TRANSMISSION VERIFICATION REPORT

TIME : 01/10/2005 19:05
NAME : USNRC
FAX : 6308299782
TEL : 6308299782

DATE,TIME	01/10 19:00
FAX NO./NAME	87346629224
DURATION	00:05:13
PAGE(S)	12
RESULT	OK
MODE	STANDARD ECM

NRC FORM 386 (RIII)
(7-2002)

UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION III
801 Warrenville Road, Suite 255
Lisle, Illinois 60532-4351

TELEFAX TRANSMITTAL

DATE: 1/10/05

NUMBER OF PAGES: 14
(including this page)

SEND TO: TOM KUMPURIS

LOCATION: MPC FOR HARPER HOSPITAL

FAX NUMBER: ~~313~~ 734 - 662 - 9224 ☐ **VERIFY BY CALLING SENDER**

FROM:
(SENDER) COLLEEN CASEY

TELEPHONE NUMBER: 630 - 829 - 9841 FAX NUMBER: 630 - 829 - 9782

If you do not receive the complete fax transmittal, please contact the sender as soon as possible at the telephone number provided above.

MESSAGE Please call me if you have questions,

Thank you.

NRC FORM 386 (RIII)
(2-2002)

UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION III
801 Warrenville Road, Suite 255
Lisle, Illinois 60532-4351

TELEFAX TRANSMITTAL

Ref Colleen (Letter only) → (4) 2nd

re-sent 1/11/05

DATE: 1/10/05

NUMBER OF PAGES: (14) 1st
(including this page)

SEND TO: TOM KUMPURIS

LOCATION: MPC FOR HARPER HOSPITAL

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Thank you.

Colleen Carol Casey

I'm sorry first fax attempt was incomplete. Colleen

NOTICE

COLLEEN CAROL CASEY
MATERIALS LICENSING BRANCH
UNITED STATES NUCLEAR REGULATORY COMMISSION
REGION III
2443 WARRENVILLE ROAD
LISLE, ILLINOIS 60532-4352
OFFICE: (630)-829-9841 FAX: (630) 829-9782

CONVERSATION RECORD |TIME Breach Tom Kumpuris by phone ~2:30 on 1/11/05 |DATE January 10, 2005

ACTUALLY FAXED? YES.

NAME OF PERSON(S) CONTACTED	ORGANIZATION	TELEPHONE NO.
Thomas M. Kumpuris, M.S., consultant for Harper University Hospital		800-321-2207, fax, 313-662-9224

SUBJECT
License No.: 21-04127-02 Control No.: **313798**

SUMMARY
We have reviewed your letter dated September 21, 2004, signed by James E. Stopford, requesting an amendment to your byproduct materials license and find that we need additional information as follows:

1. Please confirm that Richard Joyrich, M.D. is an authorized user under your license for the use of materials in 10 CFR 35.300.

2. I noted that Dr. Joyrich is the only proposed Authorized User mentioned in your letter for this research study. If you intend to involve other Authorized Users, it may be advantageous to name them now by name and specify whether each is currently authorized under your license for the use of materials in 10 CFR 35.300. If you wish to add authorized users, please advise us in your response.

3. Please indicate what the typical diagnostic and therapeutic dosages are expected to be for the Holmium-166 (Ho-166) product and what the range of dosages is expected to be.

4. Please confirm that you will follow 10 CFR 35.6, including a description of how and by whom your research will be funded and how you will comply with each provision in Pt. 35.6, for the use of the Ho-166 in this research study.

5. Your letter referred to 10 CFR 32.72. I suspect you intended to refer to 10 CFR 35.63(b)(2)(ii). Please confirm whether this is what you intended for the determination of dosages of Ho-166.

6. Please confirm that you will follow 10 CFR Subpart E and all applicable conditions of your license for the use of the Ho-166 in this research study.

7. Please refer to Information Notice IN 2000-19, copy attached, including, but not limited to, the sections on "Questions and Answers" and "Licensing Factors." Please prepare appropriate responses to the Licensing Factors, items 4 and 5, as pertains to the Ho-166 proposal. In particular, please submit a copy of the FDA IND application that contains radiation safety commitments suitable for public release. Please do not submit proprietary information subject to 10 CFR 2.390.

8. As noted in IN 2000-19:

"In order to conduct research involving human subjects NRC licensees need to: have a medical license; be licensed for the specific medical use included in the research; be licensed to use the regulated materials specifically for the medical use included in the research; comply with 10 CFR 35.6; comply with all applicable NRC requirement in 10 CFR, including those in 10 CFR Part 35, not just the requirements of 10 CFR 35.6; and comply with all license conditions.

When participating in research studies regulated by FDA, the licensee needs to be aware that: FDA review of the device, drug or biologic may not be substituted for NRC's licensing review; and following the FDA-accepted protocol does not assure compliance with NRC requirements.

