

October 9, 1997

FOR: The Commissioners

FROM: L. Joseph Callan, Executive Director for Operations /s/

SUBJECT: FINAL RULE ON EXEMPT DISTRIBUTION AND USE OF A RADIOACTIVE DRUG CONTAINING ONE MICROCURIE OF CARBON 14 UREA (PARTS 30 AND 32)

PURPOSE:

To obtain the Commission's approval for publication of the subject final rule.

BACKGROUND:

On May 30, 1997, the Commission approved the publication of a proposed rule to amend Parts 30 and 32 that would permit the exempt distribution and use of capsules containing one microcurie carbon-14 urea for "in vivo" diagnostic use. On June 16, 1997, the proposed rule was published in the Federal Register (62 FR 32552) for a 30-day public comment period. This action is being taken in response to a petition for rulemaking (PRM-35-12) submitted by Tri-Med Specialties, Inc.

DISCUSSION:

In response to a request for comment on the proposed rule, the NRC received seven public comment letters. Four commenters supported the rule, one opposed the rule, and two provided comments without explicitly stating whether they supported or opposed the rule. A summary of public comments and staff's responses are presented in the preamble of the enclosed Federal Register notice. Except for two minor changes, the final amendments are the same as the proposed amendments.

The Commission should note that one commenter suggested that research use also should be permitted under this exemption because the radiological risk is insignificant. The staff did not change the final rule in response to this comment. A common rule entitled "Federal Policy for

the Protection of Human Subjects; Notices and Rules," was promulgated by 16 Federal

agencies on June 18, 1991 (56 FR 28002) and was intended to ensure the protection of human research subjects. The Federal policy represents a societal determination that any research (including research involving radioactive material) must provide for the following minimal protections for the human subjects: (1) that the research is approved by an Institutional Review Board (IRB) and (2) that the human subject gives informed consent to participate in the research. Further, under the common rule, these protections must be provided regardless of whether or not there is any risk of consequences (including radiological consequences). This view is supported by the fact that during the public comment period of the common rule, a commenter suggested that all minimal risk research be exempt from the regulations; however, the final rule did not adopt this comment. While the common rule provides for the exemption of certain research, such as educational tests; survey, interviews, or observation of public behaviors; collection of existing data; it does not provide for an exemption of research activities involving minimal risk. However, the common rule permits department or agency heads to retain final judgment as to whether a particular activity is covered by this policy.

NRC did not participate in the promulgation of the common rule. Subsequently, the NRC adopted 10 CFR 35.6 that requires a licensee who conducts research involving human subjects using byproduct material to obtain informed consent from the human subjects and obtain prior approval by an "Institutional Review Board" (IRB). Use of the capsules in conducting human research without following these provisions could be viewed as the NRC acting contrary to a societal determination expressed in the common rule that all research involving human subjects be performed under provisions containing certain minimal protections to the human subjects participating in the research. Such action by the Commission could have the effect of eroding public confidence in the NRC. Accordingly, even though the capsules present minimal radiological risk, the staff recommends that such research use of the capsules not be exempt from 35.6.

This final rule amends Part 30 to add a new section (30.21) to permit any person to receive, possess, use, transfer, own, or acquire capsules containing one microcurie carbon-14 urea for "in vivo" diagnostic use without a license. The final amendments include a reminder that persons will not be relieved from complying with applicable FDA, other Federal, and State requirements governing drugs.

This final rule also amends Part 32 to add two new sections (32.21 and 32.21a) to establish requirements for the manufacture and distribution of carbon-14 urea capsules to persons exempt from licensing. Currently, NRC requires licensees who manufacture, prepare, or commercially distribute radioactive drugs to meet the requirements in 32.72(a)(2) (e.g., be registered or licensed with the FDA or a State as a drug manufacturer or be licensed as a pharmacy by a State Board of Pharmacy). Licensees distributing these capsules under an exempt distribution license will need to meet this same requirement. This provides high confidence that the carbon-14 urea capsules contain one microcurie of carbon-14 and do not contain other radioactive contaminants.

RESOURCES:

Resources to complete and implement this rulemaking are included in the current budget.

COORDINATION:

The Office of the General Counsel has no legal objection to the final rulemaking. The Office of the Chief Financial Officer has reviewed this Commission paper for resource impacts and has no objections. The Office of the Chief Information Officer concurs that there will be no information technology or management impacts.

