The agency agrees, however, that such an activity, when

performed by a nuclear or traditional pharmacy, should require registration. The guideline has also been modified (see pages 16-19) to clarify that since prescriptions represent a professional relationship between the prescriber, pharmacist and patient, an order written for a multi-dose vial intended for administration to several patients is considered to be a prescription, if the dispensing pharmacy or pharmacist maintains a hard copy of the prescription or physician's order as required by section 503(b)(2) of the act and the pharmacy otherwise complies with all aspects of traditional or accepted pharmacy practice. Although such a practice will not by itself subject a nuclear pharmacy to registration with the FDA as a drug establishment, a nuclear pharmacy should also determine that such practices are consistent with applicable state laws.

10. One comment stated that FDA's belief that a firm should register is not in itself justification to require registration.

FDA's conclusion regarding the registration of certain types of nuclear pharmacies result from a reasoned application of section 510 of the act to the services which those establishments actually provide. The purpose of the guideline is to give guidance to nuclear pharmacies as to when one should register. Some situations regarding the manufacture of radioactive drugs present complex questions. These guidelines are not requirements, but rather an assurance that a person following the guideline will be following procedures acceptable to FDA. Manufacturers are encouraged under FDA guideline procedures to bring to the agency's

attention in advance situations in which a guideline may not be followed. FDA will attempt to resolve in advance disagreements between nuclear pharmacies and FDA over whether registration is required.

11. One comment stated that radiolabeling of a kit, as in example c. 2, is not done according to the directions of a physician. Instead a physician identifies the end product and the pharmacist prepares the prescription for that use.

The agency agrees that a prescription for a radioactive drug does not normally contain instructions for radiolabeling a kit. The intent of this example was to cover those instances where a prescription did contain such information and to distinguish it from example C. 1, which covers those situations where the prescription does not contain information for the labeling of a kit and the nuclear pharmacist prepares the product as set forth in the manufacturer's instructions accompanying the reagent kit. However, since only rarely would a prescription contain instructions for radio labeling a kit, this example has been deleted from the guideline.

12. Several comments stated that the guideline should be integrated with the Nuclear Regulatory Commission (NRC) to limit regulatory concerns to NRC and drug manufacturing concerns to FDA.

As previously stated, the purpose of the guideline is to give guidance to nuclear pharmacies so that they can determine if they should register as drug establishments under section 510 of the Federal Food, Drug, and Cosmetic Act. The determination of whether or not a nuclear

pharmacy should register is entirely within FDA's jurisdiction; there is no overlap with NRC's area of jurisdiction. Therefore, the agency does not see any need to integrate NRC's area of jurisdiction over nuclear pharmacies into the guideline. The agency has, however, supplied a copy of the draft guideline to the NRC for review and comment and will continue to work with NRC to avoid areas of duplication and inconsistencies between the two agency's policies.

13. One comment recommended that the guideline include names of agency personnel to be contacted when nuclear pharmacists have a question concerning their operations.

Agency regulations on guidelines (21 CFR 10.90) require a guideline to contain the name of the person responsible for maintaining the guideline. This person is named as the "contact person" in the notice of availability and this person should be contacted if questions arise as a result of the guideline. If a contact person cannot answer a question he or she will refer the inquirer to FDA employees knowledgeable in the subject matter.

14. One comment stated that a requirement that the patient's name appear on a prescription is inconsistent with contemporary nuclear pharmacy practice because physicians often reassign prescriptions to other patients and is also inconsistent with the guideline examples that physicians may order drug products for their own use. One comment stated that a prescription is defined as an order for a particular patient which would require the patients name to appear on the prescription.

The agency advises that the act (Section 503(b)(2) (21 U.S.C. 353(b)(2)) requires the label of a drug dispensed by prescription to contain the name of a patient when stated in the prescription. Even though the act does not require the patient's name, it does imply that a prescription is written with a particular patient in mind. (See the response to question 9). Further, many states require the patients full name and address on all prescriptions and even when not required by state law, the common accepted practice is for physicians to include the name of the patient on a prescription. The agency recognizes, however, that there are certain differences between traditional pharmacy and nuclear pharmacy. Thus, under the guideline a nuclear pharmacy may prepare a radioactive drug intended for administration to several patients in a multi-dose vial and dispense it provided the dispensing pharmacy engaging in such activities maintains a hard copy of the prescription or physician's order as required by section 503(b)(2) of the Federal Food, Drug, and Cosmetic Act and the pharmacy otherwise complies with all aspects of accepted or traditional pharmacy practice. The guideline contains a more complete discussion of this issue (pages 16-19).

15. One comment objected to the use of the term "diluting" in the guideline. The comment said this gave the impression that pharmacists only "dilute" and dispense when in fact when they dilute a product, they must be concerned with factors such as adjusting buffers, bacteriostatic agents and stabilizers. The word "preparing" was suggested as a substitute.

The agency believes that the use of the term "preparing" in place of "diluting" may be inappropriate because it could imply that the nuclear pharmacist prepared the radioactive drug rather than just performed some activities on a product prepared by a drug manufacturer. However, because "diluting" may also not be appropriate, it has been decided for purposes of this guideline to define the term as including not only simple dilution, but also adjustment of such things as buffers, bacteriostatic agents and stabilizers.

VI.

VI. Sample definition of the practice of medicine and related definitions. Corpus Juris Secundum 70:377-379; 393-394; 411-412, 1987

BOARD OF PHARMACY
1020 N STREET
SACRAMENTO, CA 95814

CALIFORNIA PHARMACY LAW

With

RULES AND REGULATIONS

1987

Issued by

CALIFORNIA STATE BOARD OF PHARMACY
1020 N Street
Sacramento, California 95814

Amendments through 1986

STATE OF CALIFORNIA
DEPARTMENT OF
Consumer Affairs

GEORGE DEUKMEJIAN
Governor

PHARMACY LAWS AND REGULATIONS

Issued by

CALIFORNIA STATE BOAPD OF PHARMACY

1020 N Street

Sacramento, CA 95814

DEPARTMENT OF CONSUMER AFFAIRS

CALIFORNIA STATE BOARD OF PHARMACY

MEMBERS

Allan C. Blaine	Los Gatos
K. Scott Carruthers	Pasadena
Gilbert Castillo	Stockton
Jay R. Cavanaugh	North Hollywood
Stephen E. Dibble	Mission Viejo
Robert M. Hertzberg	Beverly Hills
Mary M. Runge	Moraga
William Lew Tan	Monterey Park
Robert M. Toomajian	Long Beach
Glenn Y. Yokoyama	Rolling Hills Estates

EXECUTIVE OFFICER
LORIE HARRIS RICE

HEADQUARTERS

1020 N Street
Sacramento, CA 95814
(916) 445-5014

SAN DIEGO TELEPHONE NUMBER
(714) 237-7196

LOS ANGELES OFFICE
107 South Broadway
Los Angeles, CA 90012
(213) 620-3860

LAW REFERENCES

CALIFORNIA PHARMACY LAW WITH REGULATIONS
State of California
Documents Section
P.O. Box 1015
North Highlands, CA 95660
(916) 973-3700

UNIFORM CONTROLLED SUBSTANCES ACT
State of California
Department of Justice
Bureau of Narcotic Enforcement
P.O. Box 161089
Sacramento, CA 95816-1089
(916) 739-5445

PHARMACIST'S MANUAL OF THE CONTROLLED SUBSTANCES ACT
U.S. Department of Justice
Drug Enforcement Administration
450 Golden Gate Avenue
San Francisco, CA 94102
(415) 556-3325
OR
350 S. Figueroa Street
Los Angeles, CA 90071
(213) 688-4016

SHERMAN FOOD, DRUG, AND COSMETIC LAW
State of California
Department of Health Services
Food and Drug Branch
714 P Street
Sacramento, CA 95814
(916) 445-9963

GENERAL INFORMATION ABOUT THE STATE BOARD OF PHARMACY

The California State Board of Pharmacy is an agency within the Department of Consumer Affairs, which in turn is a part of the cabinet-level State and Consumer Services Agency (Cal. Bus. & Prof. Code, Sec. 100–101). (All citations are to the California Business and Professions Code unless otherwise noted.) It is the Board's responsibility to administer and enforce California pharmacy laws and regulations (§§ 108, 4000). Its functions include issuing regulations, preparing and conducting licensure examinations, investigating violations of laws under its jurisdiction and taking disciplinary action against its licensees.

Members: The Board consists of ten members. Seven are pharmacists residing in different parts of the state and three are public or non-pharmacist members. At least one of the public members must possess expertise in one or more significant portions of the Board's regulated activities (§§ 4001, 450–451). Board members are appointed by the Governor to serve for a term of four years (§§ 4001–4002) and may serve for two terms (§§ 131, 4003). The Board elects its president, vice-president, executive officer and treasurer; the executive officer need not be a member of the Board (§ 4004).

Committees: The Board meets as a body approximately six times per year. Its meetings are held in various locations throughout the state, most often in Los Angeles, San Francisco and Sacramento. In addition, the Board has a number of standing and *ad hoc* committees which meet from time to time. These include committees on continuing education, competency, rules and regulations, legislation and credentials. The Northern and Southern Interim Committees meet approximately monthly to handle minor disciplinary matters, probation interviews, consumer complaints and similar matters.

A schedule of the dates and locations of Board and committee meetings may be obtained from the Board's Sacramento office.

Staff: The Board's staff includes an executive officer headquartered in Sacramento, supervising inspectors headquartered in Sacramento and Los Angeles and field inspectors. In addition, the Board has a clerical staff.

4014. Immunity of Officers

All authorized officers of the law, while investigating violations of this chapter in performance of their official duties, and any person working under their immediate direction, supervision, or instruction are immune from prosecution under this chapter.

Article 2. General Provisions and Definitions

4030. Definitions

For the purposes of this chapter, the definitions of the terms in this article shall govern the construction of the provisions of this chapter, unless otherwise indicated.

4031. Drug

"Drug" means (1) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement of any of them; (2) articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man or other animals; (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; (4) articles intended for use as a component of any article specified in clause (1), (2), or (3).

4031.5. Device

"Device" means instruments, apparatus, and contrivances, including their components, parts, products or byproducts of a device, and accessories which are used or intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in a man or any other animal; or (2) to affect the structure or any function of the body of a man or any other animal.

4033. Prescribers

"Physicians," "dentists," "pharmacists," "podiatrists," "veterinarians," "veterinary surgeons," "registered nurses," and "physician's assistants" are persons authorized by a currently valid and unrevoked license to practice their respective professions in this state. "Physicians" means and includes any person holding a valid and unrevoked physician's and surgeon's certificate or certificate to practice medicine and surgery, issued by the Board of Medical Quality Assurance or the Board of Osteopathic Examiners of this state, and includes an unlicensed person lawfully practicing medicine pursuant to Section 2147.5, when acting within the scope of that section.

4034. Manufacturer

"Manufacturer" means and includes every person who prepares, derives, produces, compounds, or repackages any drug excepting a pharmacy which manufactures on the immediate premises where the drug is sold to the ultimate consumer.

4035. Pharmacy

Pharmacy is an area, place, or premises in which the profession of pharmacy is practiced and where prescriptions are compounded. "Pharmacy" includes, but is not limited to, any area, place, or premises described in a permit issued by the board by reference to plans filed with and approved by the board wherein controlled substances or dangerous drugs or dangerous devices, as they are herein defined, are stored, possessed, prepared, manufactured, derived, compounded, or repackaged, and from which the controlled substances or dangerous drugs or dangerous devices are furnished, sold, or dispensed at retail.

"Pharmacy" shall not include any area in a facility licensed by the State Department of Health Services where floor supplies, ward supplies, operating room supplies, or emergency room supplies of drugs or dangerous devices are stored or possessed solely for treatment of patients registered for treatment in the facility or for treatment of patients receiving emergency care in the facility.

"Controlled substances or dangerous drugs or dangerous devices" as used herein shall include, but is not limited to, all controlled substances, drugs, or devices which are included within one or more of the following classifications:

(a) Drugs or devices bearing the legend, "Caution, federal law prohibits dispensing without prescription," or words of similar import.

(b) Controlled substances as defined in Division 10 (commencing with Section 11000) of the Health and Safety Code.

(c) Drugs or devices enumerated in Section 4211.

(d) Hypodermic syringes and needles, or other drugs or devices, the sale of which is restricted by law to a registered pharmacist.

Neither this section nor any other provision of law shall be construed as prohibiting a pharmacy from furnishing a prescription drug or device to a licensed health care facility for storage in a secured emergency pharmaceutical supplies container maintained within the facility in accordance with facility regulations of the State Department of Health Services set forth in Title 22 of the California Administrative Code.

4035.1. Hospital Pharmacy

"Hospital pharmacy" means and includes a pharmacy, licensed by the board, located within any hospital, institution or establishment which maintains and operates organized facilities for the diagnosis, care and treatment of human illnesses to which persons may be admitted for overnight stay and which meets all of the requirements of this chapter and the rules and regulations of the board.

When, in the opinion of the board, a high standard of patient safety, consistent with good patient care, can be provided by the licensure of a pharmacy within a hospital, which does not meet all of the requirements for licensure as a hospital pharmacy, the board may waive any requirements pertaining to minimum equipment, minimum space, sanitary facilities and waiting area, provided that when the waiver of any of the above requirements is granted by the board the pharmaceu-

furnishing of drugs to patients registered for treatment in the hospital, whether or not they are actually staying in the hospital, or to emergency cases under treatment in the hospital.

4035.2. Security—Pharmacy

No person other than a registered pharmacist as defined in Section 4037 or an intern pharmacist as defined in Section 4038.1 or an authorized officer of the law or a person authorized to prescribe as provided by Section 4036 shall be permitted in that area, place or premises described in the permit issued by the board pursuant to Section 4035 wherein controlled substances or dangerous drugs or dangerous devices as therein defined are stored, possessed, prepared, manufactured, derived, compounded, or repackaged, except that a registered pharmacist shall be responsible for any individual who enters the pharmacy as described in Section 4035 for the purposes of receiving consultation from the pharmacist or of performing clerical, inventory control, housekeeping, delivery, maintenance or similar functions relating to the pharmacy, if the registered pharmacist remains present in the pharmacy during all times as such authorized individual is present.

The board may by regulation establish reasonable security measures consistent with this section in order to prevent unauthorized persons from gaining access to such area, place or premises or to the controlled substances or dangerous drugs or dangerous devices therein.

4035.3. Security—Hospital Pharmacy

No person other than a registered pharmacist as defined in Section 4037 or an intern pharmacist as defined in Section 4038.1 or an authorized officer of the law or a person authorized to prescribe as provided by Section 4036, or a registered nurse, or a licensed vocational nurse or a person who enters the pharmacy for purposes of receiving consultation from a registered pharmacist or a person authorized by the registered pharmacist in charge to perform clerical, inventory control, housekeeping, delivery, maintenance or similar functions relating to the pharmacy shall be permitted in that area, place or premises described in the permit issued by the board to a licensed or county hospital as such institutions are defined by Section 4047 of this code wherein narcotics or dangerous drugs or dangerous devices as defined by Section 4035 are stored, possessed, prepared, manufactured, derived, compounded, or repackaged.

4036. Prescription—Who May Prescribe

(a) "Prescription" means an oral order given individually for the person or persons for whom prescribed, directly from the prescriber to the furnisher, or indirectly by means of a written order, signed by the prescriber, and shall bear the name or names and address of the patient or patients, the name and quantity of the drug or device prescribed, directions for use, and the date of issue, and either rubber stamped, typed, or printed by hand or typeset the name, address, and telephone number of the prescriber, his or her license classification, and his or her federal registry number, if a controlled substance is prescribed. No person other than a physician, dentist, podiatrist, or veterinarian, shall prescribe or write a prescription.

Nothing in the amendments made to this section at the 1969 Regular Session of the Legislature shall be construed as expanding or limiting the right which a chiropractor, while acting within the scope of his or her license, may have to prescribe a device.

The use of commonly used abbreviations shall not invalidate an otherwise valid prescription.

(b) Notwithstanding subdivision (a), a written order of the prescriber for a dangerous drug, except for any Schedule II controlled substance, which contains at least the name and signature of the prescriber, the name or names and address of the patient or patients in a manner consistent with paragraph (3) of subdivision (b) of Section 11164 of the Health and Safety Code, the name and quantity of the drug prescribed, directions for use, and the date of issue may be treated as a prescription by the dispensing pharmacist so long as any additional information required by subdivision (a) is readily retrievable in the pharmacy. In the event of a conflict between the provisions of this subdivision and Section 11164 of the Health and Safety Code, the provisions of Section 11164 shall prevail.

(c) Except as provided in Section 4036.1, an oral prescription shall as soon as practicable be reduced to writing by the pharmacist and shall be filled by, or under the direction of, the pharmacist. The pharmacist need not reduce to writing the address, telephone number, license classification, federal registry number of the prescriber, or the address of the patient or patients if the information is readily retrievable in the pharmacy.

4036.1. Chart Order

An "order," entered on the chart or medical record of a patient registered in a hospital or a patient under emergency treatment in the hospital, by or on the order of a practitioner authorized by law to prescribe drugs, shall be authorization for the administration of such drug from hospital floor or ward stocks furnished by the hospital pharmacy or under licensure granted under Section 4052.1, and shall be considered to be a prescription if such medication is to be furnished directly to the patient by the hospital pharmacy or another pharmacy furnishing prescribed drugs for hospital patients; provided that the chart or medical record of the patient contains all of the information required by Section 4036 and the order is signed by the practitioner authorized by law to prescribe drugs, if he is present when the drugs are given, or if he is not present, then on his next visit to the hospital.

4036.2. Prescriber's Employee Transmitting Prescriptions

Notwithstanding any other provision of law, a prescriber may authorize his or her employee on his or her behalf to orally transmit a prescription to the furnisher. The furnisher shall record the name of the

This section shall not apply to orders for Schedule II controlled substances as defined in Division 10 (commencing with Section 11000) of the Health and Safety Code.

4036.3. Identification of Patients

No prescription for a controlled substance transmitted by means of an oral order shall be furnished to any person unknown and unable to properly establish his identity. The board may by regulation establish procedure to prevent unauthorized persons from receiving prescription drugs furnished to a patient or a representative of the patient.

4036.4. Transmitting Prescriptions from a Health Care Facility

Notwithstanding any other provision of law, a registered pharmacist, registered nurse, licensed vocational nurse, licensed psychiatric technician, or other healing arts licentiate, if so authorized by administrative regulation, who is employed by or serves as a consultant for a licensed skilled nursing, intermediate care or other health care facility, may orally transmit to the furnisher a prescription lawfully ordered by a person authorized to prescribe drugs or devices pursuant to Section 4036. The furnisher shall record the name of the person who transmits the order. This section shall not apply to orders for Schedule II controlled substances as defined in Division 10 (commencing with Section 11000) of the Health and Safety Code.

In enacting this section, the Legislature recognizes and affirms the role of the Department of Health Services in regulating drug order processing requirements for licensed health care facilities as set forth in Title 22 of the California Administrative Code as they may be amended from time to time.

4037. Registered Pharmacist

"Registered pharmacist" means a person to whom a certificate has been issued by the board, under the provisions of Section 4085.

4038. Wholesaler

"Wholesaler" means and includes every person who acts as a drug wholesale merchant, broker, jobber, or agent, who sells for resale, or negotiates for distribution any drug included in Section 4211. Pharmacies and licensed manufacturers are exempt from the provisions of this section.

4038.1. Intern Pharmacist

An "intern pharmacist" means a person registered with the board pursuant to subdivision (c) of Section 4035 and Section 4087 of this chapter who shall have completed the educational requirements as determined by the board.

4039. Person

"Person" includes firm, association, partnership, corporation, state governmental agency, or political subdivision.

4041. Certificate

"Certificate," as used in this chapter, unless otherwise indicated, means a certificate issued under the provisions of Section 4085.

4044. Board

"Board" means the California State Board of Pharmacy.

4045. Chemical

"Chemical" or "chemicals" includes all chemicals intended for use in the cure, mitigation, treatment, or prevention of disease in man or other animals, but does not include chemicals used for any other purpose.

4046. Pharmacy Profession

(a) In recognition of and consistent with the decisions of the appellate courts of this state, the Legislature hereby declares the practice of pharmacy to be a profession.

(b) Pharmacy practice is a dynamic patient-oriented health service that applies a scientific body of knowledge to improve and promote patient health by means of appropriate drug use and drug-related therapy.

(c) Neither this chapter nor any other provision of law shall be construed to prohibit a registered pharmacist from:

(1) Furnishing to a prescriber a reasonable quantity of compounded medication for prescriber office use.

(2) Transmitting to another registered pharmacist a valid prescription.

(3) Administering, orally or topically, drugs and biologicals pursuant to a prescriber's order.

(4) Performing the following procedures or functions in a licensed health care facility in accordance with policies, procedures, or protocols developed by health professionals, including physicians and surgeons, pharmacists, and registered nurses, with the concurrence of the facility administrator:

(A) Ordering or performing routine drug therapy related patient assessment procedures including temperature, pulse, and respiration.

(B) Ordering drug therapy related laboratory tests.

(C) Administering drugs and biologicals by injection pursuant to a prescriber's order (the administration of immunizations under the supervision of a prescriber may also be performed outside of a licensed health care facility).