In general, when conflicts occur between protocols (or radiation safety information within protocols) and NRC requirements, it is the licensee's responsibility to resolve the conflicts and be in compliance with the NRC requirements. This may involve contacting NRC, the protocol sponsor, or both.

Licensees also need to be aware that participation in a "blind" study does not relieve the licensee from meeting the: labeling requirements in 10 CFR Part 35; written directive requirements; research subject release and the instruction requirements of 35.75; hospitalization requirements in 10 CFR Part 35; and misadministration (now called "medical events") notification and reporting requirements."

ACTION REQUIRED

Submit the requested information by referencing control number 313798 to facilitate proper handling. Upon receipt of your response we will resume our review. Address your written response to my attention at the above address.

As we cannot issue an amendment at this time we are voiding this request in order to enable you to prepare a quality application without time constraints. PLEASE NOTE THAT A "VOID" IS AN ADMINISTRATIVE PROCEDURE THAT PUTS YOUR AMENDMENT REQUEST "ON HOLD" (TAKES IT OUT OF OUR ACTIVE CASEWORK DATABASE) UNTIL YOU REACTIVATE IT VIA SUBMISSION OF A WRITTEN RESPONSE. IT "BUYS" YOU TIME TO PREPARE A QUALITY RESPONSE AND IS GENERALLY REGARDED AS A "GOOD THING."

PLEASE DIRECT ANY QUESTIONS YOU MAY HAVE TO ME AT 630-829-9841.

Please note that on October 25, 2004, the NRC suspended public access to ADAMS, and initiated an additional security review of publicly available documents to ensure that potentially sensitive information is removed from the ADAMS database accessible through the NRC's web site. Interested members of the public may obtain copies of the referenced documents for

review and/or copying by contacting the Public Document Room pending resumption of public access to ADAMS. The NRC Public Document Room is located at NRC Headquarters in Rockville, MD, and can be contacted at 800-397-4209 or 301-415-4737 or pdr@nrc.gov.

NAME OF PERSON DOCUMENTING CONVERSATION	SIGNATURE	DATE
Colleen Carol Casey	Colleen Carol Casey	January 10, 2005

TRANSMISSION VERIFICATION REPORT

TIME : 01/11/2005 14:42
NAME : USNRC
FAX : 6308299782
TEL : 6308299782

DATE,TIME	01/11 14:41
FAX NO./NAME	87346629224
DURATION	00:01:09
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NRC FORM 386 (RIII)
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UNITED STATES
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(4) 2nd

re-sent 1/11/05

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NUMBER OF PAGES: (14) 1st
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SEND TO: TOM KUMPURIS

LOCATION: MPC FOR HARPER HOSPITAL

FAX NUMBER: ~~313~~ 734 - 662 - 9224 ☐ ***VERIFY BY CALLING SENDER***

FROM: *(SENDER)* COLLEEN CASEY

TELEPHONE NUMBER: 630 - 829 - 9841 FAX NUMBER: 630 - 829 - 9782

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CONVERSATION RECORD | TIME | DATE

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Thomas M. Kumpuris, M.S., consultant for	Harper University Hospital	800-321-2207, fax, 313-662-9224

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NAME OF PERSON DOCUMENTING CONVERSATION	SIGNATURE	DATE
Colleen Carol Casey	Colleen Carol Casey	January 10, 2005

UNITED STATES
NUCLEAR REGULATORY COMMISSION
OFFICE OF NUCLEAR MATERIAL SAFETY AND SAFEGUARDS
WASHINGTON, D.C. 20555

December 5, 2000

NRC INFORMATION NOTICE 2000-19: IMPLEMENTATION OF HUMAN USE RESEARCH PROTOCOLS INVOLVING U.S. NUCLEAR REGULATORY COMMISSION REGULATED MATERIALS

Addressees:

All medical use licensees.

Purpose:

This information notice is intended to remind medical use licensees of their responsibility to ensure compliance with U.S. Nuclear Regulatory Commission (NRC) requirements and all their license conditions, when participating in the research involving human subjects using NRC regulated materials. It is also intended to remind licensees that Title 10 of the Code of Federal Regulations (CFR) Section 35.6, "Provisions for research involving human subjects," is not a blanket authority to conduct research involving human subjects.

Licensees should review this information for applicability to their own procedures and consider actions, if appropriate, to preclude violations similar to those described in this notice. However, information contained in this notice does not constitute any new NRC requirements, and no written response to this information notice is required.

Background:

The participation of four NRC licensees in research studies involving human subjects is discussed in Attachment 1. The first three licensees were participating in a U. S. Food and Drug Administration (FDA EXIT)-accepted investigational new drug (IND) trial and the fourth licensee was participating in an FDA-accepted investigative device exemption (IDE) trial. These trials involved the use of byproduct material in radioactive drugs, or sealed sources and devices for radiation therapy using "blind" research protocols.

