

ADJUNCTIVE MEDICAL KNOWLEDGE

The Submission of I.N.D. Applications for Radiopharmaceutical Research: When and Why

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Of special interest to many nuclear medicine or radiology departments is the clinical evaluation of newly developed radiopharmaceuticals before approval by the Food and Drug Administration (F.D.A.), and/or the evaluation of approved radiopharmaceuticals for non-approved indications or uses. In this regard, a question that frequently arises is whether an Investigational New Drug (I.N.D.) application is required to initiate such a research study. Frequently this question is difficult to answer because of the numerous regulations and regulating bodies that govern radiopharmaceutical research in human subjects and the potential for overlap and inconsistencies between these various regulations. The purpose of this article is to review and discuss briefly the various regulations associated with clinical radiopharmaceutical research, and to provide some insights as to when and why an I.N.D. submission may be required or, perhaps more importantly, when this process is necessary.

GOVERNING BODIES

Basically there are three principal governing bodies that may control human research involving radiopharmaceuticals: (a) the F.D.A., which has primary interest in the safety and efficacy of the radiopharmaceutical for the proposed indication; (b) the Nuclear Regulatory Commission (N.R.C.) or appropriate Agreement state, which is concerned with radiation protection and associated health of the patient, occupational workers, and general public; and (c) the local institutional review committees, which typically include (by various names) a Human Use Review Committee, Radiation Safety Committee, and perhaps, a special F.D.A.-derived

committee, the Radioactive Drug Research Committee.

Although each of these bodies exists as a separate entity, they are interrelated in many aspects (Fig. 1). On January 8, 1963, the F.D.A. exempted radiopharmaceuticals from regulations established by the Kefauver-Harris Drug Amendments, provided that these agents met the requirements of the then existent Atomic Energy Commission (A.E.C.). This exemption, however, was eventually terminated on August 26, 1975, whereupon radiopharmaceuticals became subject to the same F.D.A. regulations that govern standard pharmaceutical products. This termination process came about primarily as a result of the increase in number and use of radiopharmaceuticals. Also, at approximately this same time, the A.E.C. was divided into two new agencies: the former Energy Research and Development Administration (E.R.D.A.) and the N.R.C.

The interrelationship between the various institutional review committees is required and obvious. In addition, F.D.A. regulations, Code of Federal Regulations (C.F.R.), Title 21, address the membership requirements, functions, and reporting requirements of Human Use Review Committees and Radioactive Drug Research Committees under Parts 56 and 361, respectively. The membership and functions of the Radiation Safety Committee must comply with N.R.C. regulations (C.F.R. Title 10).

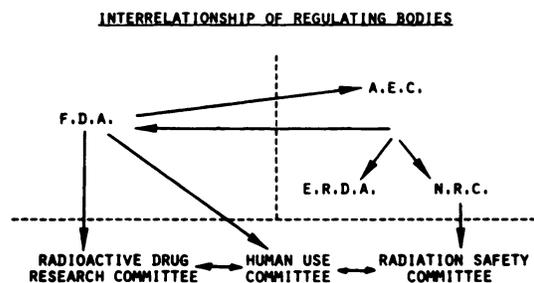


FIG. 1. Interrelationships of regulating bodies.

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N.R.C. LICENSES

The first factor a person should analyze, in determining whether an I.N.D. submission is required for a given research effort, is the type of N.R.C. license held by the physician investigator or associated institution. In this regard, the N.R.C. issues two types of licenses that authorize human, in vivo use of byproduct materials: general and specific licenses. The specific licenses are further divided into two subtypes: (a) specific licenses issued in groups (group licenses), and (b) specific licenses of broad scope (broad licenses).

The general license is the most limited of the N.R.C. licenses. Any physician may apply for, and obtain, a general license. The physician needs no special training or experience with the use of radioactive material in order to obtain such a license. The general license is effective without the filing of an application or issuance of licensing documents; the physician is simply required to register with the N.R.C. However, in vivo studies performed under a general license are limited to physician use of prepackaged, individual doses of specific radiopharmaceuticals for specified nonimaging purposes (Table 1). Total-activity possession limits are also specified. It is legally impossible to perform a research evaluation of a newly developed, nonapproved radiopharmaceutical, or to utilize a listed radiopharmaceutical (Table 1) for some other indication, under an N.R.C. general license.