(D) Initiating or adjusting the drug regimen of a patient pursuant to an order or authorization made by the patient's prescriber and in accordance with the policies, procedures, or protocols of the licensed health care facility.

As used in this paragraph, "licensed health care facility" means a facility licensed pursuant to Article 1 (commencing with Section 1250) of Chapter 2 of Division 2 of the Health and Safety Code or a facility

a health care service plan licensed pursuant to Chapter 2.2 (commencing with Section 1340) of Division 2 of the Health and Safety Code.

(d) Prior to performing any procedure authorized by paragraph (4) of subdivision (c), a registered pharmacist shall have received appropriate training as prescribed in the policies and procedures of the licensed health care facility.

4047. Hospital Defined

As used in this chapter, "licensed or county hospital" means an institution, place, building, or agency which maintains and operates organized facilities for one or more persons for the diagnosis, care, and treatment of human illnesses to which persons may be admitted for overnight stay, and includes any institution classified under regulations issued by the State Department of Health Services as a general or specialized hospital, as a maternity hospital, or as a tuberculosis hospital, but does not include a sanatorium, rest home, a nursing or convalescent home, a maternity home, or an institution for treating alcoholics.

4047.1. Health Facilities

As used in this chapter, the terms "skilled nursing facility," "intermediate care facility," and other references to health facilities shall be construed with respect to the definitions contained in Article 1 (commencing with Section 1250) of Chapter 2 of Division 2 of the Health and Safety Code.

4047.5. Prescription Label Requirements

A pharmacist shall not dispense any prescription except in a container correctly labeled with the following:

(a) Except where the prescriber orders otherwise, either the manufacturer's trade name of the drug or the generic name and the name of the manufacturer. Commonly used abbreviations may be used. Preparations containing two or more active ingredients may be identified by the manufacturer's trade name or the commonly used name or the principal active ingredients.

(b) The directions for the use of the drug.

(c) The name of the patient(s).

(d) The name of the prescriber.

(e) The date of issue.

(f) The name and address of the furnisher, and prescription number or other means of identifying the prescription.

(g) The strength of the drug or drugs dispensed.

(h) The quantity of the drug or drugs dispensed.

(i) The expiration date of the effectiveness of the drug dispensed if such information is required on the original label of the manufacturer of the drug.

If a pharmacist dispenses a prescribed drug by means of a unit dose medication system, as defined by administrative regulation, for a patient in a skilled nursing, intermediate care or other health care facility, tion system contains the aforementioned information or the information is otherwise readily available at the time of drug administration.

4047.6. Drug Product Selection

(a) Except as provided in Section 4047.7, on and after May 1, 1976, a pharmacist filling a prescription order for a drug product prescribed by its trade or brand name may select another drug product with the same active chemical ingredients of the same strength, quantity and dosage form, and of the same generic drug type, as defined in subdivision (f).

(b) In no case shall a selection be made pursuant to this section if the prescriber personally indicates, either orally or in his own handwriting, "Do not substitute," or words of similar meaning. Nothing in this subdivision shall prohibit a prescriber from checking a box on a prescription marked "Do not substitute"; provided that the prescriber personally initials such box or checkmark.

(c) Selection pursuant to this section is within the discretion of the pharmacist, except as provided in subdivision (b). The person who selects the drug product to be dispensed pursuant to this section shall assume the same responsibility for selecting the dispensed drug product as would be incurred in filling a prescription for a drug product prescribed by generic name. There shall be no liability on the prescriber for an act or omission by a pharmacist in selecting, preparing, or dispensing a drug product pursuant to this section. In no case shall the pharmacist select a drug product pursuant to this section unless the drug product selected costs the patient less than the prescribed drug product. Cost, as used in this subdivision, is defined to include any professional fee which may be charged by the pharmacist.

(d) This section shall apply to all prescriptions, including those presented by or on behalf of persons receiving assistance from the federal government or pursuant to the California Medical Assistance Program set forth in Chapter 7 (commencing with Section 14000) of Part 3 of Division 9 of the Welfare and Institutions Code.

(e) When a substitution is made pursuant to this section, the use of the cost-saving drug product dispensed shall be communicated to the patient and the name of the dispensed drug product shall be indicated on the prescription label, except where the prescriber orders otherwise.

(f) For the purposes of this section, the term "generic drug type" means the chemical or generic name, as determined by the United States Adopted Names (USAN) and accepted by the Federal Food and Drug Administration (FDA), of those drug products having the same active chemical ingredients.

4047.7. Generic Drug Formulary

(a) The State Director of Health Services shall establish by regulation a formulary of generic drug types and drug products which the State Director of Health Services determines demonstrate clinically

stituted under Section 4047.6, would pose a threat to the health and safety of patients receiving prescription medication.

(b) The drug formulary established pursuant to this section shall include generic drug types and manufactured brand drug products, including, where applicable, drug products differentiated by dosage form or strength. In compiling the generic drug types and drug products for inclusion on the formulary, the State Director of Health Services may rely on drug product research, testing, information, and formularies compiled by other states, the United States Department of Health and Human Services, and any other source which the State Director of Health Services deems reliable.

(c) Regulations establishing the drug formulary shall be promulgated within 120 days of the effective date of this section. The formulary shall be added to or deleted from as the State Director of Health Services deems appropriate. Regulations shall be adopted in accordance with Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code. Any person who requests that the State Director of Health Services make any inclusion, addition or deletion, of a generic drug type or drug product to the formulary shall have the burden of proof to show cause why such inclusion, addition, or deletion, should be made by the State Director of Health Services.

(d) Upon adoption of the formulary, and upon each addition, deletion or modification to the formulary, the State Director of Health Services shall mail a copy to each pharmacist licensed by the State Board of Pharmacy and with each physician and surgeon licensed to practice in the state with the State Board of Medical Quality Assurance and each person licensed by the Board of Osteopathic Examiners. No pharmacist shall dispense a generically equivalent drug product pursuant to Section 4047.6 if the drug product and its generic drug type is included in the formulary.

4047.8. Advertising

Notwithstanding any other provision of law, prescription drugs may be advertised provided such advertisement conforms with the requirements of Section 651.3.

4047.9. Drug Warnings

(a) A pharmacist shall inform a patient orally or in writing of the harmful effects of a drug dispensed by prescription if such drug poses substantial risk to the person consuming the drug when taken in combination with alcohol or if the drug may impair a person's ability to drive a motor vehicle, whichever is applicable, and provided the drug is determined by the board pursuant to subdivision (b) to be a drug or drug type for which such warning shall be given.

(b) The board shall determine which drugs or drug types pose a substantial risk to the person consuming the drug if taken in combination with alcohol or which may impair a person's ability to drive a motor vehicle, and the board shall provide each pharmacy in this state with

This section shall not apply to drugs furnished to patients registered for treatment or emergency cases under treatment in health facilities licensed pursuant to Section 1250(a) (b) (e) of the Health and Safety Code.

4048. Expiration Date

The label on any drugs furnished to a patient under the provisions of Section 4051 of this chapter, shall, in addition to any other information required to be stated thereon, contain the expiration date of the effectiveness of the drug if such information is required on the original label of the manufacturer of the drugs.

4048.5. Furnish

"Furnish" means to supply by any means, by sale or otherwise.

4049. Dispense

"Dispense" means the furnishing of drugs upon a prescription from a physician, dentist, podiatrist or veterinarian.

4049.5. Authorized Officers of Law

"Authorized officers of the law" means legally empowered peace officers, inspectors of the State Board of Pharmacy or the Department's Division of Investigation, and inspectors of the State Bureau of Food and Drug Inspection.

4049.6. Title

This chapter constitutes, and may be cited as, the Pharmacy Law.

Article 3. Application of Chapter

4050. License Required

Except as otherwise provided in this chapter, it is unlawful for any person to manufacture, compound, sell or dispense any dangerous drug, or to dispense or compound any prescription of a medical practitioner unless he is a registered pharmacist under the provisions of this chapter.

4050.5. Exemption

Section 4050 shall not apply to a manufacturer or wholesaler if the board shall find that sufficient, qualified supervision is employed by the manufacturer or wholesaler to adequately safeguard and protect the public health, nor shall Section 4050 apply to any laboratory licensed under Section 351 of Title III of the Public Health Service Act (Pub. Law 410, Chapter 373, 78th Cong.—2d Sess.).

4050.6. Fees for Exemption

Each person applying for an exemption under the provisions of Section 4050.5 or 4050.7 shall pay to the executive officer of the board the fees provided for in subdivision (h) of Section 4416.

4050.7. Hemodialysis Exemption

Section 4050 shall not apply to a manufacturer, wholesaler, or other

tients if the board shall find that sufficient, qualified supervision is employed by such manufacturer, wholesaler, or supplier adequately to safeguard and protect the public health.

4051. Physician Dispensing

(a) This chapter does not prohibit the dispensing of drugs by anyone who holds a physician's and surgeon's certificate or a certificate to practice podiatry, and who is duly registered as such by the Board of Medical Quality Assurance or the Board of Osteopathic Examiners of this state, if all of the following conditions are met:

(1) The drugs are dispensed to the physician's or the podiatrist's own patient and the drugs are not furnished by a nurse or attendant.

(2) The drugs are necessary to the treatment of the condition for which the physician or podiatrist is attending the patient.

(3) The physician or podiatrist does not keep a pharmacy, open shop, or drugstore, advertised or otherwise, for the retailing of drugs or poisons.

(4) The physician or podiatrist fulfills all of the labeling requirements imposed upon pharmacists by Section 4047.5, all of the record-keeping requirements of this chapter, and all of the packaging requirements of good pharmaceutical practice, including the use of child-proof containers. This paragraph shall not prohibit the furnishing of a limited quantity of samples by a physician or podiatrist, if the physician or podiatrist dispenses the samples to the patient in the package provided by the manufacturer, no charge is made to the patient therefor, and an appropriate record is entered in the patient's chart.

(5) The physician or podiatrist does not use a mechanical dispensing device unless he or she personally owns the device and the contents of it and personally dispenses the drugs to the patient packaged, labeled, and recorded in accordance with paragraph (4).

(b) The Board of Medical Quality Assurance and the Board of Osteopathic Examiners shall have authority with the Board of Pharmacy to assure compliance with this section, and those boards are specifically charged with the enforcement of this chapter with respect to their respective licensees.

4051.5. Registered Nurse Dispensing in Clinics

This chapter does not prevent the dispensing of drugs or devices by registered nurses functioning pursuant to Section 2725.1

4051.6. Nurse Practitioner Ordering in Clinics

Notwithstanding any other provision of law, a licensed pharmacist may dispense drugs or devices upon the order of a nurse practitioner functioning pursuant to Section 2836.1.

4052. Exempt Articles

(a) Except as provided in Section 4240, this chapter does not apply to the retail sale of drugs not subject to Section 4211 which are packaged or bottled in the manufacturer's or distributor's container and labeled

in accordance with applicable federal and state drug labeling requirements.

(b) This chapter does not apply to the sale of any intravenous solution of 150 cubic centimeters or over; cold sterilizing solution, sterilized sutures; hypodermic needles and syringes; sterile distilled water U.S.P.; sterile normal saline solution; laboratory chemicals and reagents, stains and dyes; chemicals and drugs used as indicators in diagnostic and X-ray examinations, soaps, detergents and tincture of green soap U.S.P.; medicinal gases, ether, chloroform and ethyl chloride; sulfa creams, ointments, and jellies used for introduction into the vaginal tract; and medicated dressings; where such sale is made to any of the following:

(1) A physician, dentist, podiatrist, veterinarian, pharmacist, medical technician, or medical technologist holding a currently valid and unrevoked license to practice his or her profession; and a chiropractor acting within the scope of his or her license.

(2) A clinic, hospital, institution, or establishment holding a currently valid and unrevoked license or permit under Division 2 (commencing with Section 1200) of the Health and Safety Code, or Chapter 2 (commencing with Section 3300) of Division 3, or Part 2 (commencing with Section 6250) of Division 6, of the Welfare and Institutions Code.

(3) An exporter for export outside the United States where such drugs or chemicals are actually shipped outside of the United States.

(c) This chapter does not apply to the retail sale of vitamins or mineral products or combinations thereof or to foods, supplements, or nutrients used to fortify the diet of man or other animal or poultry and labeled as such which are not subject to Section 4211 and which are packaged or bottled in the manufacturer's or distributor's container and labeled in accordance with applicable federal and state labeling requirements.

4052.1. Exempt Hospitals

Notwithstanding anything contained in this chapter, a licensed or county hospital as defined in Section 4047 which contains 100 beds or less and which does not employ full time a registered pharmacist may purchase drugs at wholesale for administration, under the direction of a physician, to patients registered in the hospital or to emergency cases under treatment in the hospital. The hospital shall keep records of the kind and amounts of drugs so purchased and administered, and such records shall be available for inspection by all properly authorized personnel of the Board of Pharmacy. A separate record shall be kept of the administration of hypnotic drugs including the amount given, the type, the date given, and the name and address of the person to whom administered.

4052.2. Permit Required

No hospital shall be entitled to the benefits of Section 4052.1 until it has obtained a permit from the board. Each permit shall be issued to a specific hospital and for a specific location.

4052.3. Application Form—Fee

Each application for a permit under Section 4052.2 shall be made on a form furnished by the board. Upon the filing of the application and payment of the fee prescribed in subdivision (a) of Section 4416, the executive officer of the board shall issue a permit authorizing the hospital to which it is issued to purchase drugs at wholesale pursuant to Section 4052.1. The permit shall be renewed annually on or before November 1 of each year upon payment of the renewal fee prescribed in subdivision (b) of Section 4416 and shall not be transferable.

4052.4. Information Required

The form of application for a permit under Section 4052.2 shall contain the name and address of the applicant, the number of beds, whether the applicant is a licensed or county hospital as defined in this code, whether it does or does not employ a full-time registered pharmacist, the name of its chief medical officer and the name of its administrator.

4052.5. Revocation—Suspension

The board may revoke or suspend a permit issued under Section 4052.2 in the manner and for the grounds specified in Article 11, commencing with Section 4350, of this chapter.

4054. Pharmacist in Charge

(a) Every store, dispensary, pharmacy, laboratory or office for the sale, dispensing or compounding of drugs or chemicals, or for the dispensing of prescriptions of medical practitioners, shall be in charge of a registered pharmacist.

(b) Every pharmacy shall designate a pharmacist-in-charge. The pharmacist-in-charge shall be responsible for a pharmacy's compliance with laws and regulations, both state and federal, pertaining to the practice of pharmacy.

(c) Any nonpharmacist owner who commits any act which would subvert or tends to subvert the efforts of the pharmacist-in-charge to comply with the laws governing the operation of the pharmacy is guilty of a misdemeanor.

4062. Blood Pressure Measurement

Notwithstanding Section 2013, or any other provision of law to the contrary, a licensed pharmacist may take a person's blood pressure and may inform the person of the results, render an opinion as to whether the reading is within a high, low or normal range, and may advise the person to consult a physician of the person's choice. Prior to undertaking blood pressure measurement, a pharmacist shall have received training in the standard method of blood pressure measurement. Pharmacists rendering such service shall utilize commonly accepted community standards in rendering opinions and referring patients to physicians. Enforcement of this section is vested in the Board of Pharmacy. Failure to perform such service shall not be in viola-

Article 3.5. Clinic Permits

4063. Clinic Permit

Notwithstanding anything contained in this chapter, a licensed nonprofit community clinic or free clinic as defined in paragraphs (1) and (2) of subdivision (a) of Section 1204 of the Health and Safety Code may purchase drugs at wholesale for administration or dispensing, under the direction of a physician, to patients registered for care at the clinic. The clinic shall keep records of the kind and amounts of drugs purchased, administered, and dispensed, and the records shall be available and maintained for a minimum of seven years for inspection by all properly authorized personnel.

4063.1. Specific Clinic and Location

No clinic shall be entitled to the benefits of Section 4063 until it has obtained a permit from the board. Each permit shall be issued to a specific clinic and for a specific location.

4063.2. Qualification

(a) Each application for a permit under Section 4063 shall be made on a form furnished by the board. Upon the filing of the application and payment of the fee prescribed in subdivision (s) of Section 4416, the board shall make a thorough investigation to determine whether the applicant and the premises for which application for a permit is made qualify for a permit. The board shall also determine whether the provisions of this article have been complied with, and shall investigate all matters directly related to the issuance of the permit. The board shall not, however, investigate any matters connected with the operation of a premises, including operating hours, parking availability, or operating noise, except those matters relating to the furnishing, sale, or dispensing of drugs or devices. The board shall deny an application for a permit if either the applicant or the premises for which application for a permit is made do not qualify for a permit under this article.

(b) If the board determines that the applicant and the premises for which application for permit is made qualify for a permit under this article, the executive officer of the board shall issue a permit authorizing the clinic to which it is issued to purchase drugs at wholesale pursuant to Section [illegible] the permit shall be renewed annually on or before December 31 of each year upon payment of the renewal fee prescribed in subdivision (s) of Section 4416 and shall not be transferable.

4063.3. Application Form

The form of application for a permit under Section 4063 shall contain the name and address of the applicant, whether the applicant is licensed as a primary care clinic as defined in this code, the name of its professional director, the name of its administrator, and the name of its consulting pharmacist.

Article 1. General Provisions

1703. *Delegation of Certain Functions*

The power and discretion conferred by law upon the board to receive and file accusations; issue notices of hearing, statements to respondent and statements of issues; receive and file notices of defense; determine the time and place of hearings under Section 11508 of the Government Code; set and calendar cases for hearing and perform other functions necessary to the business-like dispatch of the business of the board in connection with proceedings under the provisions of Sections 11500 through 11528 of the Government Code, prior to the hearing of such proceedings; and the certification and delivery or mailing of copies of decisions under Section 11518 of said code are hereby delegated to and conferred upon the executive secretary, or, in his or her absence from the office of the board, the acting secretary.

1704. *Change of Address*

Each person holding a certificate, license, permit, registration or exemption to practice or engage in any activity in the State of California under any and all laws administered by the Board shall file a proper and current residence address with the Board at its office in Sacramento and shall within 30 days notify the Board at its said office of any and all changes of residence address, giving both the old and new address.

1705. *Notification of Bankruptcy, Receivership or Liquidation*

Any pharmacy, wholesaler, or manufacturer who makes any assignment for the benefit of creditors or enters into any creditor compromise arrangement, or who files a petition in bankruptcy, or who has a receiver appointed, or who enters into any liquidation or other arrangement which may result in the sale or transfer of drugs, poisons, devices or appliances which are required to be sold by a registered pharmacist or other licensee, shall notify the Board immediately in writing of such fact, and shall set forth the following information, if known:

(a) Date of sale or transfer of such poisons, drugs, devices or appliances;

(b) Name and address of purchaser;

(c) Inventory of dangerous drugs and devices showing their disposition;

(d) Location of records of manufacture, sale, purchase, and disposition of dangerous drugs and devices.

1706. *Words of Similar Import*

The words "Prescription", "Prescription Service", "Medication", "Prescribed Medication", and "Medicinals" are words of similar or like import to those enumerated in Section 4391, Business and Professions Code.

Article 2. Pharmacies

1707.1. *Notice to Consumers and Duty to Consult*

(a) A Pharmacist shall provide his or her patient with consultation upon request, and whenever the pharmacist deems it warranted in the exercise of his or her professional judgment.

(b) In every pharmacy subject to the provisions of Business and Professions Code Section 4333 there shall be prominently posted in a place conspicuous to and readable by prescription drug consumers the following notice:

"NOTICE TO CONSUMERS"

At your request, this pharmacy shall provide its current retail price of any prescription without obligation. You may request price information in person or by telephone.

Ask your pharmacist if a lower-cost generic drug is available to fill your prescription.

Perscription prices for the same drug vary from pharmacy to pharmacy. One reason for differences in price is differences in services provided. The services provided by this pharmacy, in addition to professional prescription dispensing and professional consultation, are checked below. In comparing prescription prices it is important to consider the services provided.

- ☐ Personal Medication Records
- ☐ Health Services Information
- ☐ Compounded Prescription Service
- ☐ Emergency Prescription Service
- ☐ Prescription Delivery
- ☐ Credit Service
- ☐ _____

IF YOU HAVE ANY QUESTIONS REGARDING MEDICATIONS, PLEASE ASK TO SPEAK WITH A PHARMACIST.

1708.2. *Discontinuance of Business*

Any pharmacy permit holder must contact the board prior to discontinuing business or conducting bankruptcy proceedings or transferring or selling the prescription inventory to receive an official instructions sheet applicable to the transaction.

1708.3. *Radioactive Drugs*

A *radioactive drug* is any substance defined as a drug in Section 201(g)(1) of the Federal Food, Drug and Cosmetic Act or a radioactive biological product as defined in 21 CFR 600.3(ee) which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any such drug or biological product which is intended to be made radioactive. This definition includes non-radioactive reagent kits and nuclide generators which are intended to be used in the preparation of any such substance but does not include drugs such as a carbon-containing compounds, potassium-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides.

1708.4. armacist Handling Radioactive Drugs

A pharmacist handling radioactive drugs must be competent in the preparation, handling, storage, receiving, dispensing, disposition and pharmacology of radioactive drugs. He must have completed a nuclear pharmacy course and/or acquired experience in programs approved by the Board. Education and experience in non-approved programs may be granted partial or equivalent credit, if, in the opinion of the Board, such programs provide the level of competence as approved programs or the Nuclear Pharmacy Competency Statement adopted by the Board.