In three of the four cited cases, the licensees participating in the research studies were found to be conducting research using byproduct material in violation of NRC requirements. Although all of these licensees were in compliance with the requirements of 10 CFR 35.6, they overlooked other applicable NRC requirements. Additionally, one licensee (the fourth) incorrectly believed 10 CFR 35.6 provided blanket authorization to conduct research involving human subjects regardless of whether the licensee complied with the conditions of its license or other NRC requirements.

Discussion:

Some research involving human subjects and especially "blinded" research studies pose unique radiation safety challenges and issues. These issues are summarized below and discussed in more detail in a question and answer format in Attachment 2.

In order to conduct research involving human subjects NRC licensees need to:

- have a medical use license;
- be licensed for the specific medical use included in the research;
- be licensed to use the regulated material specifically for the medical use included in the research;
- comply with 10 CFR 35.6;
- comply with all applicable NRC requirements in 10 CFR, including those in 10 CFR Part 35, not just the requirements of 10 CFR 35.6; and
- comply with all license conditions.

When participating in research studies regulated by FDA, the licensee needs to be aware that:

- FDA review of the device[1], drug, or biologic may not be substituted for NRC's licensing review; and
- following the FDA-accepted protocol does not assure compliance with NRC requirements

In general, when conflicts occur between protocols (or radiation safety information within protocols) and NRC requirements, it is the licensee's responsibility to resolve the conflicts and be in compliance with the NRC requirements. This may involve contacting NRC, the protocol sponsor, or both.

Licensees also need to be aware that participation in a "blind" study does not relieve the licensee from meeting the:

- labeling requirements in 10 CFR Part 35;
- written directive requirements;
- research subject release and the instruction requirements of § 35.75;
- hospitalization requirements in 10 CFR Part 35; and
- misadministration notification and reporting requirements.

Medical broad scope licensees have a broader licensing authorization and can participate in research studies that may not be authorized for medical limited scope licensees because of the restrictions in § 35.49.

One of the cited cases involved a limited specific medical use licensee attempting to participate in an intravascular research study using sealed sources and a device that had not been evaluated and registered by NRC or an Agreement State. Attachment 3 addresses the approach NRC uses to review a limited specific scope licensee's request to participate in intravascular brachytherapy research studies on human subjects.

Summary:

Any licensee with questions concerning compliance with NRC or Agreement State requirements or license amendments related to research involving human research subjects and regulated materials, should contact either NRC regional licensing personnel or its corresponding Agreement State for advice. Licensees may also want to distribute this notice to researchers using NRC-regulated materials to conduct human research, as well as individuals responsible for radiation safety and quality management programs. This could save licensees considerable time and resources, and avoid violations of regulatory requirements.

No specific written response to this information notice is required. If you have any questions about this matter, please contact the technical contacts listed below or the appropriate regional office.

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

Technical Contacts:
Robert L. Ayres, Ph.D., NMSS
(301) 415-5746
E-mail: rxa1@nrc.gov

Donna-Beth Howe, Ph.D., NMSS
(301) 415-7848
E-mail: dbh@nrc.gov

Attachments:
1. Licensee Case Histories
2. Questions and Answers
3. Criteria for a Limited Specific Scope Licensee to Participate in Intravascular Brachytherapy Research Studies on Human Subjects
4. List of Recently Issued NMSS Information Notices
5. List of Recently Issued NRC Information Notices

(ADAMS Accession Number ML003773013)

ATTACHMENT 1

LICENSEE CASE HISTORIES

Investigational New Drug Trial Cases:

Three NRC licensees were participating in a therapeutic radioactive drug research study. The drug manufacturer was conducting Phase II clinical trials accepted by the US Food and Drug Administration (FDA) pursuant to an Investigational New Drug (IND) application. The protocol called for "blind studies" to compare the effectiveness of several dosage levels of the investigational drug against both the commercially available therapeutic radiopharmaceutical Metastron® (containing strontium-89 chloride) and a placebo. Because the studies were "blind," neither the individual administering the dosage nor the human research subject was informed of the drug/placebo or the dosage administered. To keep the identity of the drug or placebo delivered secret, the delivery administration procedures were identical.

The investigational drug was primarily a photon emitter, unlike Metastron® which is primarily a beta emitter. Research subjects administered Metastron®, which contains strontium-89, do not pose an external radiation hazard to other individuals. The photon emitter in the investigational drug could, however, pose an external radiation hazard to others. The proposed human research subject instructions in the protocol were similar to those suggested for Metastron®, and therefore did not address steps to minimize exposure to other individuals from a photon emitter. Additionally, the dosage levels under investigation included a dosage of the investigational drug that, if administered, might have required hospitalization of the human research subjects, in accordance with 10 CFR 35.75(a). Human research subject-specific information (such as biological clearance or personal behavior) needed to be considered to determine whether the total effective dose equivalent to other individuals from exposure to the released research subject could exceed 0.5 millisievert (0.5 rem).