Specific licenses may be issued to an institution with a designated physician user(s) or directly to a physician(s) in private practice. In order to facilitate application for a specific license, the N.R.C. has adopted a "Group" approach wherein an institution or physician may apply for, and be licensed to perform, studies under one or a combination of the specified Groups listed in Table 2.

The specific radiopharmaceuticals approved under an N.R.C. group license are listed under each of the respective Groups in C.F.R. (Title 10 Part 35), "Human Use of Byproduct Materials" (10 C.F.R. 35.100). In the case of Groups IV and V, specific clinical procedures are also included for each radiopharmaceutical listed, and the group medical licensee can use Group IV and V ra-

TABLE 2. N.R.C. GROUP SPECIFIC LICENSES

Group I:	Prepared radiopharmaceuticals for uptake, dilution, and excretion studies.
Group II:	Prepared radiopharmaceuticals for imaging and localization studies.
Group III:	Generators and reagent kits.
Group IV:	Prepared radiopharmaceuticals for inpatient therapy.
Group V:	Prepared radiopharmaceuticals for outpatient therapy.
Group VI:	Sealed sources, and devices containing sealed sources.

diopharmaceuticals only for the clinical procedures specified. Radiopharmaceuticals listed under Groups I, II, and III of 10 C.F.R. 35.100 do not include specific clinical procedures. Those licensees under a group medical license are authorized to use these F.D.A.-approved, Group I-III radiopharmaceuticals for any of their respective F.D.A.-approved, package-insert indications. If the licensee desires to use one of these agents for an indication not specified in the package insert, he/she must comply with 10 C.F.R. 35.14 (b) (6), which requires that the agent be used in the same chemical form, route of administration, and dosage range as specified in its own package insert (vide infra).

Of importance is that each of Groups I-V also contains the following statement as part of the list of approved agents: "Any byproduct material in a radiopharmaceutical . . . for which a 'Notice of Claimed Investigational Exemption for a New Drug' (I.N.D.) has been accepted by the Food and Drug Administration (F.D.A.)." Hence it is possible to perform clinical studies with newly developed radiopharmaceuticals or for indications not specifically listed within the package inserts (Groups I-III) or group license (Groups IV-V) provided an I.N.D. for the proposed agent/study has been submitted and accepted.

N.R.C. broad licenses are issued to institutions that have had extensive previous experience in the use of byproduct materials. These licenses typically authorize multiple chemical and physical forms and multicurie quantities of radioactive materials. Broad licenses are further categorized as Type A, B, or C with respectively increasing limitations. Under a broad license, the Radiation Safety Committee of the institution has the responsibility and authority to approve the chemical forms, routes of administration, dosages, and uses of radiopharmaceuticals as well as designate approved individual users. Broad-license requirements (10 C.F.R. 33) include stipulations for the establishment and general functions of the Radiation Safety Committee and the designation of a Radiation Safety Officer. Obviously, the performance of radiopharmaceutical research is permitted

TABLE 1. N.R.C. GENERAL LICENSE LIMITATIONS

Specific radiopharmaceuticals	Specific indications
Sodium [¹³¹ I]iodide	Thyroid uptake
Iodinated [¹³¹ I/ ¹²⁵ I] human serum albumin	Blood and plasma volume
[⁵⁸ Co] and/or [⁶⁰ Co]-cyanocobalamin	Schilling's test
Sodium [⁵¹ Cr] chromate	R.B.C. Volume/survival

under, and greatly facilitated by, an N.R.C. broad license.

RADIOACTIVE DRUG RESEARCH COMMITTEE

On January 25, 1975, the F.D.A. exempted the research use of certain radioactive drugs from I.N.D. requirements provided these agents met the conditions outlined under 21 C.F.R. 361.1, "Radioactive Drugs for Certain Research Uses". The basic conditions for this exemption include:

1. Requirements for establishment of a F.D.A.-approved Radioactive Drug Research Committee (R.D.R.C.); including membership requirements, functions, and reporting requirements.

2. Limits on the pharmacologic dose. The amount of active ingredient(s) must be known not to cause any clinically detectable pharmacologic effect, based on human data.

3. Limits on the radiation dose. Basically, the radiation dose received from a single, total study (administered radioactive agent plus x-ray procedures, if indicated) must not exceed 3 rems to the whole body, active blood-forming organs, lens of the eye, and gonads; or 5 rems to other organs.