1708.5. Pharmacy Furnishing Radioactive Drugs

A pharmacy furnishing radioactive drugs is any area, place or premises described in a permit issued by the Board by reference to plans approved by the Board where radioactive drugs are stored, processed, compounded, repackaged, or dispensed.

A detailed diagram of the dimensions, construction and operational design of the premises and a list of all equipment required for the assay, identification, storage, processing, compounding, repackaging, dispensing and analysis of the pharmaceutical quality of radioactive drugs shall be submitted to and approved by the Board before a pharmacy permit is issued by the Board.

A pharmacy exclusively furnishing radioactive drugs shall be exempt from the building standards of Title 16 Cal. Admin. Code Section 1712 unless the Board finds that the public health and safety require their application.

A pharmacist qualified under Section 1708.4 to furnish radioactive drugs shall be in the pharmacy whenever the furnishing of radioactive drugs occurs. All personnel involved in the furnishing of radioactive drugs shall be under the immediate and direct supervision of such a qualified pharmacist.

1709. Names of Owners and Pharmacist in Charge

Each permit to operate a pharmacy shall show the name and address of the pharmacy, and the form of ownership (individual, partnership or corporation). Each pharmacy shall, in its initial application and on the annual renewal form, report the name of the pharmacist-in-charge, the names of all owners and the names of the corporate officers (if a corporation). Any changes in corporate officers shall be reported to the Board within thirty (30) days. A permit to operate a hospital pharmacy, or a permit issued to a hospital under provisions of Section 4052.1 of the Business and Professions Code, must show the name of the current pharmacist-in-charge.

1711. Sanitary Standards for Pharmacies

All pharmacies, and fixtures and equipment therein, shall be maintained in a clean and orderly condition. Pharmacies shall be dry, well-ventilated, free from rodents and insects, and adequately lighted. Plumbing shall be in good repair.

1712. Building Standards

Any new pharmacy, or any existing pharmacy which is being remodeled, must comply with the following provisions:

(a) Approval of Plans. The pharmacy merchandising area, waiting area, storeroom, restroom, and all partitions, doors, windows and fixtures shall be indicated on floor plans, showing appropriate elevations submitted to the Board at the time the application for a new pharmacy is filed, or prior to remodeling. Such plans shall be submitted to the Board prior to proceeding with new construction.

Before a pharmacy permit is issued, the plans submitted must meet the approval of the Board.

(b) Pharmacy Area. The minimum area of the pharmacy, excluding enclosed storerooms, shall be not less than 240 square feet. Each pharmacy shall be of adequate size to permit effective and non-hazardous pharmacy practice of the type engaged in by the permit holder.

(c) Prescription Compounding and Dispensing Counter. There shall be a prescription compounding and dispensing counter which shall provide unobstructed working space commensurate with the compounding and dispensing work load requirements of the pharmacy and which shall be used for no other purpose.

A clear and unobstructed floor area shall extend the full length of the prescription compounding and dispensing counter.

A minimum of 16 square feet of counter space shall be provided for one pharmacist. Enough additional counter space shall be provided for each additional pharmacist to permit effective and non-hazardous pharmacy practice of the type engaged in by the permit holder.

(d) Factors to be considered in determining the adequacy of pharmacy size under subsection (b) and the adequacy of the prescription compounding and dispensing counter space under subsection (c) shall include, but are not limited to, the following: the number and type of personnel; the amount and type of equipment and stock in the pharmacy; the layout of the pharmacy; and prescription volume.

(e) Separation of Pharmacy and Access. (1) The pharmacy shall be separated from the merchandising area by a barrier with a minimum height of five feet and of sufficient width which will render the narcotics or dangerous drugs or dangerous devices, as defined in Business and Professions Code Section 4035, within the pharmacy inaccessible to the reach of any unauthorized person. The Board may permit alternate types of separations if, in its opinion, they provide equivalent security. The only access to the pharmacy shall be by doors or gates which can be locked. (2) A permanent barrier or partition extending from floor to ceiling shall be provided to separate the pharmacy, or the pharmacy and adjoining merchandising area, from the rest of the building or the

VIIii.

Duke University – Duke University Medical Center

RADIOACTIVE MATERIAL AUTHORIZATION

1. Individual User: William H. Briner	2. Authorization No: MC-176
3. Location Radi[illegible]macy Laboratory	4. Expiration Date: September 1, 1990

5. Radioactive Material

A. Any radioactive material between Atomic Numbers 1 & 83, inclusive
B. I-125 (2 sealed sources)
C. Americium-241 (2 sealed sources)
D. Strontium-82
E. Rubidium-82
F. Strontium-85 (contaminant of 5D)
G. Osmium-191
H. Iridium-191m

6. Possession Limit

A. Amount to be approved by Radiation Safety Office
B. 400 milliCuries
C. 2 milliCuries
D. 150 milliCuries
E. 150 milliCuries
F. 500 milliCuries
G. 1 Curie
H. 1 Curie

7. Conditions

A. Radioactive material shall be used by or under the direct supervision of William H. Briner.

B. Radioactive material shall be possessed and used in accordance with statements, representations and procedures described in application dated September 13, 1988 and manual entitled "radiation Safety Manual Duke Medical Center."

C. Human use of radioactive material shall be by a physician specifically authorized by the Duke Medical Center Radiation Control and Radioactive Drug Research Committee.

For The RADIATION CONTROL And RADIOACTIVE DRUG RESEARCH COMMITTEE

Date September 21, 1988

Conrad M. Knight, RSO

RETURN TO: RSO, BOX 3155, DUMC

AUTHORIZATION N

RENEWAL APPLICATION - RADIOISOTOPE AUTHORIZATION

1. Applicant: William H. Briner, Associate Professor of Radiology and Director, Radiopharmacy and Nuclear Medicine Laboratory

2. Radionuclides and quantities to be possessed:

Any radioactive materials between Atomic Numbers 1 and 83 inclusive, in amounts as required, but within the conditions of DUMC North Carolina Radioactive Materials License Number 32-085-3 and as approved by the Duke Radiological Safety Officer. Also 1. Iodine 125 (2 sealed sources, 200 mCi each); 2. Americium 241 (2mCi sealed source); 3 Strontium 82, 150 mCi (Parent of Rb 82, q.v.); 4 Rubidium 82, 150 mCi (Generator); (Continued on Supplementary Sheet 1A)

3. Building(s) and room(s) in which radioactive materials are used or stored:

Section of Radiopharmacy Space (Bell Building Rooms 144, 146, 147, 149, 151, 152 and 154) Division of Imaging Space in Duke Hospital North and South, including the PET Imaging Center in Duke Hospital South.

4. Brief description of purpose for which radioactive material is used (to include activity per experiment and number of experiments per month):

A. The formulation and dispensing of radiopharmaceuticals intended for administration to patients of Duke Medical Center Section of Nuclear Medicine, as well as other Duke Hospital patients when appropriate arrangements by authorized physicians have been made with the Director, Section of Radiopharmacy. This is, in part, made possible by the issuance of a Pharmacy Permit (license, No. 3051) to the Duke University Medical Center Radiopharmacy by the North Carolina Board of Pharmacy.

Similarly, under appropriate contractual arrangements, the function carried out of A above is performed for the Veterans Administration Medical Center, Durham, N.C., with the transfer of radioactive material from the DUMC Radioactive Material License (N.C. 32-085-3) to the VAMC Byproduct Material License (NRC 32-01134-01), being duly recorded.

quality control testing of all radiopharmaceuticals formulated and dispensed nd B above, in accordance with regulations of the N.C. Radiation Protection USNRC, USFDA, USP, N.C. Board of Pharmacy, and the professional judgment ctor, Section on Radiopharmacy.

of new radiopharmaceutical dosage forms as required at DUMC and accordance with Federal and State statutes and regulations ce of pharmacy and medicine.

arch carried out independently and in collaboration faculty and staff members.

pplementary Sheet 1A)

RETURN TO: RSO, BOX 3155, DUMC

RENEWAL APPLICATION - RADIOISOTOPE AUTHORIZATION	AUTHORIZATION NO.

1. Applicant: William H. Briner, Associate Professor of Radiology and Director, Radiopharmacy and Nuclear Medicine Laboratory

2. Radionuclides and quantities to be possessed:

Any radioactive materials between Atomic Numbers 1 and 83 inclusive, in amounts as required, but within the conditions of DUMC North Carolina Radioactive Materials License Number 32-085-3 and as approved by the Duke Radiological Safety Officer. Also 1. Iodine 125 (2 sealed sources, 200 mCi each); 2. Americium 241 (2mCi sealed source); 3 Strontium 82, 150 mCi (Parent of Rb 82, q.v.); 4 Rubidium 82, 150 mCi (Generator); (Continued on Supplementary Sheet 1A)

3. Building(s) and room(s) in which radioactive materials are used or stored:

Section of Radiopharmacy Space (Bell Building Rooms 144, 146, 147, 149, 151, 152 and 154) Division of Imaging Space in Duke Hospital North and South, including the PET Imaging Center in Duke Hospital South.

4. Brief description of purpose for which radioactive material is used (to include activity per experiment and number of experiments per month):

A. The formulation and dispensing of radiopharmaceuticals intended for administration to patients of Duke Medical Center Section of Nuclear Medicine, as well as other Duke Hospital patients when appropriate arrangements by authorized physicians have been made with the Director, Section of Radiopharmacy. This is, in part, made possible by the issuance of a Pharmacy Permit (license, No. 3051) to the Duke University Medical Center Radiopharmacy by the North Carolina Board of Pharmacy.

B. Similarly, under appropriate contractual arrangements, the function carried out of A above is performed for the Veterans Administration Medical Center, Durham, N.C., with the transfer of radioactive material from the DUMC Radioactive Material License (N.C. 32-085-3) to the VAMC Byproduct Material License (NRC 32-01134-01), being duly recorded.

C. The quality control testing of all radiopharmaceuticals formulated and dispensed in A and B above, in accordance with regulations of the N.C. Radiation Protection Program, USNRC, USFDA, USP, N.C. Board of Pharmacy, and the professional judgment of the Director, Section on Radiopharmacy.

D. The development of new radiopharmaceutical dosage forms as required at DUMC and the Durham VAMC, in accordance with Federal and State statutes and regulations relating to the practice of pharmacy and medicine.

E. Participation in basic research carried out independently and in collaboration with other DUMC, Durham VAMC faculty and staff members.

(Continued on Supplementary Sheet 1A)

RENEWAL APPLICATION - RADIOISOTOPE AUTHORIZATION, 12 SEPTEMBER 1988

Applicant: William H. Briner

SUPPLEMENTARY SHEET 1A

Application Item 2 (Con't)

5. Strontium 85 (contaminant of 4) to be used in animals only in conjuction with PET Imaging Center, Duke Hospital South. Osmium 191, 1 Ci and Iridium 191, 1 Ci in a Generator System.

Application Item 4 (Con't)

F. As required in A through E above, the use of laboratory animals, such as monkeys, swine, mice, rats, rabbits, dogs, cats, etc., may be involved.

G. Performance of a wide variety of radiobioassays for patients.

RENEWAL APPLICATION - RADIOISOTOPE AUTHORIZATION, 12 SEPTEMBER 1968

Applicant: William L. Briner

SUPPLEMENTARY SHEET 1A

Application Item 2 (Con't)

5. Strontium 85 (contaminant of 4) to be used in animals only in conjuction with PET Imaging Center, Duke Hospital South. Osmium 191, 1 Ci and Iridium 191, 1 Ci in a Generator System.

Application Item 4 (Con't)

F. As required in A through E above, the use of laboratory animals, such as monkeys, swine, mice, rats, rabbits, dogs, cats, etc., may be involved.

G. Performance of a wide variety of radiobioassays for patients.

5. Portable radiation detection instruments maintained in your laboratory (manufacturer and model):

1 ea Eberline RO-3 ionization chamber survey instrument
1 ea Eberline RM-14 GM survey instrument
1 ea Eberline E-520 GM survey instrument

6. Describe the radiological safety measures employed to minimize the possibility of contamination of personnel and facilities, including method of determining effectiveness of such measures:

A. All personnel assigned to the Section of Radiopharmacy wear TLD whole body badges.

B. Selected personnel (i.e., those working in the Radiopharmacy per se, but not the Nuclear Medicine Laboratory) wear finger TLD's.

C. All personnel who work with radioactive material wear protective gloves and laboratory coats.

D. No smoking, eating, drinking, or application of cosmetics is permitted in areas where radioactive materials are stored or handled.

E. All incoming packages of radioactive material are visually inspected upon receipt to check for loss of containment or obvious damage.

F. Packing materials are surveyed with GM meter prior to disposal.

G. Outside containers of shipments containing more than 100 mCi of nuclides with half-lives greater than 7 days are wipe tested upon receipt to detect external contamination in excess of limits prescribed by NRC and DOT; if obvious in-transit damage to any package has occurred, regardless of activity level or half-life, the package is wipe tested.

H. Lab area is checked for contamination, using wipe tests and survey instruments at intervals deemed necessary by Lab Director and Radiological Safety Officer.

I. Receipt and disposal of all radioactive material is recorded in accordance with Duke University Radiological Safety Policies and Procedures.

J. All radioactive materials are shielded appropriately as required by their nature.

K. All other procedures mandated by the Duke University Radiological Safety Policies and Procedures are followed.

7. (a) Do you provide instructions to laboratory personnel concerning the potential hazards of ionizing radiation and safe handling procedures? Yes x No ____

(b) Are special precautions or instructions provided potentially pregnant female employees? Yes x No ____

(c) If answer to a or b above is Yes, how are instructions given? Oral x Written ____

8. Do you use Hydrogen 3 in such a way that internal deposition is possible and periodic urine analysis is warranted? Yes ____ No x

9. Do you use radioactive Iodine in such a way that internal deposition is possible and periodic thyroid counting is warranted? Yes ____ No x
Periodic urine assays are done when deemed necessary. If positive, Thyroid counting would be done.

10. Do you have any of the following devices or materials under your supervision?

a. Analytical X-Ray equipment; e.g. electron microscope, X-Ray diffraction: Yes ____ No x

b. Lasers or masers: Yes ____ No x

c. Microwave equipment; e.g. oven: Yes ____ No x

d. Sealed radioactive sources; e.g. check sources for instruments, static eliminator, etc.: Yes x No ____

11. Name of individual responsible for radiation safety matters during absences of the Authorized User:

Name Nelsen Niehaus Phone 684-5636

12. Signature of Authorized User:

William H. Bennett
signature

9/3/84
date

RADIATION PROTECTION SECTION
DIVISION OF FACILITY SERVICES
N.C. DEPARTMENT OF HUMAN RESOURCES
RADIOACTIVE MATERIAL LICENSE

Pursuant to North Carolina Regulations for Protection Against Radiation and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, own, possess, transfer and import radioactive materials listed below; and use such radioactive material for the purpose(s) and at the place(s) designated below. This License is subject to all applicable rules and regulations of the North Carolina Department of Human Resources now or hereafter in effect and to any conditions specified below.

Licensee	
1. Name: Duke University Medical Center	3. License No.: 032-0085-3
2. Address: P.O. Box 3155 Durham, N.C. 27710	4. Expiration Date: March 31, 1994
	AMENDS IN ITS ENTIRETY 5. Amendment No. 63

6. Radioactive Material (element and mass no.)	7. Chemical and/or Physical Form	8. Maximum Amount of Radioactivity and/or Quantity of Radioactive Material which Licensee may Possess at any one time.
(See Pages 2, 3 & 4)	(See Pages 2, 3 & 4)	(See Pages 2, 3 & 4)

9. Authorized Use

A BB: To be used for Medical Research, Diagnosis and Therapy.

CC - HH: To be used for Calibration, Research and Development.

II - JJ: To be used as static eliminators.

KK - To be used in AECL Gamma Cell 40 Irradiator for the study of radiation effects.

LL - To be used in AECL Gamma Cell 1000 Irradiator for the irradiation of blood and blood components.

MM - To be used in J. L. Shepherd Mark I Irradiator for non-human radiation studies.

NN - UU - To be used in Electron Capture Detectors as a part of Manufacturer Gas Chromatograph Systems.

CONDITIONS

10. Unless otherwise specified, the authorized place of use is the licensee's address stated in Item 2 above.

11. The licensee shall comply with the provisions of 10 NCAC 3G .2500, "Standards for Protection Against Radiation," and 10 NCAC 3G .3100, "Notices, Instructions, Reports and Inspections." (The North Carolina Regulations for Protection Against Radiation are contained in 10 NCAC 3G).

12. Radioactive material shall be used by, or under the supervision of individuals authorized by the Radiation Safety Committee and Radioactive Drug Research Committee.

Supplementary Sheet

Radioactive Materials:

6A.	Any radioactive material between Atomic Nos. 3 & 83, inclusive, except:	7A.	Any Form	8A.	100 millicuries each (Total possession 25 curies.
B.	Carbon-14	B.	Any Form	B.	2 curies
C.	Phosphorus-32	C.	Any Form	C.	500 millicuries
D.	Iodine-131	D.	Any Form	D.	500 millicuries
E.	Iridium-192	E.	Any Form	E.	1 curie
F.	Xenon-133	F.	Any Form	F.	10 curies
G.	Iodine-125	G.	Any Form	G.	750 millicuries
H.	Hydrogen-3	H.	Any Form	H.	10 curies
I.	Molybdenum-99	I.	Any Form	I.	10 curies
J.	Technetium-99m	J.	Any Form	J.	10 curies
K	Radon-222	K.	Any Form	K.	50 millicuries
L.	Krypton-85	L.	Any Form	L.	2 curies
M.	Gold-198	M.	Seeds	M.	1 curie
N.	Strontium-90 Yttrium-90	N.	Medical Applicator (Tracerlab Model RA-2A)	N.	100 millicuries
O.	Cesium-137	O.	Sealed Sources (3M Co. Model 6D6C medical radiation sources)	O.	2.2 curies
P.	Tungsten-178/Tantalum-178	P.	Generator	P.	400 millicuries
Q.	Sulfur-35	Q.	Any Form	Q.	300 millicuries
R.	Iodine-125	R.	Sealed Source (Amersham Model IMC-129)	R.	2 sources 400 millicuries total.
S.	Iodine-125	S.	Seeds	S.	2 curies
T.	Strontium-82	T.	Generator	T.	150 millicuries
U.	Strontium-85	U.	Any Form	U.	500 millicuries
V.	Rubidium-82	V.	Any Form	V.	150 millicuries

Supplementary Sheet

Radioactive Materials (continued):

6W.	Osmium-191	7W.	Generator	8W.	1 curie
X.	Iridium-191m	X.	Any Form	X.	1 curie
Y.	Fluorine-18	Y.	Any Form	Y.	1 curie
Z.	Oxygen-15	Z.	Any Form	Z.	1 curie
AA.	Nitrogen-13	AA.	Any Form	AA.	1 curie
BB.	Carbon-11	BB.	Any Form	BB.	1 curie
CC.	Americium-241	CC.	Sealed Source (NEN Model NER-478)	CC.	600 millicuries
DD.	Radium-226	DD.	Any Form	DD.	2 millicuries
EE.	Americium-241	EE.	Sealed Source (Amersham/Searle Model 2084)	EE.	10 millicuries
FF.	Americium-241	FF.	Sealed Source (Amersham Model AMC-21)	FF.	2 millicuries
GG.	Americium-241	GG.	Sealed Source (Amersham/Searle Model AMCL type X-131)	GG.	100 millicuries
HH.	Cesium-137	HH.	Sealed Source (J.L. Shepherd and Associates Model 28-6B)	HH.	3 curies
II.	Polonium-210	II.	Static Eliminator (Nuclear Products Model 2 U-1000)	II.	1 millicurie
JJ.	Americium-241	JJ.	Custom sources (DUMC Mod-A1011)	JJ.	40 microcuries (2 sources - 20 microcuries each)
KK.	Cesium-137	KK.	Sealed Sources (AECL Model C-616, type B)	KK.	3600 curies (2 sources 1800 curies each)
LL.	Cesium-137	LL.	Sealed Source (ISO-1000)	LL.	2160 curies

Supplementary Sheet

Radioactive Materials (continued):

MM.	Cesium-137	MM. Sealed Sources (Shepherd Model 6810)	MM. 10,000 curies
NN.	Nickel-63	NN. Custom Plated Source (Amersham/ Searle or NEN)	NN. 15 millicuries
OO.	Nickel-63	OO. Custom Plated Source (Varian Model 02-001972-00)	OO. 8 millicuries
PP.	Nickel-63	PP. Custom Plated Source (Varian Model 02-001972-00)	PP. 8 millicuries
QQ.	Nickel-63	QQ. Custom Plated Source (Varian Model 02-001972-00)	QQ. 8 millicuries
RR.	Nickel-63	RR. Custom Plated Source (Varian Model 01-1028-01)	RR. 8 millicuries
SS.	Nickel-63	SS. Custom Plated Source (Varian Model 01-1028-01)	SS. 8 millicuries
TT.	Nickel-63	TT. Custom Plated Source (Varian Model 02-001972-00)	TT. 8 millicuries
UU.	Nickel-63	UU. Custom Plated Source (Hewlett Packard Model 5890)	UU. 15 millicuries

Conditions (continued):

13A. Each sealed source containing radioactive material, other than Hydrogen 3, with a half-life greater than thirty days and in any form other than gas shall be tested for leakage and/or contamination at intervals not to exceed six months. In the absence of a certificate from a transferor indicating that a test has been made within six months prior to the transfer, the sealed source shall not be put into use until tested.