NRC inspectors determined that two licensees participating in this protocol failed to recognize that the sponsor's suggested instructions to the research subjects were inappropriate for the investigational drug and that one dosage level could require hospitalization of the research subject, unless other criteria were considered. In both cases, the medical broad scope radiation safety committees did not review or approve the 10 CFR Part 33 required safety evaluations addressing radiation safety issues for proposed uses of byproduct material associated with these research studies.

The dosages administered by the third licensee were below levels that required the research subject to be released with instructions. This licensee also complied with all NRC requirements and will not be discussed further.

First IND Licensee

The first licensee administered a dosage without recognizing that the dosage could have required hospitalization, for compliance with 10 CFR 35.75. The human research subject was released with written instructions, but the instructions were inappropriate for the radionuclide administered. After learning of the apparent unauthorized release, the licensee, using subject-specific elimination rates, determined that exposures to other individuals were not likely to exceed 5 millisievert (0.5 rem). However, this determination should have been made before releasing the human research subject and appropriate

instructions provided to the research subject.

Second IND Licensee

The second licensee administered dosages of the investigational drug to two human research subjects. In the first of these administrations, the dosage to the subject was such that, if the subject were to be released, other individuals were likely to receive a total effective dose equivalent in excess of 5 millisievert (0.5 rem). This subject was hospitalized, but for reasons unrelated to the radiopharmaceutical dosage administration. Licensee personnel did not recognize that the subject was required to be hospitalized for compliance with 10 CFR 35.75. In addition, the licensee neither provided instruction to personnel providing care to the human research subject in accordance with 10 CFR 35.310, nor followed the applicable safety precautions in 10 CFR 35.315.

When the research subject was released from the hospital, other individuals were likely to receive a total effective dose equivalent between 5 millisievert (0.5 rem) and 1 millisieverts (0.1 rem). Thus, before this subject was released, the licensee was required to provide instructions on actions recommended to maintain doses to other individuals as low as reasonably achievable. However, the required instructions were not provided to the research subject. The dosage for the second research subject was high enough that this subject also needed to be provided with instructions. Instructions were not provided for this research subject either.

After identifying the first incident, NRC contacted the IND sponsor and discussed the sections of the protocol that contributed to the licensees being in noncompliance with NRC regulations. The sponsor amended its FDA IND application to revise the protocol's suggested human research subject instructions. The revised instructions now include precautions to minimize exposure to other individuals. The sponsor also alerted the protocol participants that one dosage level of the investigational drug may require hospitalization of the human research subject to meet the requirements of 10 CFR 35.75.

Investigational Device Exemption Trial Case:

A fourth licensee received an intravascular brachytherapy device, containing multiple sealed sources of strontium-90, from the device manufacturer, to participate in its Investigational Device Exemption (IDE) clinical trial. The purpose of the trial was to establish the efficacy of using intravascular brachytherapy to prevent restenosis in coronary arteries after balloon angioplasty. Although this licensee was authorized to possess this device and sources under its broad-scope research and development license, it was not authorized to use the device on humans under its medical use license of limited scope.

In this specific intravascular brachytherapy research case, NRC inspectors identified the following two failures to comply with NRC requirements:

> The Sr-90 sealed sources are not listed in 10 CFR 35.400 for the application (intravascular brachytherapy) for which they were used. Under 10 CFR 35.400, the only authorized use for strontium-90 sealed sources is for treatment of superficial eye conditions. Therefore, the licensee needed to apply for, and receive, an exemption from the requirements of 10 CFR 35.400; and,
>
> 2. Neither the Sr-90 sealed sources nor the device had been reviewed by NRC or an Agreement State for distribution authorized by a license issued pursuant to 10 CFR 32.74 as required by 10 CFR 35.49(a) nor had an exemption from this requirement been granted. Section 35.49(a) requires sealed sources or devices for medical use to be manufactured, labeled, packaged, and distributed in accordance with a license issued pursuant to 10 CFR Part 30 and 10 CFR 32.74, or the equivalent requirements of an Agreement State. Since this device (and its sources) did not meet these requirements, it could not be used on humans by a NRC limited-scope medical use licensee.

Thus, this licensee did not meet the requirements of 10 CFR 35.49(a) and 10 CFR 35.400, respectively. Had the licensee applied to NRC for the appropriate exemptions and approval to participate in this human research intravascular brachytherapy trial, these violations could have been avoided. The underlying cause of the violations are addressed in the six specific licensing review factors (Attachment 3) that NRC considers before authorizing a limited scope medical use licensee to participate in such clinical trials.

Once the cited violations related to the human use of this device were discovered, the licensee voluntarily discontinued its participation in the ongoing clinical trial. The device(s) and sources were returned to the trial's sponsor while the licensee pursued an amendment request for an alternative pathway, as described in the answer to question 13 in Attachment 2 of this

Information Notice.

ATTACHMENT 2

QUESTIONS AND ANSWERS

NRC staff developed the following questions and answers to assist licensees who are planning to conduct research involving human subjects. Closely related questions and answers will be referenced to avoid significant redundancy. However, you may find some repetition in the answers because each is, for the most part, expected to stand alone.