4. Requirements regarding qualifications of the investigator, appropriate licensure for radioactive materials, quality of the radioactive drug (including assay and labeling requirements), research protocol design, and approval by the institutional Human Use Review Committee.

Although these conditions are fairly strict, in many instances it would be possible to utilize this exemption for the clinical evaluation of newly developed radiopharmaceuticals except for the following statement: "Under conditions set forth in this section, radioactive drugs are considered safe and effective when administered to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug, or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and efficacy of the drug in humans for such purposes (i.e., to carry out a clinical trial)." Hence, a significant limitation of this exemption is the differentiation between "basic research" (exempted) and "clinical research" (not exempted). For example, a study in humans to evaluate the pharmacokinetics (blood clearance, excretion rates) of C-14 haloperidol could be approved by an R.D.R.C., whereas the use of F-18 haloperidol and positron emission tomography for the clinical diagnosis of Huntington's chorea is not approvable.

OVERLAP OF F.D.A. AND N.R.C. REGULATIONS

The remainder of this article will focus on problems that arise in determining whether an I.N.D. submission is required, due to overlap and inconsistencies in regulations between the F.D.A. and N.R.C. The F.D.A. regulates primarily at the level of the manufacturer and does not commonly regulate at the level of the user. The Atomic Energy Act authorizes the establishment of standards and instructions to govern the possession and use of special nuclear material, source material, and byproduct material. The differences in the missions of the two agencies contribute to the problems alluded to. In an attempt to alleviate the confusion involved, typical examples of clinical research studies involving newly developed radiopharmaceuticals or nonroutine imaging procedures will be presented. Then, based on a current understanding of existing regulations, the requirements of I.N.D. submission will be discussed. For ease of presentation it will be assumed that these research examples: (a) do *not* meet the conditions for R.D.R.C. exemption, due to their clinical nature, radiation dosimetry, or pharmacologic dose; and (b) can be readily approved by the institutional Human Use Review Committee. To facilitate this discussion, the examples will be presented in two categories: Category 1, radiopharmaceuticals not F.D.A.-approved; and Category 2, F.D.A.-approved (N.D.A. or I.N.D.) radiopharmaceuticals for nonapproved indications.

CATEGORY 1: EXAMPLE 1

A physician-sponsor wishes to investigate the safety and efficacy of a newly developed radiopharmaceutical, meta-[¹³¹I]iodobenzylguanidine (I-131 mIBG), for the diagnosis of pheochromocytomas. The research protocol involves a large number of patient studies with this nonapproved radiopharmaceutical. Is an I.N.D. required?

<u>Yes</u>	<u>No</u>	
x		F.D.A.: Safety and Efficacy
		N.R.C. Licensing Restrictions:
x		Group license
(?)	x	Broad license

F.D.A. It is obvious that this type of research, involving the evaluation of a newly developed radiopharmaceutical in a considerable number of patients, requires that the study be carefully designed to provide the scientific evidence necessary to substantiate the safety of the radiopharmaceutical and its efficacy for the proposed indication. Hence, a physician-sponsored I.N.D. is required by the F.D.A. to ensure radiopharmaceutical quality and uniformity, and the adherence to a well-planned clinical protocol.

N.R.C. licensing restrictions. Operation under an

N.R.C. group license would also require F.D.A. acceptance of an I.N.D. for this radiopharmaceutical. As indicated in 10 C.F.R. 35, "Human Use of Byproduct Material", the use of a prepared radiopharmaceutical for diagnostic studies (i.e., I-131 MIBG) would fall under Group II of the N.R.C. license. Because I-131 MIBG is not specifically listed under Group II, an I.N.D. must be accepted to comply with N.R.C. regulations.

In regard to a group medical license, note further that the licensee must comply with the requirements of 10 C.F.R. 35.14. These regulations state that the licensee can only receive, possess, or use Group I-V radiopharmaceuticals that have been manufactured and distributed under a license issued by the N.R.C. (10 C.F.R. 32.72)—or an Agreement State with equivalent regulations. Therefore, in this example, a group medical licensee can obtain I-131 MIBG for I.N.D. evaluation from a manufacturer licensed by the N.R.C. (or Agreement State) without having to amend his/her group license. If, however, the group medical licensee synthesizes the I-131 MIBG on-site (for use under a physician-sponsored I.N.D.), or obtains the agent from a source not licensed under 10 C.F.R. 32.72, an amendment to the group license is required.