B. Notwithstanding the periodic leak test required by this condition, any licensed sealed source is exempt from such leak tests when the source contains 100 microcuries or less of beta and/or gamma-emitting material or 10 microcuries or less of alpha-emitting material.

The periodic leak test required by this condition does not apply to sealed sources that are stored and not being used. The sources excepted from this test shall be tested for leakage at intervals not to exceed three (3) years and prior to any use or transfer to another person unless they have been leak tested within six months prior to the date of use or transfer.

Supplementary Sheet

Conditions (continued):

13D. Notwithstanding Condition No. 13A the Cesium 137 listed in item 0 of 6, 7, 8 & 9 shall be tested for leakage and/or contamination at intervals not to exceed three years. In the absence of a certificate from a transferor indicating that a test has been made within six months prior to the transfer, the sealed source shall not be put into use until tested.

E. The test shall be capable of detecting the presence of 0.005 microcurie of radioactive material on the test sample. The test sample shall be taken from the sealed source or from the surfaces of the device in which the sealed source is permanently mounted or stored on which one might expect contamination to accumulate. Records of leak test results shall be kept in units of microcuries and maintained for inspection by the Agency.

F. If the test reveals the presence of 0.005 microcurie or more of removable contamination, the licensee shall immediately withdraw the sealed source from use and shall cause it to be decontaminated and repaired or to be disposed of in accordance with Agency regulations. A report shall be filed within five (5) days of the test with the Radiation Protection Section, Division of Facility Services, Department of Human Resources, 701 Barbour Dr., Raleigh, North Carolina 27603, describing the equipment involved, the test results, and the corrective action taken.

Tests for leakage and/or contamination shall be performed by licensee, or by other persons specifically authorized by the Agency to perform such services.

14. In lieu of using the conventional radiation caution colors (magenta or purple on yellow background) as provided in 10 NCAC 3G .2511(a)(1), the licensee is hereby authorized to label detector cells and cell baths, containing radioactive material and used in gas chromatography devices, with conspicuously etched or stamped radiation caution symbols without a color requirement.

15. Experimental animals administered radioactive materials or their products shall not be used for human consumption.

16A. Individuals involved in operations which utilize, at any one time, more than 100 millicuries of Hydrogen 3 in a non-contained form, other than metallic foil, shall have bioassays performed within one week following a single operation and at weekly intervals for continuous operation. The urine specimen shall be collected on the same day of the week insofar as possible.

B. Notwithstanding the bioassay at weekly intervals for continuous operations required by the preceding paragraph, bioassay may be performed at monthly intervals on any individual for the following calendar quarter, if the average concentration of Hydrogen 3 in the urine of the individual during a calendar quarter was less than 10 microcuries per liter. Bioassay may continue at monthly intervals so long as the average concentration remains below 10 microcuries per liter.

C Hydrogen 3 shall not be used in such a manner as to cause any individual to receive a radiation exposure such that the urinary excretion rates exceed 28 microcuries of Hydrogen 3 per liter when averaged over a calendar quarter.

Supplementary Sheet

Conditions (continued):

16D. A report of an average concentration in excess of the limit specified in the preceding paragraph for any individual shall be filed, in writing, within thirty (30) days of the end of the calendar quarter with the Radiation Protection Section, Division of Facility Services, Department of Human Resources, 701 Barbour Dr., Raleigh, North Carolina 27603. The report shall contain the results of all urinalysis for the individual during the calendar quarter, the cause of the excessive concentrations and the corrective steps taken or planned to assure against a recurrence.

17. The foil may be removed from the electron capture cell for cleaning only, in accordance with procedures contained in the manufacturer's operating manual.

18. The Nickel 63 Electron Capture Detector designated in items NN through UU of 6, 7, 8 & 9 shall be used in conjunction with a properly operating temperature limiting device as specified by the manufacturer.

19. Technetium 99m penetate as an aerosol for lung function studies must be administered with a closed, shielded system that either is vented to the outside atmosphere through an air exhaust or provides for collection and disposal of the aerosol.

20. Radioactive material shall not be used in humans until its pharmaceutical quality and assay have been established.

7 Radioactive gases as free gas or in solution, to be administered to humans, shall be procured from a supplier who distributes the product indicated for human use in accordance with the Federal Food, Drug, and Cosmetic Act.

22. Notwithstanding 10 NCAC 3G .2504 and .2507 of "North Carolina Regulations for Protection Against Radiation," the maximum permissible concentration (MPC) for Xenon 127 in air shall be 9×10^{-6} microcurie per milliliter for a restricted area and 2×10^{-7} microcurie per milliliter for an unrestricted area.

23. The licensee shall comply with the provisions of 10 NCAC 3G .2800, "Use of Sealed Radioactive Sources in the Healing Arts."

24. Patients containing Iodine 131 for the treatment of thyroid carcinoma, or patients containing therapeutic quantities of Gold 198, shall remain hospitalized until the residual activity is 30 millicuries or less.

25. Patients containing Radon 222 implants shall remain hospitalized until the residual activity is 30 millicuries or less.

26. Patients containing Cobalt 60, Cesium 137, Radium 226, or Iridium 192, implants shall remain hospitalized until surveys made with an appropriate radiation detection instrument indicate that all implants have been removed.

27. Patients containing implants shall remain hospitalized until the implants are removed, except that patients containing Iodine 125 seeds may be released from the hospital, provided the attending physician has determined the seeds are secured and are not likely to be lost by the patient.

RADIATION PROTECTION SECTION
DIVISION OF FACILITY SERVICES
N.C. DEPARTMENT OF HUMAN RESOURCES
RADIOACTIVE MATERIAL LICENSE

License No. 032-0085-3

Supplementary Sheet

Conditions (continued):

28. The licensee shall conduct a physical inventory every six (6) months to account for all sealed sources received and possessed under the license. The records of the inventories shall be maintained for two (2) years from the date of the inventory for inspection by the Agency and shall include the quantities and kinds of radioactive material, location of sealed sources, and the date of the inventory.

29. Except as specifically provided otherwise by this license, the licensee shall possess and use radioactive material described in Items 6, 7 and 8 of this license in accordance with statements, representations and procedures contained in:

A. Application with attachments dated March 28, 1989 and signed by Kenneth W. Lyles, M.D., Chairman, Radiation Control Committee.

Date of Issuance March 7, 1989

For - Dayne H. Brown
Chief, Radiation Protection Section

Form No. DFS-5211
(Rev. 3/88)

VIII.

The Hippocratic Oath

I swear by Apollo the Physician, and Aesculapius, Hygeia, and Panacea, and all the gods and goddesses, and by whatever I hold most sacred, that I will be loyal to the Profession of Medicine and just and generous to its members; that I will lead my life and practice my art in uprightness and honour; that into whatsoever house I shall enter, it shall be for the good of the sick to the utmost of my power, holding myself far aloof from wrong, from corruption, from the tempting of others to vice; that I will exercise my art solely for the cure of my patients and will give no drug, perform no operation for a criminal purpose, even if solicited, far less suggest it; that whatsoever I shall see or hear of the lives of men which is not fitting to be spoken, I will keep inviolably secret.

IX.

PART I. THE ATOMIC ENERGY ACT OF 1954[1] AS AMENDED

Public Law 83-703
(68 Stat. 919)

AN ACT

To amend the Atomic Energy Act of 1946, as amended, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That the Atomic Energy Act of 1946, as amended, is amended to read as follows:

"ATOMIC ENERGY ACT OF 1954

[1] For index to legislative history, see appendix 3, *infra*.

See next page →

so notify the Commission. Violation of the condition prescribed by this subsection may, in the Commission's discretion, constitute grounds for license revocation. In accordance with section 187 of this Act, the Commission shall promptly amend each license for a utilization facility issued under this section or section 104 b. which is in effect on the date of enactment of this subsection to include the provisions required under this subsection."[83] 42 U.S.C. 2237

"SEC 104. MEDICAL THERAPY AND RESEARCH AND DEVELOPMENT — Medical therapy and research and development 42 U.S.C. sec. 2134

"a. The Commission is authorized to issue licenses to persons applying for use in medical therapy. In issuing such licenses the Commission is directed to permit the widest amount of effective medical therapy possible with the amount of special nuclear material available for such purposes and to impose the minimum amount of regulation consistent with its obligations under this Act to promote the common defense and security and to protect the health and safety of the public.

"b. As provided for in subsection 102b., or 102c., or where specifically authorized by law, the Commission is authorized to issue licenses under this subsection to persons applying therefor for utilization and production facilities for industrial and commercial purposes. In issuing licenses under this subsection, the Commission shall impose the minimum amount of such regulations and terms of license as will permit the Commission to fulfill its obligations under this Act.[84]

"c. The Commission is authorized to issue licenses to persons applying therefor for utilization and production facilities useful in the conduct of research and development activities of the types specified in section 31 and which are not facilities of the type specified in subsection 104b. The Commission is directed to impose only such minimum amount of regulation of the licensee as the Commission finds will permit the Commission to fulfill its obligations under this Act to promote the common defense and security and to protect the health and safety of the public and will permit the conduct of widespread and diverse research and development.

"d. No license under this section may be given to any person for activities which are not under or within the jurisdiction of the United States, except for the export of production or utilization facilities under terms of an agreement for cooperation arranged pursuant to section

---

[83] Public Law 96-295 (94 Stat. 786) (1980) sec. 201, added subsec. (f) without prior enactment of subsec. (e).

[84] Public Law 91-560 (84 Stat. 1472) (1970), sec. 5, amended subsec. 104 b. Before amendment it read as follows:

"b. The Commission is authorized to issue licenses to persons applying therefor for utilization and production facilities involved in the conduct of research and development activities leading to the demonstration of the practical value of such facilities for industrial or commercial purposes. In issuing licenses under this subsection, the Commission shall impose the minimum amount of such regulations and terms of license as will permit the Commission to fulfill its obligations under the Act to promote the common defense and security and to protect the health and safety of the public and will be compatible with the regulations and terms of license which would apply in the event that a commercial license were later to be issued pursuant to section 103 for that type of facility. In issuing such licenses, priority shall be given to those activities which will, in the opinion of the Commission, lead to major advances in the application of atomic energy for industrial or commercial purposes."

123 or except under the provisions of section 109. No license may be issued to any corporation or other entity if the Commission knows or has reason to believe it is owned, controlled, or dominated by an alien, a foreign corporation, or a foreign government. In any event, no license may be issued to any person within the United States if, in the opinion of the Commission, the issuance of a license to such person would be inimical to the common defense and security or to the health and safety of the public.

Antitrust provisions. 42 U.S.C. sec. 2135.

"SEC. 105. ANTITRUST PROVISIONS.—

"a. Nothing contained in this Act[83] shall relieve any person from the operation of the following Acts, as amended, An Act to protect trade and commerce against unlawful restraints and monopolies, approved July second, eighteen hundred and ninety; sections seventy-three to seventy-seven inclusive, of an Act entitled 'An Act to reduce taxation, to provide revenue for the Government, and for other purposes approved August twenty-seven, eighteen hundred and ninety-four; 'An Act to supplement existing laws against unlawful restraints and monopolies, and for other purposes, approved October fifteen, nineteen hundred and fourteen; and 'An Act to create a Federal Trade Commission, to define its powers and duties, and for other purposes, approved September twenty-six, nineteen hundred and fourteen. In the event a licensee is found by a court of competent jurisdiction, either in an original action in that court or in a proceeding to enforce or review the findings or orders of any Government agency having jurisdiction under the laws cited above, to have violated any of the provisions of such laws in the conduct of the licensed activity, the Commission may suspend, revoke, or take such other action as it may deem necessary with respect to any license issued by the Commission under the provisions of this Act.

26 Stat. 209; 15 U.S.C. 1-7.

28 Stat. 570; 15 U.S.C. 80-11.

38 Stat. 730; 15 U.S.C. 41-51, 44; 18 U.S.C. 402; 29 U.S.C. 52; 53, 38 Stat. 717; 15 U.S.C. 41-58.

"b. The Commission shall report promptly to the Attorney General any information it may have with respect to any utilization of special nuclear material or atomic energy which appears to violate or to tend toward the violation of any of the foregoing Acts, or to restrict free competition in private enterprise.

"c. (1) The Commission shall promptly transmit to the Attorney General a copy of any license application provided for in paragraph (2) of this subsection, and a copy of any written request provided for in paragraph (3) of this subsection; and the Attorney General shall, within a reasonable time, but in no event to exceed 180 days after receiving a copy of such application or written request, render such advice to the Commission as he determines to be appropriate in regard to the finding to be made by the Commission pursuant to paragraph (5) of this subsection. Such advice shall include an explanatory statement as to the reasons or basis therefor.

---

[83] Public Law 88-489 (78 Stat. 602) (1964), sec. 14, deleted the phrase ", including the provisions which vest title to all special nuclear material in the United States," which appeared after the word "Act".

1. Marcus CS, Kuperus JH, Butler JA et al.: Phagocytic labeling of leukocytes with Tc-99m-albumin colloid for nuclear imaging. Nuc. Med. Biol. 15:673-682, 1988.

Henneman PL, Marcus CS, Butler JA et al.: Appendicitis: Evaluation by Tc-99m-leukocyte scan. Ann. Emerg. Med. 17:111-116, 1988.

11. Conroy RM, Lyons KP, Kuperus JH et al.: New technique for localization of therapeutic emboli using radionuclide labeling. Am. J. Roentgenol. 130:523-528, 1978.

iii. Marcus CS, Myhre BA, Angulo MC et al.: Radiolabeled red cell viability I. Comparison of Cr-51, Tc-99m, and In-111 for measuring the viability of autologous stored red cells. Transfusion 27:415-419, 1987.

Marcus CS, Myhre BA, Angulo MC et al.: Radiolabeled red cell viability II. Tc-99m and In-111 for measuring the viability of homologous red cells in vivo. Transfusion 27:420-424, 1987.

iv. Hollander L: Treatment of malignant blood disease with radioactive phosphorus. Chapter 29 of Blahd WH: Nuclear Medicine, Mcgraw-Hill, NY, NY, pp. 760-774, 1971.

XI.

Federal Food, Drug, and Cosmetic Act, as Amended, and Related Laws

U S DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20857
HHS Publication No. (FDA) 87-1158

CONTENTS

[illegible] Act, as amended, is published [illegible] through August 1985. The Act appears [illegible] under title 21. Corresponding section numbers [illegible] after the section number of the Act.

Parallel [illegible] regulations promulgated under the Federal Food, Drug, and Cosmetic Act by parts numbered according to the Code of Federal Regulations, title 21.

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

section (except that such amendment or repeal may be initiated either by a proposal of the Secretary or by a petition of any interested person) and (2) the Secretary finds, on the basis of new information with respect to such drug evaluated together with the information before him when the application under section 505 became effective or was approved, that there is a lack of substantial evidence (as defined in section 505(d)) that the drug has the effect it purports or is represented to have under such conditions of use.

AUTHORITY TO DESIGNATE OFFICIAL NAMES

SEC. 508.[46] [358] (a) The Secretary may designate an official name for any drug or device if he determines that such action is necessary or desirable in the interest of usefulness and simplicity. Any official name designated under this section for any drug or device shall be the only official name of that drug or device used in any official compendium published after such name has been prescribed or for any other purpose of this Act. In no event, however, shall the Secretary establish an official name so as to infringe a valid trademark.

(b) Within a reasonable time after the effective date of this section, and at such other times as he may deem necessary, the Secretary shall cause a review to be made of the official names by which drugs are identified in the official United States Pharmacopeia, the official Homeopathic Pharmacopeia of the United States, and the official National Formulary, and all supplements thereto and at such times as he may deem necessary shall cause a review to be made of the official names by which devices are identified in any official compendium (and all supplements thereto), to determine whether revision of any of those names is necessary or desirable in the interest of usefulness and simplicity.

(c) Whenever he determines after any such review that (1) any such official name is unduly complex or is not useful for any other reason, (2) two or more official names have been applied to a single drug or device, or to two or more drugs which are identical in chemical structure and pharmacological action and which are substantially identical in strength, quality, and purity or to two or more devices which are substantially equivalent in design and purpose, or (3) no official name has been applied to a medically useful drug or device, he shall transmit in writing to the compiler of each official compendium in which that drug or drugs or device are identified and recognized his request for the recommendation of a single official name for such drug or drugs or device which will have usefulness and simplicity. Whenever such a single official name has not been recommended within one hundred and eighty days after such request, or the Secretary determines that any name so recommended is not useful for any reason, he shall designate a single official name for such drug or drugs or device. Whenever he determines that the name so

[46]Sec. 508 amended by sec. 5(b) of P.L. 94-295.

recommended is useful, he shall designate that name as the official name of such drug or drugs or device. Such designation shall be made as a regulation upon public notice and in accordance with the procedure set forth in section 4 of the Administrative Procedure Act (5 U.S.C. 1003).

(d) After each such review, and at such other times as the Secretary may determine to be necessary or desirable, the Secretary shall cause to be compiled, published, and publicly distributed a list which shall list all revised official names of drugs or devices designated under this section and shall contain such descriptive and explanatory matter as the Secretary may determine to be required for the effective use of those names.

(e) Upon a request in writing by any compiler of an official compendium that the Secretary exercise the authority granted to him under section 508(a), he shall upon public notice and in accordance with the procedure set forth in section 4 of the Administrative Procedure Act (5 U.S.C. 1003) designate the official name of the drug or device for which the request is made.

NONAPPLICABILITY TO COSMETICS

SEC. 509. [359] This chapter, as amended by the Drug Amendments of 1962, shall not apply to any cosmetic unless such cosmetic is also a drug or device or component thereof.

REGISTRATION OF PRODUCERS OF DRUGS[47] AND DEVICES[48]

SEC. 510. [360] [48, 49, 50] (a) As used in this section –

(1) the term "manufacture, preparation, propagation, compounding, or processing" shall include repackaging or otherwise changing the container, wrapper, or labeling of any drug package or device

[47]The Congress hereby finds and declares in order to make regulation of interstate commerce in drugs effective, it is necessary to provide for registration and inspection of all establishments in which drugs are manufactured, prepared, propagated, compounded, or processed; that the products of all such establishments are likely to enter the channels of interstate commerce and directly affect such commerce; and that the regulation of interstate commerce in drugs without provision for registration and inspection of establishments that may be engaged only in intrastate commerce in such drugs would discriminate against and burden interstate commerce in such drugs, and adversely burden, obstruct, and affect such interstate commerce. Amended by sec. 701 of P.L. 91-513.

[48]Secs. 10 and 11 of P.L. 89-74 apply to certain provisions in sec. 510 and to all of sec. 511. Secs. 10 and 11 of P.L. 89-74 provide that –

Nothing in this Act shall be construed as authorizing the manufacture, compounding, processing, possession, sale, delivery, or other disposal of any drug in any State in contravention of the laws of such State.

No provision of this Act nor any amendment made by it shall be construed as indicating an intent on the part of the Congress to occupy the field in which such provision or amendment operates to the exclusion of any State law on the same subject matter, unless there is a direct and positive conflict between such provision or amendment and such State law so that the two cannot be reconciled or consistently stand together.

No amendment made by this Act shall be construed to prevent the enforcement in the courts of any State of any statue of such State prescribing any criminal penalty for any act made criminal by such amendment.

[49]Subsec. (a)(2) repealed and sec. (a)(3) redesignated as sec. (a)(2) by sec. 701 of P.L. 91-513. Subsec. (b), (c), (d) amended by sec. 701 of P.L. 91-513.

[50]Sec. 510 amended by sec. 4 of P.L. 94-295.

package in furtherance of the distribution of the drug or device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer or user; and

(2) the term "name" shall include in the case of a partnership the name of each partner and, in the case of a corporation, the name of each corporate officer and director, and the State of incorporation.

(b) On or before December 31 of each year every person who owns or operates any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices shall register with the Secretary his name, places of business, and all such establishments.

(c) Every person upon first engaging in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices in any establishment which he owns or operates in any State shall immediately register with the Secretary his name, place of business, and such establishment.

(d) Every person duly registered in accordance with the foregoing subsections of this section shall immediately register with the Secretary any additional establishment which he owns or operates in any State and in which he begins the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices.

(e) The Secretary may assign a registration number to any person or any establishment registered in accordance with this section. The Secretary may also assign a listing number to each drug or class of drugs listed under subsection (j). Any number assigned pursuant to the preceding sentence shall be the same as that assigned pursuant to the National Drug Code. The Secretary may by regulation prescribe a uniform system for the identification of devices intended for human use and may require that persons who are required to list such devices pursuant to subsection (j) shall list such devices in accordance with such system.

(f) The Secretary shall make available for inspection, to any person so requesting, any registration filed pursuant to this section, except that any list submitted pursuant to paragraph (3) of subsection (j) and the information accompanying any list or notice filed under paragraph (1) or (2) of that subsection shall be exempt from such inspection unless the Secretary finds that such an exemption would be inconsistent with protection of the public health.