1. **What kind of NRC license do I need to conduct research involving human research subjects using byproduct material?**

   You must have a medical use license (or a medical use authorization) because 10 CFR Part 35, "Medical Use of Byproduct Material," is the only part in NRC regulations that permits the intentional internal or external administration of byproduct material or the radiation therefrom to human research subjects. Depending on the experience, size and complexity of the medical use program, either a broad scope or limited scope medical use license may be issued.

2. **I have an NRC medical use license. What other NRC regulatory requirements do I have to comply with to conduct research involving NRC regulated materials and human research subjects?**

   Licensees conducting human research using radioactive drugs, sealed sources, and/or devices are responsible for ensuring that, in addition to 10 CFR 35.6, they comply with all other applicable NRC requirements and license conditions. Radioactive drug, sealed source, and device manufacturers and other research protocol sponsors may not always be cognizant of NRC and Agreement State requirements and the radiation safety implications of their proposed research. Therefore, it is the licensee's responsibility to ensure that: (1) it is authorized to possess the materials and devices needed to participate in the research studies; (2) the materials and devices to be used in the research are included in the specific medical uses authorized in the license; (3) the procedures in the research protocols do not conflict with NRC regulatory and license requirements; and (4) it is in compliance with 10 CFR 35.6, its license, and any other NRC regulatory requirements.

   When conflicts occur between the protocols and NRC requirements, it is the licensee's responsibility to seek resolution of such conflicts with the protocol sponsor or the NRC. In addition, the research to be conducted may include uses, radionuclides, or quantities which are not authorized by the license, in which case the NRC must be contacted. For example, licensees may need to apply for and obtain a license amendment to authorize the possession and use of radionuclides not authorized in the license and/or to increase the possession limit(s) for one or more radionuclides. Also, the broad scope medical use licensee's radiation safety committee should be diligent in its review of new procedures, to assure compliance with all NRC requirements.

   In the intravascular brachytherapy device case, the licensee believed that compliance with the requirements of 10 CFR 35.6 provided sufficient authorization to conduct human research with the device, notwithstanding any other applicable requirements of NRC regulations. The licensee was authorized to possess and use the material on the research and development (non-medical use) part of the license but was not authorized to posses or use it on the "medical use" part of the license. A licensee conducting research with byproduct material involving human subjects must use only material authorized by the medical use license and in accordance with all applicable provisions of the license (e. g., the quantities, a particular medical use, use by individuals identified on the license for the particular medical use, etc.) and NRC regulations (e.g. the requirements in 10 CFR 19, 20, 30, 33, 35, etc.).

3. **I intend to participate in a clinical trial that has been reviewed by FDA. As long as I have a medical use license and the device[2], drug, or biologic has been reviewed by FDA, I can use it, right?**

   Not necessarily. As discussed in the previous response, before you can participate in a clinical trial, you must, among other things, be authorized to possess the materials and devices needed to participate in the research studies and you must only use the materials and devices for the specific medical uses as authorized in the license. Although the device, drug, or biologic may have been reviewed by FDA, it is not necessarily included in the authorization in your NRC license. Generally, a sealed source and /or device will require a radiation safety review and registration by NRC or an

Agreement State before its use can be authorized by NRC or an Agreement State. If you have any questions, you should contact NRC.

Problems occur when a licensee mistakenly assumes the FDA IDE application review and acceptance processes[3] are equivalent to, and can be substituted for, NRC or Agreement State radiation safety review and registration of the source/device. The focus of FDA's IND and IDE application reviews is on informed consent, institutional review board approval, and medical safety and effectiveness issues as related to the protection of the patient. The FDA reviews do not specifically address non-FDA compliance issues.

The NRC review and approval process is broader in terms of radiation safety. In particular, the NRC review evaluates not only the radiation safety of the patient or human research subject, but radiation protection of workers and the general public from unintentional radiation exposures from such devices. Thus, FDA's IDE review is not the equivalent to the NRC radiation safety review and cannot be substituted for it. The same is true of the FDA review and acceptance of IND applications for radioactive drugs and biologics.

4. **If I have a medical use license and will follow an FDA reviewed protocol, can I be assured of meeting NRC requirements?**

Not necessarily. There is no assurance the research sponsor and FDA are aware of all the NRC requirements, your license authorizations, and all the radiation safety implications of the sponsor's protocol. You need to review the protocol and ensure the radiation safety aspects are in compliance with NRC's requirements. As discussed in the response to question 2, licensees need to resolve any conflicts between the protocols and NRC requirements.