Technically a broad license Radiation Safety Committee does have the authority to approve this use of I-131 MIBG without its prior I.N.D. approval. However, because a large number of clinical studies may be involved, the submission and acceptance of an I.N.D. for I-131 MIBG would, in the light of previously discussed F.D.A. requirements, greatly facilitate approval by a broad license Committee.

CATEGORY 1: EXAMPLE 2

A physician requests, on a prescription order, that a nuclear pharmacist compound a single dose of I-131 Monoclonal Antibody to Testicular Carcinoma for injection into a single patient for diagnosis of suspected cancer of the testes. Is an I.N.D. required for this non-approved radiopharmaceutical?

<u>Yes</u>	<u>No</u>
x	F.D.A.: "Traditional Practice of Medicine"
	N.R.C. Licensing Restrictions:
x	Group license
x	Broad license

F.D.A. It is the F.D.A.'s opinion that good medical practice and patient interests require that physicians be free to use drugs according to their best knowledge and medical judgement (1). Thus, the single use of a compounded drug as described in this example is considered to be traditionally part of the practice of medicine, and an I.N.D. submission is not required. However, when a physician uses a nonapproved, compounded drug he/she

has the responsibility to be well informed about the drug, to base such use on firm scientific and medical rationale, and to maintain adequate records of the drug's utility and effects. Primary legal constraints in this regard are state laws on medical practice and product-liability laws. Of course, it is the responsibility of the physician or pharmacist, where applicable, to ensure the quality and safety of the radiopharmaceutical. If, however, the F.D.A. should discern a pattern developing in this type of practice (i.e., the same physician writing prescriptions for the same drug for several clinical studies) a physician-sponsored I.N.D. will be requested.

N.R.C. licensing restrictions. As described in the previous example, in order for the physician to comply with an N.R.C. group license, an I.N.D. must be submitted because I-131 Monoclonal Antibody to Testicular Carcinoma is not specifically listed under Group II. As indicated by policy statements that appeared in the Federal Register, Vol. 43, March 17, 1978, the N.R.C. believes that it is necessary to continue its restrictions on the availability of radioactive drugs to those that meet F.D.A. requirements. It is further stated that "the N.R.C. will regulate the radiation safety of patients where justified by the risk to the patient and where voluntary standards are inadequate". Furthermore, a license amendment is required, since the I-131 Monoclonal Antibody is not obtained in accordance with the requirements of 10 C.F.R. 35.14 (b) (1) as previously discussed.

Broad license Radiation Safety Committees do have the authority to approve, and typically will, the single administration of a nonapproved radiopharmaceutical provided the quality of the radiopharmaceutical and safety of the patient are ensured and documented.

CATEGORY 1: EXAMPLE 3

A physician requests, on prescription, that his nuclear pharmacist compound a single dose of In-111 conjugated Monoclonal Antibody to Testicular Carcinoma for injection into a single patient for diagnosis of suspected cancer of the testes. Is an I.N.D. required?

<u>Yes</u>	<u>No</u>
x	F.D.A.: "Traditional Practice of Medicine"
x	N.R.C. Licensing Restrictions: No Authority

F.D.A.: The F.D.A. does not require an I.N.D., due to the same conditions (i.e., "traditional practice of medicine") described in the previous example.

N.R.C. licensing restrictions. The Atomic Energy Act of 1954, as amended, limits the authority of the N.R.C. to the regulation of byproduct, source, and special nuclear materials. This authority does not extend to naturally occurring or accelerator-produced radioactive

materials (NARM). Since indium-111 is cyclotron-produced, the N.R.C. has no authority over this application, and legal constraints are controlled by state laws governing accelerator-produced radionuclides.

CATEGORY 2: EXAMPLE 1

A physician wishes to investigate the clinical use of Tc-99m pyrophosphate for the diagnosis of acute *bowel* infarction. The radiopharmaceutical will be administered intravenously at a dose of 15 mCi. Is an I.N.D. required for this nonapproved use of an N.D.A.-approved radiopharmaceutical?