(g) The foregoing subsections of this section shall not apply to—

(1) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail;

(2) practitioners licensed by law to prescribe or administer drugs or devices and who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in the course of their professional practice;

(3) persons who manufacture, prepare, propagate, compound, or process drugs or devices solely for use in research, teaching, or chemical analysis and not for sale;

(4) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that registration by such classes of persons in accordance with this section is not necessary for the protection of the public health.

(h) Every establishment in any State registered with the Secretary pursuant to this section shall be subject to inspection pursuant to section 704 and every such establishment engaged in the manufacture, propagation, compounding, or processing of a drug or drugs or of a device or devices classified in class II or III shall be so inspected by one or more officers or employees duly designated by the Secretary at least once in the two-year period beginning with the date of registration of such establishment pursuant to this section and at least once in every successive two-year period thereafter.

(i) Any establishment within any foreign country engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices shall be permitted to register under this section pursuant to regulations promulgated by the Secretary. Such regulations shall require such establishment to provide the information required by subsection (j) and shall require such establishment to provide the information required by subsection (j) in the case of a device or devices and shall include provisions for registration of any such establishment upon condition that adequate and effective means are available, by arrangement with the government of such foreign country or otherwise, to enable the Secretary to determine from time to time whether drugs or devices manufactured, prepared, propagated, compounded or processed in such establishment, if imported or offered for import into the United States, shall be refused admission on any of the grounds set forth in section 801(a) of this Act.

(j)(1) Every person who registers with the Secretary under subsection (b), (c), or (d) shall, at the time of registration under any such subsection, file with the Secretary a list of all drugs and a list of all devices and a brief statement of the basis for believing that each device included in the list is a device rather than a drug (with each drug and device in each list listed by its established name as defined in section 502(e) and by any proprietary name) which is being manufactured, prepared, propagated, compounded, or processed by him for commercial distribution and which he has not included in any list of drugs or devices filed by him with the Secretary under this paragraph or paragraph (2) before such time of registration. Such list shall be prepared in such form and manner as the Secretary may prescribe and shall be accompanied by—

except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

(q) The term "pesticide chemical" means any substance which, alone, in chemical combination or in formulation with one or more other substance, is "a pesticide" within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C., sec. 136(u)) as now in force or as hereafter amended, and which is used in the production, storage, or transportation of raw agricultural commodities.

(r) The term "raw agricultural commodity" means any food in its raw or natural state, including all fruits that are washed, colored, or otherwise treated in their unpeeled natural form prior to marketing.

(s) [5] The term "food additive" means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include—

(1) a pesticide chemical in or on a raw agricultural commodity; or

(2) a pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity; or

(3) a color additive; or

occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the first day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.]

[5] Subsec. 201(s)(5) added by sec. 102(c) of P.L. 90-399.

(4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following); or

(5) a new animal drug.

(t)(1) The term "color additive" means a material which—

(A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and

(B) when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto;

except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.

(2) The term "color" includes black, white, and intermediate grays.

(3) Nothing in subparagraph (1) of this paragraph shall be construed to apply to any pesticide chemical, soil or plant nutrient, or other agricultural chemical solely because of its effect in aiding, retarding, or otherwise affecting, directly or indirectly, the growth or other natural physiological processes of produce of the soil and thereby affecting its color, whether before or after harvest.

(u) [6] The term "safe," as used in paragraph (s) of this section and in sections 409, 512, and 706, has reference to the health of man or animal.

(v) [7] • • •

(w) [8] The term "new animal drug" means any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed—

(1) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof; except that such a drug not so recognized shall not be deemed to be a "new animal drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under

[6] Sec. 201(u) amended by sec. 102(d) of P.L. 90-399.

[7] Subsec. 201(v) repealed by sec. 701 of P.L. 91-513.

[8] Secs. 201(w) and (x) added by sec. 102(e) of P.L. 90-399.

FEDERAL FOOD, DRUG, AND COSMETIC ACT, AS AMENDED

CHAPTER I – SHORT TITLE

SEC. 1. This Act may be cited as the Federal Food, Drug, and Cosmetic Act.

CHAPTER II – DEFINITIONS

SEC. 201. [321] For the purposes of this Act –

(a) (1) The term "State", except as used in the last sentence of section 702(a), means any State or Territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.

(2) [1] The term "Territory" means any Territory or possession of the United States, including the District of Columbia, and excluding the Commonwealth of Puerto Rico and the Canal Zone.

(b) The term "interstate commerce" means (1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body.

(c) The term "Department" means the U.S. Department of Health and Human Services.

(d) The term "Secretary" means the Secretary of Health and Human Services.

(e) The term "person" includes individual, partnership, corporation, and association.

(f) [*] The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any other such article.

(g) (1) The term "drug" means (A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the

---

[1] Subsec. 201(a)(2) amended by sec. 4(a) of P.L. 90-639 and by Sec. 701 of P.L. 91-513.

NOTE – References in brackets [ ] are to title 21 U.S. Code.

[*] The following additional definitions for food are provided for in other acts:

Sec. 201a [321a]. Butter. The Act of March 4, 1923 (42 Stat. 1500), defines butter as "For the purposes of this chapter 'butter' shall be understood to mean the food product usually known as butter, and which is made exclusively from milk or cream, or both, with or without common salt, and with or without additional coloring matter, and containing not less than 80 per centum by weight of milk fat, all tolerances having been allowed for."

Sec. 201b [321b]. Package. The Act of July 24, 1919 (41 Stat. 271), declares "The word 'package' where it occurs in this chapter shall include and shall be construed to include wrapped meats enclosed in papers or other materials as prepared by the manufacturers thereof for sale."

Sec. 201c [321c]. Nonfat Dry Milk. The Act of July 2, 1956 (70 Stat. 486), defines nonfat dry milk as follows: "* * * for the purposes of the Federal Food, Drug, and Cosmetic Act of June 26 sec. 1938 (ch. 675, sec. 1, 52 Stat. 1040), nonfat dry milk is the product resulting from the removal of fat and water from milk, and contains the lactose, milk proteins, and milk minerals in the same relative proportions as in the fresh milk from which made. It contains not over 5 per centum by weight of moisture. The fat content is not over 1½ per centum by weight unless otherwise indicated."

"The term 'milk', when used herein, means sweet milk of cows."

The definition of oleomargine appears preceding sec. 407a.

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 articles specified in clause (A), (B), or (C); but does not include devices or their components, parts, or accessories.

(2) The term "counterfeit drug" means a drug which, or the container or labeling of which, without authorization, bears the trademark, trade name, or other identifying mark, imprint, or device, or any likeness thereof, of a drug manufacturer, processor, packer, or distributor other than the person or persons who in fact manufactured, processed, packed, or distributed such drug and which thereby falsely purports or is represented to be the product of, or to have been packed or distributed by, such other drug manufacturer, processor, packer, or distributor.

(h) [2] The term "device" (except when used in paragraph (n) of this section and in sections 301 (i), 403 (f), 502 (c), and 602 (c)) 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 any of its principal 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 any of its principal intended purposes.

(i) The term "cosmetic" means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.

(j) The term "official compendium" means the official United States Pharmacopeia, offical Homeopathic Pharmacopeia of the United States, official National Formulary, or any supplement to any of them.

(k) The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also

[2] Sec. 201(h) amended by sec. 3(a)(1) of P.L. 94-295.

appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

(l) The term "immediate container" does not include package liners.

(m) The term "labeling" means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

(n) [3] If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.

(o) The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body.

(p) [4] The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof,

[3] Sec. 201(n) amended by sec. 501(a)(2)(A) of P.L. 94-278.

[4] Sec. 201(p) amended by secs. 107(a) and (b) of P.L. 90-399.

"ENACTMENT DATE" AS DEFINED IN DRUG AMENDMENTS ACT OF 1962

Sec. 107 of P.L. 87-781

Sec. 107(c)(1) [As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the date immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act, insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first

(continued)

XII.

OPRR Reports

NIH PHS HHS

PROTECTION OF HUMAN SUBJECTS

CODE OF FEDERAL REGULATIONS

45 CFR 46

Revised as of March 8, 1983

"INSTITUTIONAL REVIEW BOARDS; ETHICS GUIDANCE PROGRAM

"SEC. 491. (a) The Secretary shall by regulation require that each entity which applies for a grant, contract, or cooperative agreement under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant, contract, or cooperative agreement assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an 'Institutional Review Board') to review biomedical and behavioral research involving human subjects conducted at or supported by such entity in order to protect the rights of the human subjects of such research.

"(b)(1) The Secretary shall establish a program within the Department of Health and Human Services under which requests for clarification and guidance with respect to ethical issues raised in connection with biomedical or behavioral research involving human subjects are responded to promptly and appropriately.

"(2) The Secretary shall establish a process for the prompt and appropriate response to information provided to the Director of NIH respecting incidences of violations of the rights of human subjects of research for which funds have been made available under this Act. The process shall include procedures for the receiving of reports of such information from recipients of funds under this Act and taking appropriate action with respect to such violations.

CODE OF FEDERAL REGULATIONS

TITLE 45
PUBLIC WELFARE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
OFFICE FOR PROTECTION FROM RESEARCH RISKS

PART 46—PROTECTION OF HUMAN SUBJECTS
REVISED AS OF MARCH 8, 1983

PART 46—PROTECTION OF HUMAN SUBJECTS

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

Subpart B—Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Subpart D—Additional Protections for Children Involved as Subjects in Research

Authority: 5 U.S.C. 301; sec. 474(a), 88 Stat. 352 (42 U.S.C. 289i-3(a)).

Subpart A—Basic HHS Policy for Protection of Human Research Subjects

Source: 46 FR 8336, January 26, 1981, 48 FR 9269, March 4, 1983.

§ 46.101 To what do these regulations apply?

(a) Except as provided in paragraph (b) of this section, this subpart applies to all research involving human subjects conducted by the Department of Health and Human Services or funded in whole or in part by a Department grant, contract, cooperative agreement or fellowship.

(1) This includes research conducted by Department employees, except each Principal Operating Component head may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or funded by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of this section waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from these regulations unless the research is covered by other subparts of this part:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), if

information taken from these sources is recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(3) Research involving survey or interview procedures, except where all of the following conditions exist: (i) responses are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the subject's responses, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior, such as illegal conduct, drug use, sexual behavior, or use of alcohol. All research involving survey or interview procedures is exempt, without exception, when the respondents are elected or appointed public officials or candidates for public office.

(4) Research involving the observation (including observation by participants) of public behavior, except where all of the following conditions exist: (i) observations are recorded in such a manner that the human subjects can be identified, directly or through identifiers linked to the subjects, (ii) the observations recorded about the individual, if they became known outside the research, could reasonably place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing or employability, and (iii) the research deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

(5) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(6) Unless specifically required by statute (and except to the extent specified in paragraph (i)), research and demonstration projects which are conducted by or subject to the approval of the Department of Health and Human Services, and which are designed to study, evaluate, or otherwise examine: (i) programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(c) The Secretary has final authority to determine whether a particular activity is covered by these regulations.

(d) The Secretary may require that specific research activities or classes of research activities conducted or funded by the Department, but not otherwise covered by these regulations, comply with some or all of these regulations.

(e) The Secretary may also waive applicability of these regulations to specific research activities or classes of research activities, otherwise covered by these regulations. Notices of these actions will be published in the *Federal Register* as they occur.

(f) No individual may receive Department funding for research covered by these regulations unless the individual is affiliated with or sponsored by an institution which assumes responsibility for the research under an assurance satisfying the requirements of this part or the individual makes other arrangements with the Department.

(g) Compliance with these regulations will in no way render inapplicable pertinent federal, state, or local laws or regulations.

(h) Each subpart of these regulations contains a separate section describing to what the subpart applies. Research which is covered by more than one subpart shall comply with all applicable subparts.

(i) If, following review of proposed research activities that are exempt from these regulations under paragraph (b)(6), the Secretary determines that a research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject of the research or demonstration project, then federal funds may not be expended for such a project without the written, informed consent of each participant or subject.

§ 46.102 Definitions.

(a) "Secretary" means the Secretary of Health and Human Services and any other officer or employee of the Department of Health and Human Services to whom authority has been delegated.

(b) "Department" or "HHS" means the Department of Health and Human Services.

(c) "Institution" means any public or private entity or agency (including federal, state, and other agencies).

(d) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(e) "Research" means a systematic investigation designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute "research" for purposes of these regulations, whether or not they are supported or funded under a program which is considered research for other purposes. For example, some "demonstration" and "service" programs may include research activities.

(f) "Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. "Intervention" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

(g) "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(h) "Certification" means the official notification by the institution to the Department in accordance with the requirements of this part that a research project or activity involving human subjects has been reviewed and approved by the Institutional Review Board (IRB) in accordance with the approved assurance on file at HHS. (Certification is required when the research is funded by the Department and not otherwise exempt in accordance with § 46.101(b)).

§ 46.103 Assurances.

(a) Each institution engaged in research covered by these regulations shall provide written assurance satisfactory to the Secretary that it will comply with the requirements set forth in these regulations.

(b) The Department will conduct or fund research covered by these regulations only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Secretary that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. This assurance shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of source of funding. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt provisions of these regulations applicable to Department-funded research and is not applicable to any research in an exempt category listed in § 46.101.

(2) Designation of one or more IRBs established in accordance with the requirements of this subpart, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the Secretary.[1]

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; (iii) for insuring prompt reporting to the IRB of proposed changes in a research activity, and for insuring that changes in approved research, during the period for which IRB approval has already been given may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the subject; and (iv) for insuring prompt reporting to the IRB and to the Secretary[1] of unanticipated problems involving risks to subjects or others.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by these regulations, and shall be filed in such form and manner as the Secretary may prescribe.

(d) The Secretary will evaluate all assurances submitted in accordance with these regulations through such officers and employees of the Department and such experts or consultants engaged for this purpose as the Secretary determines to be appropriate. The Secretary's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be

[1] Reports should be filed with the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205.

involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the Secretary may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The Secretary may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Within 60 days after the date of submission to HHS of an application or proposal, an institution with an approved assurance covering the proposed research shall certify that the application or proposal has been reviewed and approved by the IRB. Other institutions shall certify that the application or proposal has been approved by the IRB within 30 days after receipt of a request for such a certification from the Department. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

§ 46.104 [Reserved]

§ 46.105 [Reserved]

§ 46.106 [Reserved]

§ 46.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' backgrounds including consideration of the racial and cultural backgrounds of members and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, including but not limited to subjects covered by other subparts of this part, the IRB shall include one or more individuals who are primarily concerned with the welfare of these subjects.

(b) No IRB may consist entirely of men or entirely of women, or entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in nonscientific areas; for example, lawyers, ethicists, members of the clergy.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participating in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§ 46.108 IRB functions and operations.

In order to fulfill the requirements of these regulations each IRB shall:

(a) Follow written procedures as provided in § 46.103(b)(4).

(b) Except when an expedited review procedure is used (see § 46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

(c) Be responsible for reporting to the appropriate institutional officials and the Secretary[1] any serious or continuing noncompliance by investigators with the requirements and determinations of the IRB.

§ 46.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 46.116. The IRB may require that information, in addition to that specifically mentioned in § 46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § 46.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification

[1] Reports should be filed with the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205.

a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

§46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary has established, and published in the *Federal Register*, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the *Federal Register*.

(b) An IRB may review some or all of the research appearing on the list through an expedited review procedure, if the research involves no more than minimal risk. The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Secretary may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to insure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§ 46.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 46.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Secretary.[1]

[1] Reports should be filed with the Office for Protection from Research Risks, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20205.

§ 46.114 Cooperative research.

Cooperative research projects are those projects, normally supported through grants contracts, or similar arrangements, which involve institutions in addition to the grantee or prime contractor (such as a contractor with the grantee, or a subcontractor with the prime contractor). In such instances, the grantee or prime contractor remains responsible to the Department for safeguarding the rights and welfare of human subjects. Also, when cooperating institutions conduct some or all of the research involving some or all of these subjects, each cooperating institution shall comply with these regulations as though it received funds for its participation in the project directly from the Department, except that in complying with these regulations institutions may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

§ 46.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members as required by § 46.103(b)(3).

(6) Written procedures for the IRB as required by § 46.103(b)(4).

(7) Statements of significant new findings provided to subjects, as required by § 46.116(b)(5).

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Department at reasonable times and in a reasonable manner.

§ 46.116 General requirements for informed consent.

Except as provided elsewhere in this or other subparts, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) programs under the Social Security Act, or other public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

§ 46.117 Documentation of informed consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by § 46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A "short form" written consent document stating that the elements of informed consent required by § 46.116 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the "short form."

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

§ 46.118 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to the Department with the knowledge that subjects may be involved within the

period of funding, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants (including bloc grants) where selection of specific projects is the institution's responsibility; research training grants where the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research described in § 46.101(b), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in these regulations, and certification submitted to the Department.

§ 46.119 Research undertaken without the intention of involving human subjects.

In the event research (conducted or funded by the Department) is undertaken without the intention of involving human subjects, but it is later proposed to use human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in these regulations, a certification submitted to the Department, and final approval given to the proposed change by the Department.

§ 46.120 Evaluation and disposition of applications and proposals.

(a) The Secretary will evaluate all applications and proposals involving human subjects submitted to the Department through such officers and employees of the Department and such experts and consultants as the Secretary determines to be aporopriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the proposed research to the subjects and others, and the importance of the knowledge to be gained.

(b) On the basis of this evaluation, the Secretary may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§ 46.121 Investigational new drug or device 30-day delay requirement.

When an institution is required to prepare or to submit a certification with an application or proposal under these regulations, and the application or proposal involves an investigational new drug (within the meaning of 21 U.S.C. 355(i) or 357(d)) or a significant risk device (as defined in 21 CFR 812.3(m)), the institution shall identify the drug or device in the certification. The institution shall also state whether the 30-day interval required for investigational new drugs by 21 CFR 312.1(a) and for significant risk devices by 21 CFR 812.30 has elapsed, or whether the Food and Drug Administration has waived that requirement. If the 30-day interval has expired, the institution shall state whether the Food and Drug Administration has requested that the sponsor continue to withhold or restrict the use of the drug or device in human subjects. If the 30-day interval has not expired, and a waiver has not been received, the institution shall send a statement to the Department upon expiration of the interval. The Department will not consider a certification acceptable until the institution has submitted a statement that the 30-day interval has elapsed, and the Food and Drug Administration has not requested it to limit the use of the drug or device, or that the Food and Drug Administration has waived the 30-day interval.

§ 46.122 Use of Federal funds.

Federal funds administered by the Department may not be expended for research involving human subjects unless the requirement of these regulations, including all subparts of these regulations, have been satisfied.

§ 46.123 Early termination of research funding; evaluation of subsequent applications and proposals.

(a) The Secretary may require that Department funding for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the Secretary finds an institution has materially failed to comply with the terms of these regulations.

(b) In making decisions about funding applications or proposals covered by these regulations the Secretary may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person who would direct the scientific and technical aspects of an activity has in the judgment of the Secretary materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not Department funds were involved).

§ 46.124 Conditions.

With respect to any research project or any class of research projects the Secretary may impose additional conditions prior to or at the time of funding when in the Secretary's judgment additional conditions are necessary for the protection of human subjects.

Subpart B—Additional Protections Pertaining to Research Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Source: 40 FR 33528, Aug. 8, 1975, 43 FR 1758, January 11, 1978, 43 FR 51359, November 3, 1978

§ 46.201 Applicability.

(a) The regulations in this subpart are applicable to all Department of Health, Education, and Welfare

grants and contract supporting research, development, and related activities involving: (1) The fetus, (2) pregnant women, and (3) human *in vitro* fertilization.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will in any way render inapplicable pertinent State or local laws bearing upon activities covered by this subpart.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.202 Purpose.

It is the purpose of this subpart to provide additional safeguards in reviewing activities to which this subpart is applicable to assure that they conform to appropriate ethical standards and relate to important societal needs.

§ 46.203 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(b) "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

(c) "Fetus" means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or a medically acceptable pregnancy test), until a determination is made, following explusion or extraction of the fetus, that it is viable.

(d) "Viable" as it pertains to the fetus means being able, after either spontaneous or induced delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart. If a fetus is viable after delivery, it is a premature infant.

(e) "Nonviable fetus" means a fetus *ex utero* which, although living, is not viable.

(f) "Dead fetus" means a fetus *ex utero* which exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

(g) "*In vitro* fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

§ 46.204 Ethical Advisory Boards.

(a) One or more Ethical Advisory Boards shall be established by the Secretary. Members of these board(s) shall be so selected that the board(s) will be competent to deal with medical, legal, social, ethical, and related issues and may include, for example, research scientists, physicians, psychologists, sociologists, educators, lawyers, and ethicists, as well as representatives of the general public. No board member may be a regular, full-time employee of the Department of Health, Education, and Welfare.

(b) At the request of the Secretary, the Ethical Advisory Board shall render advice consistent with the policies and requirements of this Part as to ethical issues, involving activities covered by this subpart, raised by individual applications or proposals. In addition, upon request by the Secretary, the Board shall render advice as to classes of applications or proposals and general policies, guidelines, and procedures.