If the research sponsor is unaware of NRC requirements, following the sponsor's protocols (or the radiation safety information contained in the protocol) may create dilemmas for licensees. The sponsor expects the licensee to follow the protocol to maintain the scientific integrity of the study, and the NRC expects the licensee to be in compliance with its license and other NRC requirements. Sometimes these two expectations are in conflict. For example, if the licensee follows the sponsor's protocol that contains incorrect radiation safety information, the licensee may be in a position of noncompliance with NRC requirements. Conversely, if the licensee complies with NRC requirements, the licensee may deviate from the protocol in a manner that could invalidate the scientific integrity of the study. Before this happens, licensees should make both the NRC and the research sponsor aware of any conflicts between the sponsor's protocols and NRC regulatory requirements. It may take coordination between all three to resolve the conflicts.

5. **I intend to participate in a "blind" clinical trial. Are there any special concerns I should be aware of in terms of compliance with NRC requirements?**

Many medical research protocols call for comparison treatments in which groups of human research subjects receive different treatments. Some of these studies are "blind," i.e., only the research sponsor (or the sponsor's agent) knows which treatment group a particular research subject is in. In a "blind" clinical trial, the treatment protocols are standardized so that all research subjects are handled the same way and neither the human research subject nor the physician monitoring that research subject knows which treatment is given.

Research sponsors use "blind studies" because they are an important means of obtaining unbiased scientific data. However, if the research sponsor is unaware of NRC requirements, the "blind" aspect of the study may cause additional dilemmas for licensees. The sponsor expects the licensee to keep certain information from the research subject and the physician following the research subject. However, the licensee may have labeling, measurement, posting, and notification requirements that may reveal this information which could affect the "blind" nature of the study and thus possibly invalidate its scientific integrity. Before this happens, the licensee needs to make both the NRC and the research sponsor aware of any conflicts between the sponsor's protocols and NRC regulatory requirements, so that such conflicts may be resolved.

Regulatory compliance may present problems in following "blind" protocols when subjects receive placebos, approved products, or investigational products that are governed by significantly different radiation safety precautions. In order to maintain the "blind" nature of the study, a licensee may elect to treat all human research subjects, even those administered placebos, as if they had received the byproduct material requiring the most stringent radiation safety instructions and precautions. The intent of this approach would be to ensure licensee compliance with NRC requirements for those human research subjects that need the most stringent radiation safety instructions and precautions. However, as will be discussed later, such an approach may not be practical for research subjects that do not need such instructions and precautions.

Examples of NRC medical use requirements that should be considered when reviewing "blind" protocols include, but are not limited to, those related to syringe labeling (§ 35.60), written directives (§ 35.2), release of individuals receiving certain therapeutic treatments (§35.75), misadministration reporting (§ 35.33), and providing appropriate safety instructions and safety precautions (§§ 35.75, 35.310, 35.315, 35.410, and 35.415).

6. **Does NRC require me to perform radiation surveys, provide radiation instructions to the human research subject, and/or hospitalize the research subject, post rooms as radioactive, etc., even if the research subject received no byproduct material?**

   No, whether you, as a medical use licensee, are required to take such actions as performing radiation surveys, providing radiation instructions to human research subjects, hospitalizing research subjects, and posting rooms as radioactive depends upon the type and dose or dosages of byproduct material administered. However, the research sponsor will expect you to treat all research subjects the same, to the extent necessary to maintain the "blind" nature of the study.

   For example, NRC would require hospitalization for those human research subjects that could not be released in accordance with 10 CFR 35.75, "Release of individuals containing radiopharmaceuticals or permanent implants." Differentiation between these human research subjects and others could reveal to the subjects and their physicians which treatment they received, and jeopardize the scientific integrity of the study. On the other hand, not hospitalizing the research subject when required by 10 CFR 35.75 would violate NRC requirements. Resolving the conflicts as discussed below could ensure the integrity of the study and compliance with NRC requirements.

   In the specific IND cases discussed in this Information Notice, the licensees overlooked applicable NRC requirements. When the conflict was first identified, NRC contacted the IND sponsor to identify other licensees conducting the research with similar problems and discussed the protocol sections that put both licensees in noncompliance with NRC regulations. The sponsor amended its FDA IND application to revise the protocol's suggested human research subject instructions. The sponsor also alerted the protocol participants that one dosage level of the investigational drug may require hospitalization to meet the requirements of 10 CFR 35.75.

7. **I intend to participate in a "blind" clinical trial that compares a nonradioactive treatment with a byproduct material therapy treatment. The authorized user will know when the written directive is dated and signed that the subject is receiving the byproduct material treatment and the trial will no longer be "blind." How do I comply with NRC's requirement and the "blind" protocol?**

   All administrations of byproduct material, or the radiation therefrom, identified in 10 CFR 35.32, "Quality management program," must have a written directive signed and dated by an authorized user prior to the administration. Licensees participating in "blind" research studies using therapeutic radioactive drugs and devices are not relieved from this requirement.

   Both the IDE and IND studies discussed in this Information Notice were "blind" studies and included placebo treatments, i.e., dummy sources or saline injections. Three of the licensees complied with the written directive requirement; one did not. The two methods described below have been used to meet NRC's written directive requirements and maintain the "blind" nature of the research. Licensees may develop other alternatives that meet the same objectives.