<u>Yes</u>	<u>No</u>	
	x	F.D.A.: Exempt
		N.R.C. Licensing Restrictions:
	x	Group license
	x	Broad license

F.D.A. The use of an approved drug for indications that have not been approved in the product labeling has been discussed by the F.D.A. in Federal Register Announcement No. 15,932: "the drug labeling is not intended either to preclude the physician's use of his best judgment in the interest of the patient or to impose liability if he/she does not follow the package insert indications". To alleviate confusion in this area, the F.D.A. recently defined the criteria necessary for exempting the nonapproved use of approved drugs from I.N.D. requirements (2). Briefly, in order to be exempted, the investigation: (a) must not significantly increase patient risks, because of similarities in the route of administration, dosage range, and patient population; and (b) must not be intended directly to support a new indication for use or a significant change in product labeling (i.e., this exemption can be used by physician investigators in their clinical practice but cannot be utilized by drug manufacturers attempting to obtain approval of the new indication for their package labeling). Since the presented example does not represent an increased risk to the patient (same route of administration, dosage form, and dosage range as indicated in the package labeling), and the study is being performed by a physician investigator, an I.N.D. submission is not required.

N.R.C. licensing restrictions. In 10 C.F.R. 35, "Human Use of Byproduct Material," the N.R.C. also recognizes that the use of F.D.A.-approved radiopharmaceuticals for nonapproved diagnostic procedures represents a low risk to the patient. Thus, for specific license Groups I, II and III radiopharmaceuticals, any licensee may perform clinical procedures other than those indicated in the product labeling, provided that the radiopharmaceutical is administered: (a) in the same chemical and physical form; (b) by the same route of administration; and (c) in the same dosage range. Since the presented example meets these criteria, an I.N.D.

submission is not required to meet N.R.C. regulations. Note, however, that these N.R.C. criteria do not apply to Groups IV and V, radiopharmaceuticals for therapy, due to the increased risks involved. (Note: Group VI sources are not drugs, but "medical devices" under F.D.A. regulations.)

Again, broad license Radiation Safety Committees do have the authority to approve alternate indications for approved radiopharmaceuticals. Typically such applications are readily accepted due to the low risks involved.

CATEGORY 2: EXAMPLE 2

A physician wishes to investigate the clinical use of Tc-99m DTPA for evaluating liquid gastric emptying rates. The radiopharmaceutical will be administered orally at a dose of 1 mCi. Is an I.N.D. required?

<u>Yes</u>	<u>No</u>	
	x	F.D.A.: Exempt
		N.R.C. Licensing Restrictions:
	x	Group license: Alternate Route of Administration
	x	Broad license

F.D.A. Although the proposed dosage range and route of administration in this example differ from the package-insert indications (e.g., 10-20 mCi administered intravenously), it is obvious that this study "does not significantly increase the risk to the patient." Hence, the study would apparently fulfill the F.D.A. criteria for exemption as discussed in the previous example.

N.R.C. The N.R.C. criteria for permitting the clinical evaluation of approved radiopharmaceuticals for non-approved indications are more specific than the F.D.A. criteria (see previous example). Therefore to meet N.R.C. group license regulations, an I.N.D. submission is required, due to the alternate route of administration and dosage range proposed in this example. A license amendment would not be required for this example, since the Tc-99m DTPA would be prepared using materials obtained in accordance with 10 C.F.R. 35.14 (b) (2).

Again, broad license Radiation Safety Committees can approve this alternate indication, provided adequate dosimetry and protocol information is made available.

Note that the F.D.A. and its Radiopharmaceutical Drug Advisory Committee are actively engaged in substantiating the efficacy of commonly used alternate indications for approved radiopharmaceuticals (i.e., Tc-99m DTPA and Tc-99m sulfur colloid for oral administration, [Tc-99m]pertechnetate for dacrocystography, Tc-99m macroaggregated albumin for hepatic arterial perfusion studies) in order to facilitate incorporation of these indications into product labeling and to alleviate this problem. The N.R.C. also has recently shown a willingness to directly approve alternate indi-

cations for approved radiopharmaceuticals. In their approval of Tc-99m DTPA as an aerosol for lung function studies, the N.R.C. outlined the criteria for evaluating exceptions to the product labeling (3). This evaluation must demonstrate no unnecessary radiation dose to the patient and adequate occupational radiation-protection measures.

CONCLUSION

In conclusion, it is obvious that clinical investigators must develop a working knowledge of all of the bodies (F.D.A., N.R.C., institutional review committees) governing the human use of radiopharmaceuticals. This knowledge must then be carefully applied to each individual research effort in order to determine whether an I.N.D. submission is required. It is recommended that investigators with unresolved problems or questions

should contact the appropriate F.D.A. and/or N.R.C. staff directly to discuss their particular situations (e.g., nature of study, type of N.R.C. license, etc.).

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