(c) A Board may establish, with the approval of the Secretary, classes of applications or proposals which: (1) Must be submitted to the Board, or (2) need not be submitted to the Board. Where the Board so establishes a class of applications or proposals which must be submitted, no application or proposal within the class may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

(d) No application or proposal involving human *in vitro* fertilization may be funded by the Department or any component thereof until the application or proposal has been reviewed by the Ethical Advisory Board and the Board has rendered advice as to its acceptability from an ethical standpoint.

§ 46.205 Additional duties of the Institutional Review Boards in connection with activities involving fetuses, pregnant women, or human in vitro fertilization.

(a) In addition to the responsibilities prescribed for Institutional Review Boards under Subpart A of this part, the applicant's or offeror's Board shall, with respect to activities covered by this subpart, carry out the following additional duties:

(1) Determine that all aspects of the activity meet the requirements of this subpart;

(2) Determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or offeror for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the Institutional Review Board or subject advocates in: (i) Overseeing the actual process by which individual consents required by this subpart are secured either by approving induction of each individual into the activity or

verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen);

(3) Carry out such other responsibilities as may be assigned by the Secretary.

(b) No award may be issued until the applicant or offeror has certified to the Secretary that the Institutional Review Board has made the determinations required under paragraph (a) of this section and the Secretary has approved these determinations, as provided in § 46.120 of Subpart A of this part.

(c) Applicants or offerors seeking support for activities covered by this subpart must provide for the designation of an Institutional Review Board, subject to approval by the Secretary, where no such Board has been established under Subpart A of this part.

§ 46.206 General limitations.

(a) No activity to which this subpart is applicable may be undertaken unless:

(1) Appropriate studies on animals and nonpregnant individuals have been completed;

(2) Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

(3) Individuals engaged in the activity will have no part in: (i) Any decisions as to the timing, method, and procedures used to terminate the pregnancy, and (ii) determining the viability of the fetus at the termination of the pregnancy; and

(4) No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

(b) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

[40 FR 33528, Aug. 8, 1975, as amended at 40 FR 51638 Nov. 6, 1975]

§ 46.207 Activities directed toward pregnant women as subjects.

(a) No pregnant woman may be involved as a subject in an activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if: (1) The purpose of the activity is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape.

§ 46.208 Activities directed toward fetuses in utero as subjects.

(a) No fetus *in utero* may be involved as a subject in any activity covered by this subpart unless: (1) The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(b) An activity permitted under paragraph (a) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's consent need not be secured if: (1) His identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.209 Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

(a) Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity covered by this subpart unless:

(1) There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

(2) The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

(b) No nonviable fetus may be involved as a subject in an activity covered by this subpart unless:

(1) Vital functions of the fetus will not be artificially maintained,

(2) Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

(3) The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(c) In the event the fetus *ex utero* is found to be viable, it may be included as a subject in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(d) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is

not reasonably available, or (3) the pregnancy resulted from rape.

§ 46.210 Activities involving the dead fetus, fetal material, or the placenta.

Activities involving the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable State or local laws regarding such activities.

§ 46.211 Modification or waiver of specific requirements.

Upon the request of an applicant or offeror (with the approval of its Institutional Review Board), the Secretary may modify or waive specific requirements of this subpart, with the approval of the Ethical Advisory Board after such opportunity for public comment as the Ethical Advisory Board considers appropriate in the particular instance. In making such decisions, the Secretary will consider whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant such modification or waiver and that such benefits cannot be gained except through a modification or waiver. Any such modifications or waivers will be published as notices in the FEDERAL REGISTER.

Subpart C—Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Source: 43 FR 53655, Nov 16, 1978

§ 46.301 Applicability.

(a) The regulations in this subpart are applicable to all biomedical and behavioral research conducted or supported by the Department of Health, Education, and Welfare involving prisoners as subjects.

(b) Nothing in this subpart shall be construed as indicating that compliance with the procedures set forth herein will authorize research involving prisoners as subjects, to the extent such research is limited or barred by applicable State or local law.

(c) The requirements of this subpart are in addition to those imposed under the other subparts of this part.

§ 46.302 Purpose.

Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable.

§ 46.303 Definitions.

As used in this subpart:

(a) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(b) "DHEW" means the Department of Health, Education, and Welfare.

(c) "Prisoner" means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

(d) "Minimal risk" is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

§ 46.304 Composition of Institutional Review Boards where prisoners are involved.

In addition to satisfying the requirements in § 46.107 of this part, an Institutional Review Board, carrying out responsibilities under this part with respect to research covered by this subpart, shall also meet the following specific requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

§ 46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(a) In addition to all other responsibilities prescribed for Institutional Review Boards under this part, the Board shall review research covered by this subpart and approve such research only if it finds that:

(1) The research under review represents one of the categories of research permissible under § 46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to

all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

(b) The Board shall carry out such other duties as may be assigned by the Secretary.

(c) The institution shall certify to the Secretary, in such form and manner as the Secretary may require, that the duties of the Board under this section have been fulfilled.

§ 46.306 Permitted research involving prisoners.

(a) Biomedical or behavioral research conducted or supported by DHEW may involve prisoners as subjects only if:

(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under § 46.305 of this subpart; and

(2) In the judgment of the Secretary the proposed research involves solely the following:

(A) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(B) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(C) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

(D) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology medicine and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research.

(b) Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHEW shall not involve prisoners as subjects.

Subpart D—Additional Protections for Children Involved as Subjects in Research.

Source: 48 FR 9818, March 8, 1983

§ 46.401 To what do these regulations apply?

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of § 46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions (1), (2), (5) and (6) as listed in Subpart A at § 46.101(b) are applicable to this subpart. Exemption (4), research involving the observation of public behavior, listed at § 46.101(b), is applicable to this subpart where the investigator(s) does not participate in the activities being observed. Exemption (3), research involving survey or interview procedures, listed at § 46.101(b) does not apply to research covered by this subpart.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of § 46.101 of Subpart A are applicable to this subpart.

§ 46.402 Definitions.

The definitions in § 46.102 of Subpart A shall be applicable to this subpart as well. In addition, as used in this subpart:

(a) "Children" are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.

(b) "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

(c) "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.

(d) "Parent" means a child's biological or adoptive parent.

(e) "Guardian" means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

§ 46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§ 46.404 Research not involving greater than minimal risk.

HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in § 46.408.

§ 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §§ 46.404, 46.405, or 46.406 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: (1) That the research in fact satisfies the conditions of §§ 46.404, 46.405, or 46.406, as applicable, or (2) the following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The research will be conducted in accordance with sound ethical principles;

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

§ 46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment

may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with § 46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by § 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under §§ 46.404 or 46.405. Where research is covered by §§ 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) In addition to the provisions for waiver contained in § 46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by § 46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§ 46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §§ 46.406 or 46.407 only if such research is:

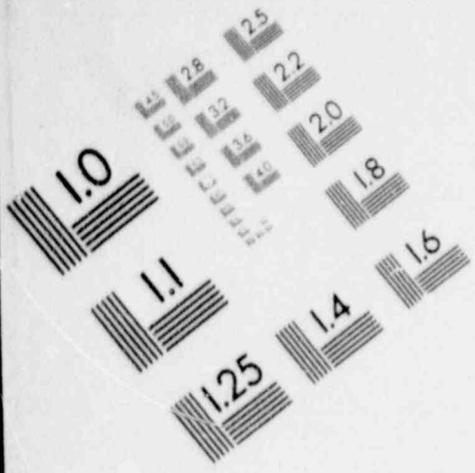
(1) Related to their status as wards; or

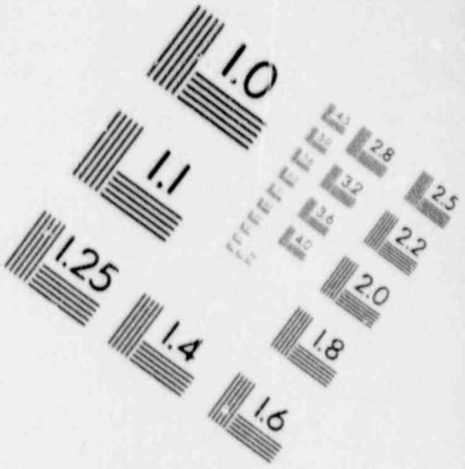
(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

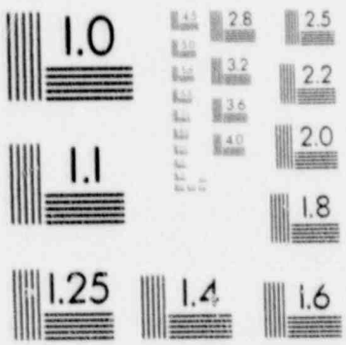
(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

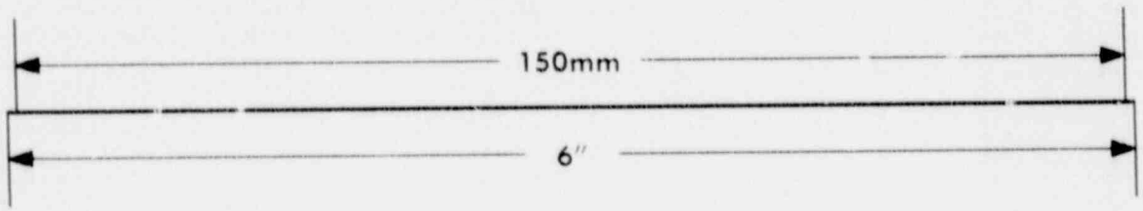
1

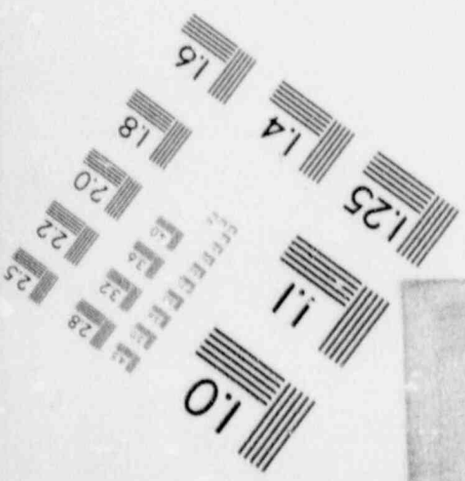
IMAGE EVALUATION TEST TARGET (MT-3)

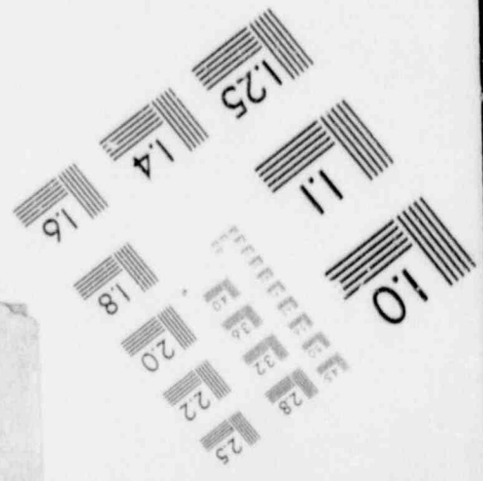


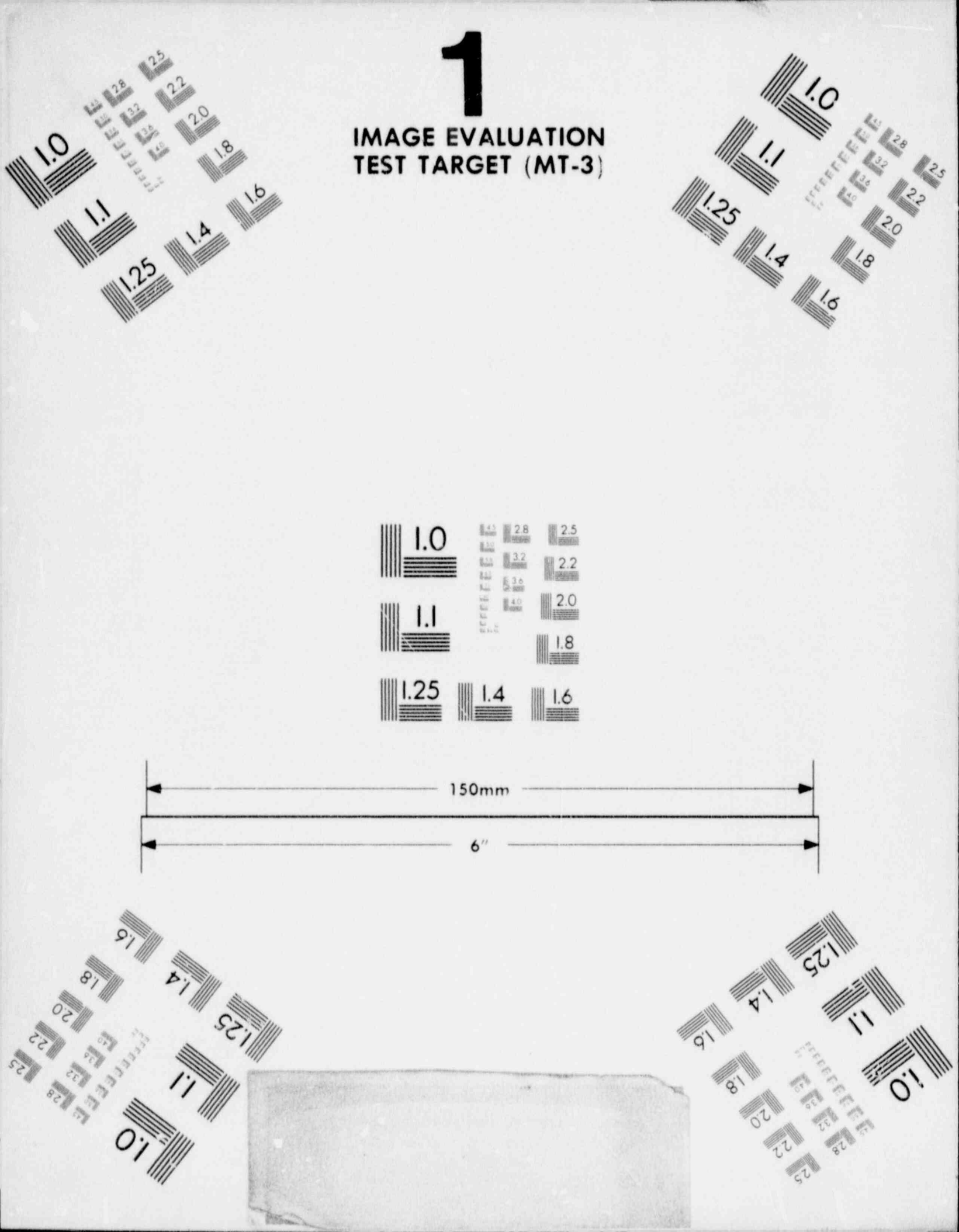


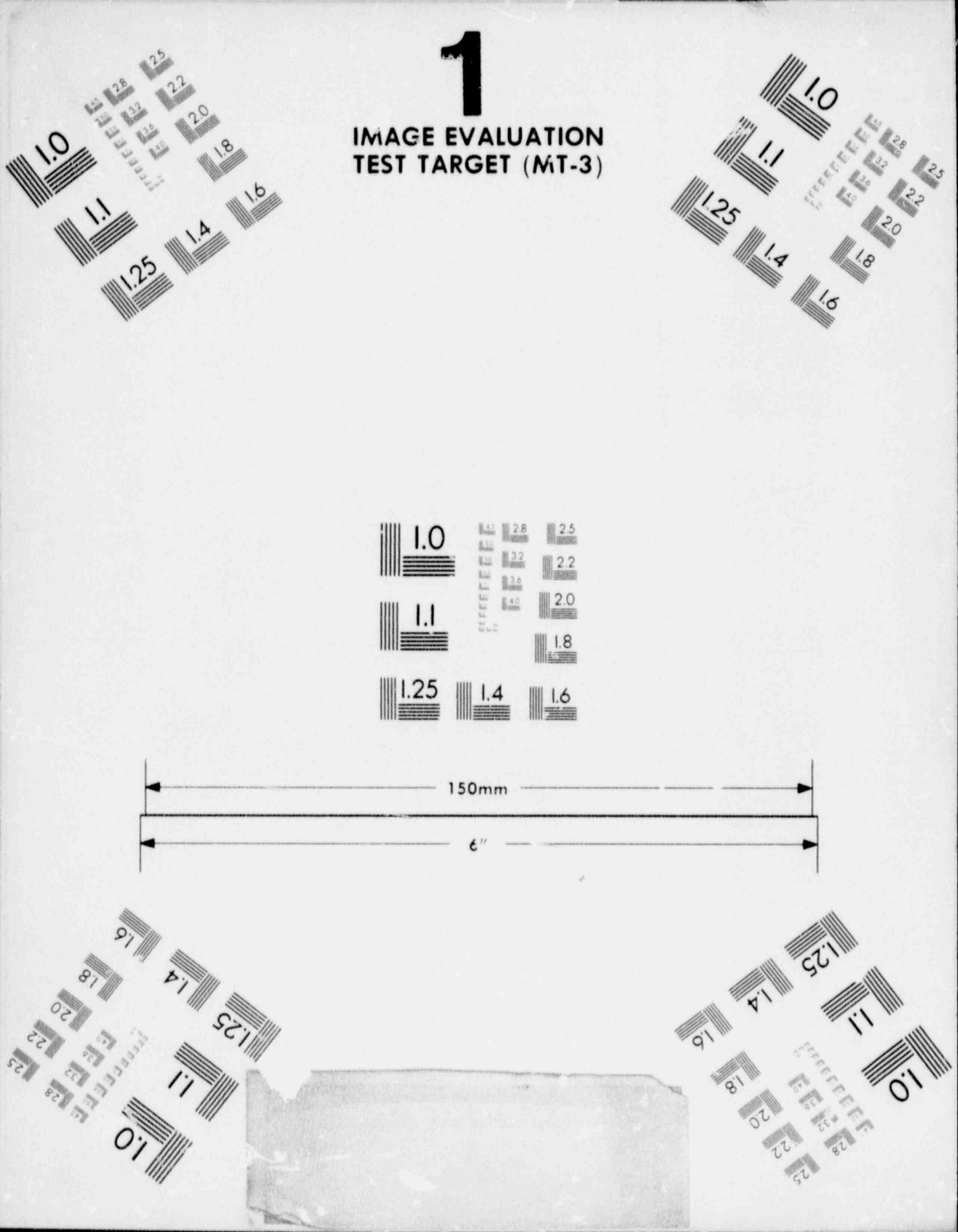


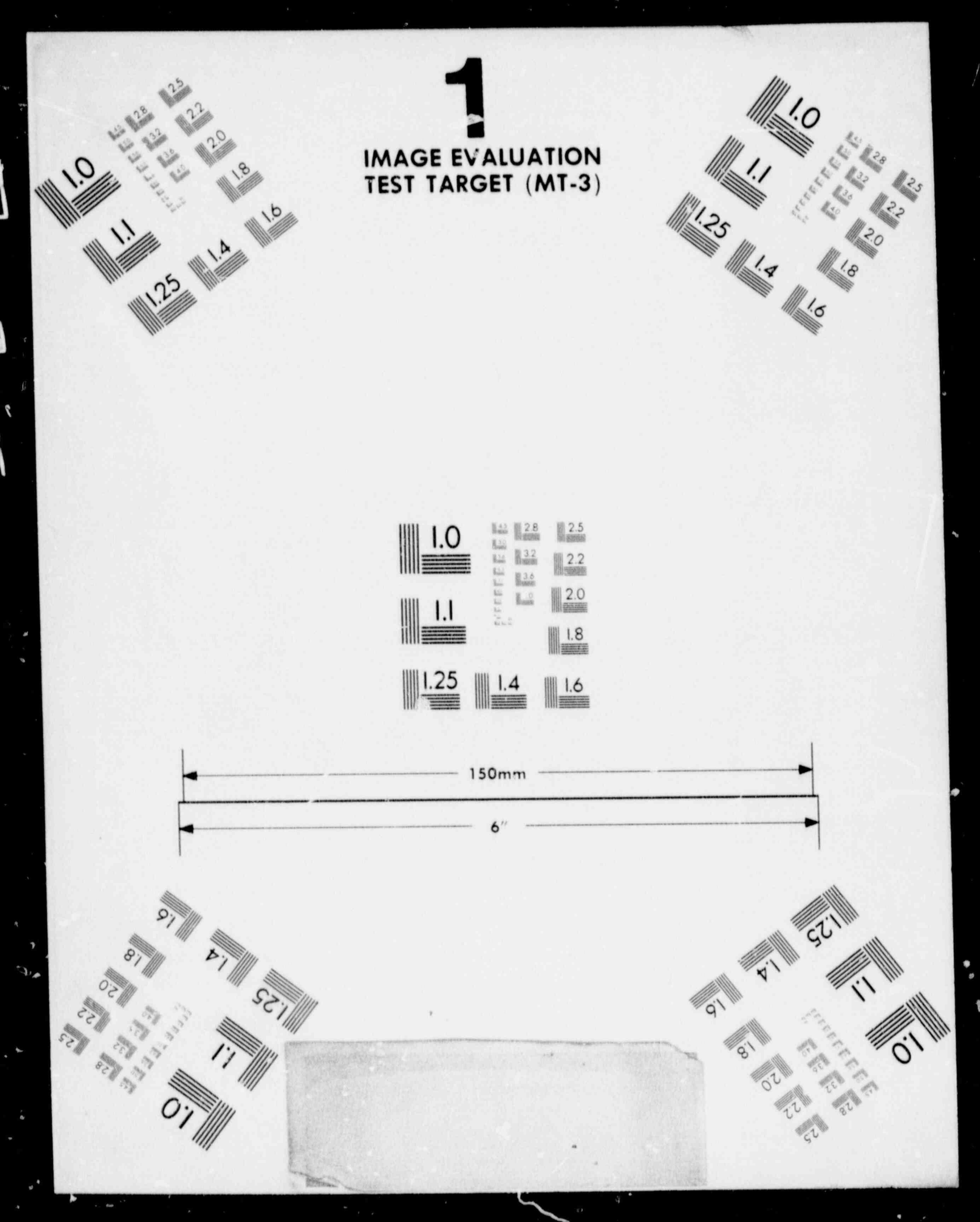







1
IMAGE EVALUATION
TEST TARGET (MT-3)
1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
150mm
6"


1
IMAGE EVALUATION
TEST TARGET (MT-3)
1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
150mm
6"


1
IMAGE EVALUATION
TEST TARGET (MT-3)
1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
150mm
6"

NOTICES

HUMAN SUBJECTS
Minimum Criteria Identifying the Viable Fetus

On March 13, 1975, regulations were published in the FEDERAL REGISTER (40 FR 11854) relating to the protection of human subjects in research, development, and related activities supported by Department of Health, Education, and Welfare grants and contracts. These regulations are codified at 45 CFR Part 46.