   One method is to prepare a specific written directive containing required information, i.e., the isotope and the dose or dosage to be given to individually identified human research subjects. No written directive is needed or prepared for the placebo recipients. In this method, the authorized user who signs and dates the written directive is not the physician monitoring the human research subject. The licensee maintains the "blind" nature of the study by ensuring the research subject and the physician monitoring the human research subject do not have access to, or knowledge of, the written directive.

   In another method, the authorized user signs and dates a written directive for each human research subject regardless of whether a written directive is required. All directives include identical information and instructions addressing all possible administrations covered in the research. In this case, because all the instructions are identical, the authorized user is not aware of ("blind" to) the specific administration to a particular human research subject. NRC has accepted the use of written directives containing such identical instructions listing all the possible administrations to be delivered and indicating that the one delivered will be in accordance with the protocol. The protocol provides a methodology to match individual research subjects with specific administrations.

8. **What happens if there is a misadministration during a "blind" clinical trial?**

   If a misadministration occurs, the licensee must comply with the misadministration notification, reporting, and record keeping requirements in 10 CFR 35.33, even if this affects the "blind" nature of the study. Depending on the research and the nature of the error, compliance with the notification and reporting requirements for misadministrations may not necessarily compromise the "blind" nature of the study.

9. **The clinical protocol calls for a therapy procedure to be conducted as an outpatient treatment. Are there any special concerns I should be aware of?**

   When considering protocols involving radiopharmaceuticals, sealed sources, and devices for therapeutic purposes, licensees must be especially vigilant to ensure that the human research subjects and patients administered the investigational drugs or permanent implants are released in accordance with 10 CFR 35.75. The research sponsor may not be aware of this regulation.

   NRC's Regulatory Guide 8.39, "Release of Patients Administered Radioactive Materials," aids licensees in determining, in part: (1) when the licensee may authorize the release of an individual who has been administered radiopharmaceuticals or permanent implants containing radioactive material; (2) when instructions to the individual are required by 10 CFR 35.75(b); and (3) when records required by 10 CFR 35.75(c) and (d) are to be generated and maintained. The guide lists "default values" for administered activities of commonly used radionuclides and corresponding dose rates that can be used to determine if patients and human research subjects may be released in compliance with the dose limits in 10 CFR 35.75.

   The guide also provides suggested procedures, based on patient-specific factors, that licensees may use to calculate doses to other individuals from exposure to patients who have been administered activities higher than the "default values" listed in the guide.

   Regardless of the instructions in the protocol, if you are unable to determine, based on the "default values" or calculations or measurements, that the individual can be released in accordance with 10 CFR 35.75, then the individual human research subject must be hospitalized to comply with 10 CFR 35.75. If an individual is hospitalized for compliance with 10 CFR 35.75, then you must also comply with the safety instruction and safety precautions in §§ 35.310, 35.315, 35.410 and 35.415, as appropriate. As discussed earlier, if this affects the "blind" nature of the study, the research sponsor needs to be made aware of the situation.

10. **I have a limited scope medical use license and intend to participate in a clinical trial for a new sealed source or medical device. Are there any special concerns I should be aware of?**

    A number of regulatory issues may arise when a limited scope medical use licensee needs to use a new sealed source or device in a clinical trial. Intravascular brachytherapy was selected for discussion to illustrate some of these issues because it is presently the most active area of human research using sealed sources and devices.

    Intravascular brachytherapy currently involves a very diverse set of devices, sources, and procedures. NRC noted a number of common deficiencies in reviewing applications and responding to inquires from limited specific medical use licensee seeking to use intravascular brachytherapy devices to participate in intravascular brachytherapy human trials. The six licensing review factors, in Attachment 3 of this Information Notice, were developed from this practical experience and represent the minimum information necessary for review of an intravascular brachytherapy application. As stated earlier, licensees conducting human research using sealed sources and/or devices are responsible for insuring that, in addition to 10 CFR 35.6, they comply with all other applicable NRC requirements and license conditions (e.g., 10 CFR 35.49 and 10 CFR Part 35, Subpart G).

11. **What is the regulatory basis for the licensing review factors in Attachment 3 to this Information Notice?**

    The licensing review factors in Attachment 3 are specific to intravascular brachytherapy, a medical use that is not specifically listed in 10 CFR 35. The regulatory basis for each review factor is provided for clarification. In licensing review factor 2, for example, participation in the FDA-accepted IDE satisfies the requirements of 35.6.[4] The licensee must, however, provide the IDE number and copy of the IDE to meet the requirements in 10 CFR 30.33.

    Other research studies involving medical uses specifically included in 10 CFR Part 35 may not involve all or any of these

review factors because the basic radiation safety programs are already reflected in the regulations. In fact, depending on your license (i.e., the license authorizes the byproduct material for the same medical uses as the research) and the nature of the research (i.e., it is conducted, funded, supported, or regulated by a Federal agency that has implemented the Federal Policy for the Protection of Human Subjects), you may already be authorized to conduct research involving human subjects without applying for and obtaining a license amendment from NRC.