Elsewhere in this issue of the FEDERAL REGISTER, the Secretary is amending 45 CFR Part 46 by, among other things, adding a new Subpart B to provide additional protections pertaining to research, development, and related activities involving fetuses, pregnant women, and in vitro fertilization.

Section 46.203(d) of Subpart B provides inter alia as follows:

> The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a fetus is viable for purposes of this subpart.

This notice is published in accordance with § 46.203(d). For purposes of Subpart B, the guidelines indicating that a fetus other than a dead fetus within the meaning of § 46.203(f) is viable include the following:

> an estimated gestational age of 20 weeks or more and a body weight of 500 grams or more.

RESEARCH ACTIVITIES WHICH MAY BE REVIEWED THROUGH EXPEDITED REVIEW PROCEDURES

Research activities involving no more than minimal risk and in which the only involvement of human subjects will be in one or more of the following categories (carried out through standard methods) may be reviewed by the Institutional Review Board through the expedited review procedure authorized in 46.110 of 45 CFR Part 46.

(1) Collection of: hair and nail clippings, in a nondisfiguring manner; deciduous teeth; and permanent teeth if patient care indicates a need for extraction.

(2) Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

(3) Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.

(5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(6) Voice recordings made for research purposes such as investigations of speech defects.

(7) Moderate exercise by healthy volunteers.

(8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

(9) Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.

(10) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

source: 46 FR 8392
1/26/81

*U.S. GOVERNMENT PRINTING OFFICE: 1988-201-778/61195

XIII.

oil: *Indication.* "For visualization of biliary ducts during cholecystography."

PART 361—PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED: DRUGS USED IN RESEARCH

AUTHORITY: Secs. 505, 701(a), 52 Stat. 1052-1053, as amended, 1055 (21 U.S.C. 355, 371(a)); the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262)).

§ 361.1 Radioactive drugs for certain research uses.

(a) Radioactive drugs (as defined in § 310.3(n) of this chapter) are generally recognized as safe and effective when administered, under the conditions set forth in paragraph (b) of this section, to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial). Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of this section.

(b) The conditions under which use of radioactive drugs for research are considered safe and effective are:

(1) *Approval by Radioactive Drug Research Committee.* A Radioactive Drug Research Committee, composed and approved by the Food and Drug Administration in accordance with paragraph (c) of this section, has determined, in accordance with the standards set forth in paragraph (d) of this section, that:

(i) The pharmacological dose is within the limits set forth in paragraph (b)(2) of this section;

(ii) The radiation dose is within the limits set forth in paragraph (b)(3) of this section;

(iii) The radiation exposure is justified by the quality of the study being undertaken and the importance of the information it seeks to obtain;

(iv) The study meets the other requirements set forth in paragraph (d) of this section regarding qualifications of the investigator, proper licensure for handling radioactive materials, selection and consent of research subjects, quality of radioactive drugs used, research protocol design, reporting of adverse reactions, and approval by an appropriate Institutional Review Committee; and

(v) The use of the radioactive drug in human subjects has the approval of the Radioactive Drug Research Committee.

(2) *Limit on pharmacological dose.* The amount of active ingredient or combination of active ingredients to be administered shall be known not to cause any clinically detectable pharmacological effect in human beings. If the same active ingredients (exclusive of the radionuclide) are to be administered simultaneously, e.g., under a "Notice of Claimed Investigational Exemption for a New Drug" or for a therapeutic use in accordance with labeling for a drug approved under Part 314 of this chapter, the total amount of active ingredients including the radionuclide shall be known not to exceed the dose limitations applicable to the separate administration of the active ingredients excluding the radionuclide.

(3) *Limit on radiation dose.* The amount of radioactive material to be administered shall be such that the subject receives the smallest radiation dose with which it is practical to perform the study without jeopardizing the benefits to be obtained from the study.

(i) Under no circumstances may the radiation dose to an adult research subject from a single study or cumulatively from a number of studies conducted within 1 year be generally rec-

ognized as safe if such dose exceeds the following:

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

	Rems
Single dose	3
Annual and total dose commitment	5
Other organs	
Single dose	5
Annual and total dose commitment	15

(ii) For a research subject under 18 years of age at his last birthday, the radiation dose shall not exceed 10 percent of that set forth in paragraph (b)(3)(i) of this section.

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

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

(c) A Radioactive Drug Research Committee, in order to comply with paragraph (b)(1) of this section, shall be composed, shall function, and shall obtain and maintain approval of the Food and Drug Administration in conformity with the following:

(1) *Membership.* A Radioactive Drug Research Committee shall consist of at least five individuals. Each committee shall include the following three individuals: (i) A physician recognized as a specialist in nuclear medicine, (ii) a person qualified by training and experience to formulate radioactive drugs, and (iii) a person with special competence in radiation safety and radiation dosimetry. The remainder of the committee shall consist of individuals qualified in various disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics, and radiopharmacy). Membership shall be sufficiently diverse to permit expert review of the technical and scientific aspects of proposals submitted to the committee. The addition of consultants in other pertinent medical disciplines is encouraged. A Radioactive Drug Research Committee shall be either associated with a medical institution operated for care of patients and with sufficient scientific expertise to allow for selection of committee members from its faculty, or with a committee established by a State authority to provide advice on radiation health matters. Joint committees involving more than one medical institution which have been established in order to achieve a high level and diversity of experience will be acceptable. The Director of the Center for Drugs and Biologics may modify any of the foregoing requirements in a particular situation where alternative factors provide substantially the same composition and association.

(2) *Function.* Each Radioactive Drug Research Committee shall select a chairman, who shall sign all applications, minutes, and reports of the committee. Each committee shall meet at least once each quarter in which research activity has been authorized or conducted. A quorum consisting of more than 50 percent of the membership must be present with appropriate representation of the required fields of specialization. Minutes shall be kept and shall include the numerical results of votes on protocols involving use in human subjects. No member shall vote on a protocol in which he is an investigator.

(3) *Reports.* Each Radioactive Drug Research Committee shall submit an annual report on or before January 31 of each year to the Food and Drug Administration, Center for Drugs and Biologics, HFN-150, 5600 Fishers Lane, Rockville, MD 20857. The annual report shall include the names and qualifications of the members of, and of any consultants used by, the Radioactive Drug Research Commit-

21CFR Ch I 4-1-88

tor, and, for each study conducted during the preceding year, a summary of information presented in the following format:

REPORT ON RESEARCH USE OF RADIOACTIVE DRUG

1. Title of the research project.
2. Brief description of the purpose of the research project.
3. Name of the investigator responsible.
4. Pharmacological dose:
a. Active ingredients.
b. Maximum amount administered per subject.
5. Name of the radionuclide(s) used, including any present, as significant contaminants or impurities.
6. Radiation absorbed dose. Provide the maximum dose commitement to the whole body and each organ specified in 21 CFR 361.1(b)(3)(i) that was received by a representative subject and the calculations or references that were used to estimate these maximum dose commitments. The report shall include the dose contribution of both the administered radionuclide(s) and any X-ray procedures associated with the study. If the study elicits data on the uptake or excretion of the radioactive drug pertinent to the estimation of dose commitment, report the mean value and range of values. For each subject provide:
(a) Age, sex, and approximate weight.
(b) Total activity of each radionuclide administered for each radioactive drug used in the study. Report each X-ray procedure used in conjunction with the study.
(c) If the subject has participated in other radioactive drug research studies, report the name of the radioactive drug used in these other studies, the date of administration, and the total activity of each radionuclide administered. If any X-ray procedures were used, identify the X-ray procedure(s) and include an estimate of the absorbed radiation doses.
(d) If more than one administration of a radioactive drug per subject, cumulative radiation dose and dose commitment, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ doses from the administered radionuclides.
7. A claim of confidentiality, if any.

NOTE: Contents of this report are available for public disclosure unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 20.61.

_____
Investigator

_____
Chairman, Radioactive Drug Research Committee

At any time a proposal is approved which involves exposure either of more than 30 research subjects, or of any research subject under 18 years of age, the committee shall immediately submit to the Food and Drug Administration a special summary of information in the format shown in this paragraph. Contents of these reports are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in § 20.61 of this chapter.

(4) *Approval.* Each Radioactive Drug Research Committee shall be specifically approved by the Center for Drugs and Biologics of the Food and Drug Administration. Applications shall be submitted to the Food and Drug Administration, Center for Drugs and Biologics, HFN-150, 5600 Fishers Lane, Rockville, MD 20857, and shall contain the names and qualifications of the members of the committee, and a statement that the committee agrees to comply with the requirements set forth in this section. Approval shall be based upon an assessment of the qualifications of the members of the committee, and the assurance that all necessary fields of expertise are covered. Approval of a committee may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section. Approval of a committee shall remain effective unless and until the FDA withdraws such approval. Changes in membership and applications for new members shall be submitted to the Food and Drug Administration as soon as, or before, vacancies occur on the committee.

(5) *Monitoring.* The Food and Drug Administration shall conduct periodic reviews of approved committees. Monitoring of the activities of the commit-

tee shall be conducted through review of its annual report, through review of minutes and full protocols for certain studies, and through on-site inspections.

(d) In making the determination required in paragraph (b)(1) of this section, a Radioactive Drug Research Committee shall consider the following requirements and assure that each is met:

(1) *Radiation dose to subjects.* To assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the criteria of § 361.1(b)(3), the Radioactive Drug Research Committee shall require that:

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

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

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

(iv) The investigator utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.

(2) *Pharmacological dosage.* To determine that the amount of active ingredients to be administered does not exceed the limitations set forth in paragraph (b)(2) of this section, the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

(3) *Qualifications of investigators.* Each investigator shall be qualified by training and experience to conduct the proposed research studies.

(4) *License to handle radioactive materials.* The responsible investigator or institutions shall, in the case of reactor-produced isotopes, be licensed by the Nuclear Regulatory Commission or Agreement State to possess and use the specific radionuclides for research use or be a listed investigator under a broad license, or in the case of non-reactor-produced isotopes, be licensed by other appropriate State or local authorities, when required by State or local law, to possess and use the specific radionuclides for research use.

(5) *Human research subjects.* Each investigator shall select appropriate human subjects and shall obtain the review and approval of an institutional review committee that conforms to the requirements of Part 56 of this chapter, and shall obtain the consent of the subjects or their legal representatives in accordance with Part 50 of this chapter. The research subjects shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situations when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not currently available, requires the use of research subjects less than 18 years of age, and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radioactive Drug Research Committee. Each female research subject of childbearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test be confirmed as not pregnant, before she may participate in any study.

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

(7) *Research protocol.* No matter how small the amount of radioactivity, no study involving administration of a radioactive drug, as defined in § 310.3(n) of this chapter, to research subjects under this section, shall be

permitted unless the Radioactive Drug Research Committee concludes, in its judgment, that scientific knowledge and benefit is likely to result from that study. Therefore, the protocol shall be based upon a sound rationale derived from appropriate animal studies or published literature and shall be of sound design such that information of scientific value may result. The radiation dose shall be both sufficient and no greater than necessary to obtain valid measurement. The projected number of subjects shall be sufficient but no greater than necessary for the purpose of the study. The number of subjects shall also reflect the fact that the study is intended to obtain basic research information referred to in paragraph (a) of this section and not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial).

(8) *Adverse reactions.* The investigator shall immediately report to the Radioactive Drug Research Committee all adverse effects associated with the use of the radioactive drug in the research study. All adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported by the Radioactive Drug Research Committee to the Food and Drug Administration, Center for Drugs and Biologics, HFN-150, 5600 Fishers Lane, Rockville, MD 20857.

(9) *Approval by an institutional review board.* The investigator shall obtain the review and approval of an institutional review board that conforms to the requirements of Part 56 of this chapter.

(e) The results of any research conducted pursuant to this section as part of the evaluation of a drug pursuant to § 312.1 of this chapter shall be included in the submissions required under § 312.1 of this chapter.

(f) A radioactive drug prepared, packaged, distributed, and primarily intended for use in accordance with the requirements of this section shall be exempt from section 502(f)(1) of the act and §§ 201.5 and 201.100 of this chapter if the packaging, label, and labeling are in compliance with Federal, State, and local law regarding radioactive materials and if the label of the immediate container and shielded container, if any, either separate from or as part of any label and labeling required for radioactive materials by the Nuclear Regulatory Commission or by State or local radiological health authorities bear the following:

(1) The statement "Caution: Federal law prohibits dispensing without prescription";

(2) The statement "To be administered in compliance with the requirements of Federal regulations regarding radioactive drugs for research use (21 CFR 361.1)";

(3) The established name of the drug, if any;

(4) The established name and quantity of each active ingredient;

(5) The name and half-life of the radionuclide, total quantity of radioactivity in the drug product's immediate container, and amount of radioactivity per unit volume or unit mass at a designated referenced time;

(6) The route of administration, if it is for the other than oral use;

(7) The net quantity of contents;

(8) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug;

(9) The name and address of the manufacturer, packer, or distributor;

(10) The expiration date, if any;

(11) If the drug is intended for parenteral use, a statement as to whether the contents are sterile;

(12) If the drug is for other than oral use, the names of all inactive ingredients, except that:

(i) Trace amounts of harmless substances added solely for individual product identification need not be named.

(ii) If the drug is intended for parenteral use, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust pH or to make the drug isotonic may be declared by name and a statement of their effect; if the vehicle is water for injection, it need not be named. *Provided, however,* That in the case of containers too small or otherwise unable to accommodate a label with

sufficient space to bear all such information, the information required by paragraph (f) (1) and (12) of this section may be placed on the shielded container only.

[40 FR 31308, July 25, 1975, as amended at 40 FR 44543, Sept. 29, 1975; 42 FR 15674, Mar. 22, 1977; 43 FR 14646, Apr. 7, 1978; 46 FR 8955, Jan. 27, 1981; 49 FR 44480, Nov. 7, 1984; 50 FR 8996, Mar. 6, 1985]

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

Subpart A—Definitions and Interpretations

Sec.

Subpart B—Warning and Caution Statements for Drugs

AUTHORITY: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050-1052 as amended, 1055-1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

SOURCE: 39 FR 11745, Mar. 29, 1974, unless otherwise noted.

Subpart A—Definitions and Interpretations

§ 369.1 Purpose of issuance.

The warning and caution statements suggested in Subparts B and C of this part, for inclusion in the label or labeling of drugs and devices subject to section 502(d) and (f)(2) and other relevant provisions of the Federal Food, Drug, and Cosmetic Act are issued for the purpose of assisting industry in preparing proper labeling for these articles for over-the-counter sale and in meeting the legal requirements of the act that the label or labeling of drugs and devices bear adequate warnings, in such manner and form as are necessary for the protection of users. Only section 502(d) of the act requires use of the specific language included in these suggested warning and caution statements. These suggested warning or caution statements are illustrative of those that may be necessary or desirable. It is the responsibility of the manufacturer, packer, shipper, or distributor in interstate commerce to see that such statements are adequate for compliance with the provisions of the law. Omission of any article from this suggested list does not relieve drugs and devices subject to provisions of the act from bearing adequate warning or caution statements where such statements are necessary or desirable for the protection of the user.

§ 369.2 Definitions.

(a) As used in this part, the term "act" means the Federal Food, Drug, and Cosmetic Act.

(b) The terms "drugs" and "devices" are defined in section 201(g) and (k) of the act.

(c) Official compendia are defined in section 201(j) of the act.

§ 369.3 Warnings required on drugs exempted from prescription-dispensing requirements of section 503(b)(1)(C).

Drugs exempted from prescription-dispensing requirements under section 503(b)(1)(C) of the act are subject to the labeling requirements prescribed in § 310.201(a) of this chapter. Although, for convenience, warning and caution statements for a number of

Food and Drug

the drugs nam
chapter (cross-
of this part) are
of this part,
drugs in §§ 369.
way affects the
pliance with § 3
..., or the pro
application pur
of the act.

§ 369.4 Warning
formal or
policy.

The warning
included in Sub
no way affect
suggested for s
any statement
tion in Subchap

[39 FR 11745, Ma
40 FR 13496, Mar.

§ 369.5 Warning
tended for ov

Warning and
insulin product
must comply wi
provisions of t
this chapter.

§ 369.6 Warnings
antibiotics ex
dispensing re

Certain certif
are exempted
pensing require
507 of the act,
specific labeling
ing warning or
the applicable s
regulations.

EFFECTIVE DATE
removed at 52 FR
fective December 1

§ 369.7 Warnings
pendia.

Any drug incl
compendia defin
bear such warn
ment as may be
pendia, and no st
of Subpart C of
to alter, modify,
tion of any such
of such compend

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 27 1985

Dear Radioactive Drug Research Chairperson

Since the initiation of research with radioactive drugs in 1975 under 21 CFR 361.1, we have observed with satisfaction the acceptance and growth of the concept within the Nuclear Medicine community. Inevitably, as decisions by your committees have been made under the provisions of 21 CFR 361.1 and reviewed by FDA staff, some questions have arisen as to what the regulations would permit. In particular, there has been a tendency to try to utilize 361.1 to carry out early clinical trials of a radiopharmaceutical drug that properly are conducted under an IND. We would like to provide our views on these questions.

Part 361.1 designates certain research uses of radioactive drugs as "generally recognized as safe and effective". When a drug is generally recognized as safe and effective it is not a "new drug", as defined by the Food, Drug, and Cosmetic Act which states that a "new drug" is one "not generally recognized,....as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling..." When a "new drug" is used in humans and the drug is not yet approved for marketing an IND is required. No IND, however, is needed to study a drug that is not a new drug. The RDRC cannot provide an exemption from the act for new drugs, but can determine, under the specific requirements set forth in 361.1 that the drug to be used is, under the conditions specified by the investigator's protocol and approved by the committee, not a new drug.

The provisions of the RDRC regulations specifying how a committee can determine that a drug is "generally recognized as safe and effective" and, therefore, not a new drug, are detailed in 361.1. Let me address these briefly.

The type of research that may be undertaken with the drug must be intended to obtain basic information and not to carry out a clinical trial. The types of basic research permitted are specified in the regulation, and include studies of metabolism, human physiology, pathophysiology, or biochemistry. Types of research studies not permitted under this regulation are also specified, and include those "intended for (the) immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial)." The notice of proposed rule making for this regulation stated "the evaluation of the drug as a clinical tool, including comparison with other agents, should be considered as part of a clinical trial and subject to the requirements of 312.1.", i.e. require an IND, (Federal Register, Monday, July 29, 1974). Although the distinction is clearly stated, there can be areas of overlap between "research" and "clinical trial" studies. It is recognized, for

example, that the earliest studies showing localization of a drug in a particular organ or fluid space will have obvious relevance to the later trials; nonetheless, these early localization studies are considered basic research. We have reviewed RDRC-approved protocols, however, in which the evaluation of the drug as a clinical tool for particular organs or spaces was clearly the research objective. While, the distinction is not always clearcut, where doubt exists as to whether the research proposal is basic research, as defined in the regulation, the drug should be considered a new drug for which an IND is required.

The limitation on radiation dose is clearly stated and some have felt that these limits mean that FDA has determined these radiation doses to be safe. The FDA does not feel that any dose of radiation is absolutely safe, or that higher doses than those proposed are necessarily unsafe. There was a need for the purposes of this regulation to find some reasonable level below which the radiation doses would present minimal risk. Based on the radiation dose limitations established by NRC for basic occupational radiation protection (10 CFR 20.101 and 20.102), we proposed these as levels below which a drug could be considered as not a new drug, so long as all other portions of the regulations were met.

Although methodology is specified in the regulation by which radiation dose estimates are to be derived and reported, with special attention to whole body, active blood forming organs, lens of the eye, and gonads, taking into account the contribution of radiocontaminants and other radiation exposure procedures associated with the study, the reporting has frequently been incomplete. The total calculated radiation dose exposure per study must include all aspects of exposure, including X-Ray examinations and other isotope procedures related to the study. This should also include the radiation dose from possible radiocontaminants. The method of calculating the radiation exposure should be one that estimates a "worst case" situation as we would like to have adequate evidence that the radiation dose levels will not be exceeded. With radiopharmaceuticals in early investigation, adequate biodistribution data may not be available or may be equivocal so that the committee may not be able to establish that the radiation dose limits will not exceed the levels set by the regulation. Available methodology may also leave uncertainty as to whether radiation dose to the critical organs will be within the specified limits. Where the committee cannot be certain that the radiation dosage criteria will be met, an IND should be sought.

Similar reasoning extends to the limitations on pharmacologic dose which "shall be known not to cause any clinically detectable pharmacologic effect in human beings." For the committee to conclude that this criterion has been satisfied, there must be pharmacologic data available from studies in human subjects that would form the basis of the committee's action. If no data are

available, even the smallest amount of the drug must be assumed to produce pharmacologic activity, and an IND should be sought.

Once approved, the study should be the subject of continuing review at the committee's quarterly meetings so that it does not evolve into a research project that no longer satisfies the criteria for RDRC approval. Reports of the progress of approved studies are made to us yearly, but there is a requirement for immediate reporting if the study involves exposure of more than 30 research subjects or of any research subject under 18 years of age. This requirement has not been complied with in some cases, and we consider it important to our overview responsibility.

There are several other issues that have been the source of some confusion in the past:

(a) The RDRC, as defined in 21 CFR 361.1 has no oversight responsibility or authority over an investigation carried out under an IND exemption. This authority is retained by the FDA. Title 21 CFR 361.1 however, does not in any way prohibit an institution from involving the RDRC in other policy matters, including the use of radioactive drugs, if it so chooses.

(b) The RDRC is distinct from all other investigational drug review committees within an institution such as the radiation safety committee and the Institutional Review Board (IRB). The approval of both of these committees in addition to RDRC approval, is required before an RDRC investigation can be permitted to start.

(c) The RDRC is established and chartered by the FDA under 21 CFR 361.1. It is not related to any specific type of license granted by the NRC or State-Regulatory bodies. These licensing authorities, of course, make their own regulations, rules, and requirements. For their own purposes they may make an RDRC a requirement for a specific type of license, but these are not requirements under 21 CFR 361.1.

In sharing these observations with you, I also invite your comments. My intent is to preserve and improve the implementation of the RDRC regulations.

Questions and comments should be directed to Mr. Neil Abel, a Reviewing Pharmacist and the Executive Secretary of the Radiopharmaceutical Drugs Advisory Committee to the FDA. His address is the Division of Oncology and Radiopharmaceutical Drug Products, Office of Drug Research and Review

(HFN-150), Food and Drug Administration, Center for Drugs and Biologics, 5600 Fishers Lane, Rockville, Maryland 20857.

Sincerely yours,

Robert Temple

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

XIV.

2/16/39

C.S.M.

RADIOPHARMACEUTICAL COST, PROCEDURE REIMBURSEMENT, AND RADIATION ABSORBED DOSE

The cost of Quality Nuclear Medicine in America

Quality costs money, and one of the major aspects of the quality of nuclear medicine procedures is the choice of radiopharmaceutical. The manner and level at which third party payers reimburse for nuclear medicine procedures play a pivotal role in the nuclear physician's choice of radiopharmaceutical. The radiopharmaceutical of choice for a given procedure is the one that gives the most useful diagnostic information for the least radiation absorbed dose. If the drug of choice is expensive and the costs are not covered by third party payers, the physician will choose a second or third line drug that is cheaper. The patient therefore gets a lower quality study and/or higher radiation absorbed dose, but at least he gets the study. The only reasonable alternative at present is to perform no study at all, which is medically inappropriate. It is important to realize that even if the Food and Drug Administration (FDA) approves a radiopharmaceutical and agrees to its safety and efficacy for a specific indication, there is no guarantee that a third party payer will reimburse at a level that will permit the physician to choose that drug for that indication.

The most influential party that sets standards for third party payer reimbursement for nuclear medicine procedures (and other medical costs) is the Health Care Finance Administration (HCFA). The purpose of this report is to demonstrate that nuclear medicine quality, in terms of radiopharmaceutical choice, is often jeopardized by HCFA reimbursement policy, which completely ignores consideration of radiation absorbed dose to the patient. The goal of this report is to stimulate enough concern by the Nuclear Regulatory Commission (NRC) to have them use their influence with HCFA to resolve this quality issue. One method of resolution would be for HCFA to reimburse on a "cost plus" basis, that is, the cost of the radiopharmaceutical of choice plus an appropriate additional payment for technologist, equipment physician, radiopharmacist, etc. (professional and technical component). Such a reimbursement scheme would remove the disincentive for the nuclear physician to choose more appropriate but more costly radiopharmaceuticals.

Considering the relentless demands of NRC on the nuclear medicine community for a higher quality of performance

in the medical use of byproduct materials, it is hoped that NRC will appropriately investigate this source of quality disincentive.

In this report, we present the following information. (1) type of procedure, (2) cost of radiopharmaceutical by standard vendors, (3) reimbursement by HCFA, (4)radiopharmaceutical of choice for the procedure, and (5) radiation absorbed dose for each procedure. It should be understood that if the procedure results are not sufficiently diagnostically useful, the patient is often referred for other radiologic studies that contribute additional radiation absorbed dose. The nuclear medicine procedures chosen for this report are those for which the issue in question applies. (This is definitely not a comprehensive list for all nuclear medicine procedures.)

RADIOPHARMACEUTICAL COST, PROCEDURE REIMBURSEMENT, AND RADIATION ABSORBED DOSE

Type of Procedure	Procedure Code	Radiopharm-aceutical	Order of choice	Radiopharm-aceutical cost[2] in dollars	HCFA Re-imbursement[1] in dollars Global	Prof.	Tech.	Radiation absorbed Dose to target organ (Rad/procedure)
Thyroid uptake; Single determin-ation	78000	I-131-NaI	(2)	15.60(MKI)(CUD) 15.00(MPI)(CUD) 11.00(SYN)(CUD)	60.34	16.43	43.91	6.5,20,32.5[7] (thyroid)
"	"	I-123-NaI	(1)	26.00(MKT)(CUD) 24.50(MPI)(CUD) 26.00(SYN)(CUD)				0.24,0.75,1.3[8] (thyroid)
Thyroid uptake; Multiple deter-minations	78001	I-131-NaI	(2)	as above	81.82	22.48	59.34	as above
"	"	I-123-NaI	(1)					
Thyroid stimula-tion,suppression or discharge	78003	I-131-NaI	(2)	as above	72.45	28.54	43.91	as above
"	"	I-123-NaI	(1)					
Thyroid imaging, with uptake, single determin-ation	78006	I-131-NaI	(2)	15.60(MKT)(CUD)[3] 15.00(MPI)(CUD) 11.00(SYN)(CUD)	151.24	43.24	108.00	26,80,130 (thyroid)
"	"	I-123-NaI	(1)	104.00(MKT)(CUD) 98.00(MPI)(CUD) 100.00(SYN)(CUD)				0.96,3.0,5.2 (thyroid)
Thyroid imaging, with uptake, multiple deter-minations	78007	I-131-NaI	(2)	as above	161.28	44.97	116.31	as above
"	"	I-123-NaI	(1)					

(continued)

RADIOPHARMACEUTICAL COST, PROCEDURE REIMBURSEMENT, AND RADIATION ABSORBED DOSE.

Type of Procedure	Procedure Code	Radiopharm-aceutical	Order of choice	Radiopharm-aceutical cost[2] in dollars	HCFA Re-imbursement[1] in dollars Global	Prof.	Tech.	Radiation absorbed Dose to target organ (Rad/procedure)
Thyroid imaging, only	78010	I-131-NaI	(±2)	as above	116.05	34.16	81.89	as above
"	"	I-123-NaI	(1)	as above				
"	"	Tc-99m-$NaTcO_4$	(±2)	15.72(MPI)(COC)				3.0[9] (thyroid)
"	"	(less sensitive for thyroid cancer)						
Thyroid carcinoma metastases imaging (neck & chest only)	78015	I-131-NaI, 1mCi	(2)	106;156(MKT)(CUD)[4] 30;30(MPI)(CUD) 67.50;95(SYN)(CUD)	175.55	59.24	116.31	0.14 (red marrow)
"	"	I-131-NaI,10 mCi	(1)	178;327(MKT)(CUD) 80;120(MPI)(CUD) 99;171.50(SYN)(CUD)				1.4 (red marrow)
Brain imaging, limited procedure;static	78600	Tc-99m-$NaTcO_4$	(±3)	15.72(MPI)(COC)	169.03	38.48	130.55	12(thyroid)[10] 3.4(bladder)
"	"	Tc-99m-DTPA	(±3)	35(MKT)(CUD) 30(MPI)(CUD) 26.55(SYN)(COC) 38.03(DUP)(COC)				5.4 (bladder wall)[11]
"	"	Tc-99m-HMPAO	(1)	165.72(AMS)(COC)				2.8 (kidneys)[12]
"	"	I-123-iodoamphetamine	(2)	396(MPI)(CUD)[19]				1.2(liver),1.3(lungs)[18]
Brain imaging, limited procedure, static; with vascular flow	78601	as above		as above	200.12	45.83	154.28	as above
Brain imaging, complete study; static	78605	as above		as above	201.85	47.56	154.28	as above
Brain imaging,complete study; static;with vascular flow	78606	as above		as above	231.86	56.21	175.65	as above

(continued)

RADIOPHARMACEUTICAL COST, PROCEDURE REIMBURSEMENT, AND RADIATION ABSORBED DOSE

Type of Procedure	Procedure Code	Radiopharmaceutical	Order of choice	Radiopharmaceutical cost[2] in dollars	HCFA Reimbursement[1] in dollars Global	Prof.	Tech.	Radiation absorbed Dose to target organ (Rad/procedure)
Brain imaging, complete study; static; tomographic (ECT)	78607	as above		as above	404.80	108.10	296.70	as above
Brain imaging, vascular flow only	78610	above 3 agents probably equivalent		as above	96.72	25.51	71.21	as above
Cerebral blood flow	78615	Xe-133 gas Xe-133 gas in saline	(2) (1)	114(MKT)(CUD) 30(MPI)(CUD) 40(SYN)(CUD) 32.48(DUP)(CUD) (COC)for gas in saline same as gas	211.21	36.75	174.46	0.34(brain)[13]
Kidney imaging with function study(i.e., imaging renogram)	78704	I-131-hippuran I-123-hippuran	(2) (1)	56(MKT)(CUD)[5] 28.33(MPI)(CUD) 33.33(SYN)(CUD) 75(MPI)(CUD)	244.07	64.86	179.21	32(thyroid)[14] 8.0(bladder wall) 0.6(thyroid) 3(bladder wall)
Radionuclide localization of abscess; limited area	78805	Ga-67-citrate (compared with WBC's)	(3)	78(MKT)(CUD) 60(SYN)(CUD) 57.60(DUP)(CUD)	213.96	59.67	154.28	1.4(LLI)[15]
Radionuclide localization of abscess; whole body	78806	Ga-67-citrate (compared with WBC's)	(3)	as above	324.79	74.37	250.41	as above

(continued)

RADIOPHARMACEUTICAL COST, PROCEDURE REIMBURSEMENT, AND RADIATION ABSORBED DOSE

Type of Procedure	Procedure Code	Radiopharmaceutical	Order of choice	Radiopharmaceutical cost[2] in dollars	HCFA Reimbursement[1] in dollars Global	Prof.	Tech.	Radiation absorbed Dose to target organ (Rad/procedure)
White blood cell localization; limited area scanning	78192	In-111-WBC	(2)	180(MPI)(COC)[6] 200(SYN)(COC)[6] 365(SYN)(CUD) 399(MKT)(CUD)	223.90	69.62	154.28	20(spleen)[16]
		Tc-99m-micro-lite-WBC (cannot use at present in NRC states; not suitable for gall-bladder or renal evaluation)	(1)	29.72(DUP)(COC)[6]				2.5 (spleen)[17]
White blood cell localization; whole body	78193	as above		as above	518.46	76.97	441.49	as above

[1] 1989 Radiology Fee Schedule for Area 26.

[2] For drugs labeled with Tc-99m, cost is cost of kit + $15.72, which is cost of list price Tc-99m at Harbor-UCLA Medical Center. All kit costs and unit dose costs are list price in a less than full service category (i.e. all drugs are not necessarily bought from one place). Large institutions have all kinds of deals and discounts, but we will not consider them here.

Abbreviations used are: Syncor (SYN), Medi-Physics, Inc. (MPI), Mallinckrodt (MKT), DuPont (DUP), cost of components if you make it up yourself (not including labor, misc. laboratory supplies or equipment but including cost of kit and radionuclide (COC), cost of unit dose (CUD), Amersham (AMS).

[3] These are for 100 μCi doses of I-131 and 400 μCi doses of I-123. Some labs use 200 μCi doses of I-123, but this does not suit our practice for imaging performed 24 hrs. post administration.

[4] Former number is for oral solution, latter number is for oral capsule.

[5] For I-131 hippuran, actually multidose vial for 3 patients.

[6] Significant laboratory work needed for preparation.

[7] From MIRD Dose Estimate Report no. 5, 1975, for 5,15, and 25% maximum thyroid uptake; 25 μCi admin. act.

[8] As for footnote 7, but 100 μCi admin. act.

(continued)

[9]For 5 mCi dose (from package insert for Mallinckrodt Tc-99m-$NaTcO_4$ generator, 1982).

[10]20 mCi admin. act. If thyroid blocked with perchlorate, bladder wall is target organ. Dose doubled from MIRD no 8, 1976 because of decreased uptake in GI tract.

[11]20 mCi admin. act; from Syncor package insert, 1984.

[12]20 mCi admin. act.; Soundy RG, Tyrrell DA, Pickett RD. Nuc. Med. Comm. in press, 1989. 500 mg. perchlorate administered.

[13]20 mCi admin. act; Roedler HD, Raul A. Hine GJ: Internal Radiation Dose in Diagnostic Nuclear Medicine. Berlin, Verlag Hoffmann, 1978, p.35.

[14]333 µCi I-131-OIH: 500 µCi I-123-OIH; ibid.,p.69.

[15]3 mCi; ibid., p.55

[16]500 µCi In-111-WBC at expiry, and 0.25% In-114m/In-114. Amersham package insert, 1985.

[17]5 mCi admin. act. Marcus CS, Stabin MG, Watson EE et al.: Nuc Med Comm 9:249-254, 1988.

[18]3 mCi admin. act. assumes thyroid has been blocked. ICRP no. 53, pp. 279-280, 1988.

[19]Add $52.50 shipping charge (Fed. Express) if ordered from MPI directly. If ordered through their radiopharmacy, shipping cost may not apply if you're getting other deliveries that morning.

(continued)

RADIOPHARMACEUTICAL COST, PROCEDURE REIMBURSEMENT, AND RADIATION ABSORBED DOSE

Type of Procedure	Procedure Code	Radiopharm-aceutical	Order of choice	Radiopharm-aceutical cost[2] in dollars	HCFA Re-imbursement[1] in dollars Global	Prof.	Tech	Radiation absorbed Dose to target organ (Rad/procedure)
MIBG (Metaiodo-benzylguan-idine; goes to adrenergic receptors)	78099	I-131	(2)	$660/2.2 mCi (CUD) (U. of Michigan Radiopharmacy)	0[21]	0	0	bladder: 2.2[20] liver: 3.1
		I-123	(1)	$93/2.2 mCi (COC)	0	0	0	bladder: 0.26[20] liver: 0.26

[20]Assumes 1 mCi Admin. Act. and perchlorate to block thyroid uptake of free iodide.

[21]HCFA does not reimburse for unlisted procedures, and MIBG is unlisted. However, I-131-MIBG is an Orphan Drug, and although you need an IND to use it, you may bill the patient for it.

Statements of Consideration

5. *Temporary absence.* Several commenters asked if a license amendment or notification was required if an authorized user, Radiation Safety Officer, or Teletherapy Physicist was absent for illness, vacation, sabbatical, or continuing education. Because the specific facts and circumstances would dictate the appropriate action by the licensee, it would be impossible for the NRC to make generic determinations in advance of the situation.

The point can not be reiterated sufficiently that the licensee, despite the absence of personnel, remains responsible for assuring continued compliance with NRC radiation safety requirements.

6. *Deletion of the general medical license in § 35.31.* As noted in the discussion of the transition policy for general licensees for medical use, the general medical license, which authorizes a few radiopharmaceuticals for a few listed clinical procedures, is not frequently used and therefore no longer an efficient way of regulating the medical use of byproduct material. Thus, it has been deleted. However, current general medical licensees will be allowed to continue using materials under specific licenses that the NRC will issue.

7. *Fees.* One licensee said NRC should reduce its medical license fees when applicants propose to use radiation safety procedures that are published in regulatory guides because that reduces the time NRC needs to review the application. The comment can not be addressed in this rulemaking because the proposed rulemaking did not propose any changes to the fee schedule in 10 CFR Part 170. A petition for rulemaking to change Part 170 may be submitted.

8. *Records.* A few commenters said the detailed nature of some recordkeeping requirements ran counter to the philosophy of flexibility on which the revision is based, and may require a change in other administrative procedures. The NRC has retained the detailed prescriptive requirements that describe the information that must be included in each record. The NRC has carefully reviewed each element of data required and believes each is an important part of the record or indicates completion of an important step in a procedure.

Some commenters said a certain record requirement duplicated other records kept elsewhere—for example, diagnostic radiopharmaceutical dosages may be listed in a clinical procedures manual. There is no need to duplicate that information unless the regulation specifically requires that the information be posted or recorded in a certain place.

The NRC notes that, as a separate rulemaking, it is reviewing *all* of its record retention requirements. Some of the retention periods in this final rulemaking may be changed as a result of that project, which will be published for public comment.

9. *SI Units.* A few commenters recommended that the newer International System of Units (SI), which has new units for amount of radioactivity, radiation exposure, radiation dose, and dose equivalent, be used in place of the special radiation units because the SI system is now being used more frequently. The NRC believes that, if indicated, such a change should be made through all NRC regulations at one time, not where it would affect only one group of licensees.

10. *Specialty certification.* Some commenters questioned whether certain physicians who have successfully completed an examination in a medical specialty (diplomates) should be authorized to serve as Radiation Safety Officer, and some recommended that other additional certifications be recognized. The NRC compared the examination criteria applied to diplomates to the responsibilities shouldered by certain individuals and made a judgment that the certifications identified for certain individuals provide an appropriate demonstration of adequate training and experience. Thus, some certifications have been added that were not listed in the proposed rule: American Board of Nuclear Medicine or Board of Pharmaceutical Specialties in Nuclear Medicine for Radiation Safety Officer; and American Board of Radiology for therapeutic use of radiopharmaceuticals.

11. *Training and experience criteria.* Several commenters recommended changes in the training and experience criteria the NRC applies to physicians who want to use radiopharmaceuticals for diagnostic clinical procedures. In the notice of proposed rulemaking the NRC noted that it had "received and is reviewing suggested alternative training standards for some methods of use. The review is being handled as a separate project. If any changes in training standards come out of that project, they will be published for public comment. . . ." The NRC is continuing to review recommendations for alternative training criteria; they will be published for public comment at a later date.

A few commenters said authorized users and Teletherapy Physicists should be at least "board eligible," meaning that they have training and experience sufficient to allow the individual to apply for the certification examination. The NRC notes that most boards do not use this term (instead saying an individual is certified, not certified, or in the examination process), and believes the use of the term might create more confusion than it would resolve.

A few commenters said the required hour-by-hour distribution of content in the classroom and laboratory portions of the training and experience sections was overly restrictive, and would not recognize differences in students or programs. The NRC agrees, and has simply listed required topics, but has retained the *total time* requirements.

12. *Effect on medical broad licensees.* A few commenters said the NRC should indicate which sections apply to broad licensees authorized for medical use under Part 33; some are allowed to name authorized users and some are also allowed to develop new byproduct materials for medical use. The NRC has retained the solution to this question that was in the notice of proposed rulemaking. "These licensees would be required to comply with the proposed prescriptive and performance criteria of Part 35, but would be exempted from the training and experience requirements of Subpart J and the authorized materials and authorized use restrictions in proposed §§ 35.49, 35.100, 35.200, 35.300, 35.400, and 35.500." These changes will not limit broad licensees' authority to conduct medical research and identify authorized users.

13. *Therapy patients.* One commenter suggested that requirements be drafted regarding the handling of deceased patients who had been administered therapeutic radiopharmaceuticals or implants. The NRC notes that § 35.404 requires that the licensee retrieve temporary implants. The regulations, in §§ 35.315 and 35.415, require prompt notification of the Radiation Safety Officer in case of the patient's death, who then is responsible for taking steps to ensure compliance with requirements in Part 20. In case of death after release from confinement for radiation safety purposes, the NRC expects licensees to take steps to reduce doses to pathologists, morticians, and other individuals, but also recognizes the licensee may no longer have control over the remains. Therefore, the NRC can not expect that the licensee is able to take appropriate action.

14. *Voluntary submission of economic data.* Several commenters noted that the application form asks applicants to indicate their annual receipts, number of employees, number of beds, and willingness to furnish additional cost information on the economic impact of