12. **I have a broad scope medical use license and intend to participate in a clinical trial for an unregistered sealed source or medical device. Are there any special concerns I should be aware of?**

    A medical use licensee of broad scope is exempt from the requirements of 10 CFR 35.49(a) and 10 CFR 35.400 by a standard license conditions and generally does not need to seek a license amendment to participate in these studies. However, problems have been reported with broad-scope licensees' radiation safety committee reviews and approvals of these unregistered sources and/or devices used in these trials. This issue is addressed separately in NRC Information Notice 99-24 "Broad-Scope Licensees' Responsibilities for Reviewing and Approving Unregistered Sealed Sources and Devices." The Internet address is http://www.nrc.gov/NRC/GENACT/GC/IN/1999/in99024.txt for this Information Notice.

13. **I have a limited scope medical use license. How can I participate in medical device clinical trials normally open only to broad scope medical use licensees?**

    Frequently, a limited scope medical use licensee applies for authorization to participate in clinical trials using a source or device that has not been reviewed and approved by the NRC or an Agreement State.

    Such a licensee may consider one of the following approaches to assuring compliance with NRC requirements:

    1. Ask the trial sponsor to have its source or device evaluated and registered by NRC or an Agreement State, and submit their application to participate in the trials after the source or device is registered;

       Submit an application that requests a "custom" review of the source or device from NRC. This provides NRC with all the necessary information for this review, but delays authorization to participate in the trial(s) until the source or device review is successfully completed;

       Submit an application that requests authorization for the limited scope medical use Radiation Safety Committee to perform the requisite radiation safety and engineering review of the source and/or device in-house, following the criteria set forth in 10 CFR 32.210. The in-house expertise available may need to be augmented to perform this review and there can be no prior assurance that the results of the review would be acceptable to NRC or an Agreement State; or,

       Submit an application to become a broad-scope medical use licensee, if the medical use program meets the criteria in 10 CFR Part 33.

ATTACHMENT 3

LICENSING REVIEW FACTORS USED FOR REVIEWING A LIMITED-SCOPE MEDICAL USE LICENSEE'S REQUEST TO PARTICIPATE IN INTRAVASCULAR BRACHYTHERAPY RESEARCH STUDIES

Each of the following six licensing review factors are specifically used by NRC to approve participation by a limited specific scope licensee in intravascular brachytherapy research studies on humans using sealed sources of byproduct materials and/or devices. The regulatory basis for each review factor is either clearly stated within the factor or placed at the end of the factor. Compliance with all other applicable Nuclear Regulatory Commission (NRC) requirements is presumed.

1. The radiation sources and/or devices used in the research must have undergone an appropriate sealed source and/or device safety evaluation and been issued a certificate of registration by NRC, or by an Agreement State, for intravascular brachytherapy applications. (10 CFR 30.32 and 10 CFR 35.49)

2. The provisions for protecting human research subjects, pursuant to 10 CFR 35.6, "Provisions for Research Involving Human Subjects," must be satisfied. For "significant-risk" procedures, such as intravascular brachytherapy, this may be satisfied through participation in an U.S. Food and Drug Administration (FDA) approved Investigational Device Exemption (IDE) trial.[5] The FDA-assigned IDE number should be identified in the licensing request and a copy of the IDE application provided. (10 CFR 30.33)

3. Only those physicians already authorized to use 10 CFR 35.400 byproduct materials or who meet the training and experience requirements in 10 CFR 35.940 can be designated as authorized users for the procedure. In the later case, an NRC amendment and approval is required before use.

4. Radiation safety commitments (which are part of the radiation safety program required by 10 CFR 20.1101) must be contained in a document suitable for public release. Important radiation safety commitments, which are not proprietary, are often contained in the FDA IDE application, which is a proprietary document. These commitments must be in a separate document that can be incorporated in the license by reference and available to the public. (10 CFR 2.790)

5. The NRC must have access to proprietary information pertaining to medical use, device performance, and radiation safety concerns with the device, for use during licensing and inspection activities. (10 CFR 30.33 and 10 CFR 30.52)

6. An exemption from the requirements of 10 CFR 35.400 must be applied for and granted to use any sealed source and/or device for intravascular brachytherapy.

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1. FDA classifies a source as a device.

2. FDA classifies a source as a device.

3. Because FDA designated intravascular brachytherapy devices as "significant risk" devices, FDA regulations mandate that FDA review and accept IDE submissions for all clinical trials using intravascular brachytherapy devices.

4. The research is regulated by FDA, a Federal Agency that has implemented "The Federal Policy for the Protection of Human Subjects."

5. The research is regulated by FDA, a Federal agency that has implemented "The Federal Policy for the protection of Human Subjects."