RECOMMENDATION:

That the Commission:

1. Approve the Notice of Final Rulemaking for publication (Enclosure 1).
2. Certify that this rule, if promulgated, will not have a negative economic impact on a substantial number of small entities in order to satisfy the requirements of the Regulatory Flexibility Act, 5 U.S.C. 605(b).
3. Note:
 - a. The final rule will be published in the Federal Register;
 - b. The Chief Counsel for Advocacy of the Small Business Administration will be informed of the certification regarding economic impact on small entities and the reasons for it as required by the Regulatory Flexibility Act.
 - c. A regulatory analysis has been prepared (Enclosure 2);
 - d. An Environmental Assessment has been prepared (Enclosure 3);
 - e. The appropriate Congressional committees will be informed (Enclosure 4);
 - f. Congressional review letters for Small Business Regulatory Enforcement Fairness Act will be sent (Enclosure 5);
 - g. A public announcement will be issued (Enclosure 6);
 - h. This final rule amends information collection requirements that are subject to the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et seq.). This rule has been approved by Office of Management and Budget;
 - i. All Agreement States will be sent a copy of the final rule upon approval for publication;
 - j. The petitioner will be notified of this action and will be sent a copy of the Federal Register notice; and
 - k. Copies of the Federal Register notice of final rulemaking will be distributed to affected licensees and commenters on the proposed rule. The notice will also be sent to other interested parties upon request.

L. Joseph Callan
Executive Director
for Operations

Enclosures: As stated (6)

[7590-01-P]

NUCLEAR REGULATORY COMMISSION

10 CFR Parts 30 and 32

RIN: 3150-AF70

Exempt Distribution of a Radioactive Drug

Containing One Microcurie of Carbon-14 Urea

AGENCY: Nuclear Regulatory Commission.

ACTION: Final rule.

SUMMARY: The Nuclear Regulatory Commission (NRC) is amending its regulations to permit NRC licensees to distribute a radioactive drug containing one microcurie of carbon-14 urea to any person for "in vivo" diagnostic use. The NRC has determined that the radioactive component of such a drug in capsule form presents a minimal radiation risk and, therefore, regulatory control of the drug for radiation safety is not necessary. This amendment makes the drug more widely available and reduces costs to patients, insurers, and the health care industry. This action grants a petition for rulemaking (PRM-35-12) from Tri-Med Specialties, Inc. and completes action on the petition.

EFFECTIVE DATE: (30 days from date of publication in the Federal Register).

ADDRESS: Copies of the public record, including the final regulatory analysis and any public comments received on the proposed rule, may be examined

and copied for a fee in the Commission's Public Document Room at 2120 L Street, NW. (Lower Level), Washington, DC.

FOR FURTHER INFORMATION CONTACT: Dr. Anthony N. Tse, Office of Nuclear Regulatory Research, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, telephone (301) 415-6233 or e-mail at ANT@nrc.gov.

SUPPLEMENTARY INFORMATION:

- I. The Petition for Rulemaking.
- II. Proposed Rule, Public Comments, and NRC Responses.
- III. Summary of the Final Amendments.
- IV. Description of the Final Amendments.
- V. Agreement State Compatibility.
- VI. Finding of No Significant Environmental Impact: Availability.
- VII. Paperwork Reduction Act Statement.
- VIII. Regulatory Analysis.
- IX. Regulatory Flexibility Certification.
- X. Small Business Regulatory Enforcement Fairness Act.
- XI. Backfit Analysis.
- XII. List of Subjects.

I. The Petition for Rulemaking

On October 6, 1994, the Commission docketed a petition for rulemaking (Docket No. PRM-35-12) from Tri-Med Specialties, Inc (Tri-Med). In a letter dated August 23, 1994, Tri-Med petitioned the NRC to amend its regulations "to allow for the general licensing and/or exemption for the commercial distribution by licensed pharmaceutical manufacturers of a capsule containing one micro-Curie (Ci) of C-14-urea for in vivo diagnostic testing." The purpose of this diagnostic test is to detect the presence of the bacterium *Helicobacter pylori* (*H. pylori*), a cause of peptic ulcers in humans.

Following the receipt of the petition, the NRC published for public comment a notice of receipt of petition for rulemaking in the Federal Register on December 2, 1994 (59 FR 61831). The comment period closed on February 15, 1995. The NRC received 315 public comment letters, of which 313 supported the petition (they were mostly form letters) and 2 letters opposed the petition.

II. Proposed Rule, Public Comments, and NRC Responses

A proposed rule was published on June 16, 1997 (62 FR 32552) that would permit NRC licensees to distribute capsules containing one microcurie C-14 urea to any person for "in vivo" diagnostic use. The public comment period closed on July 16, 1997.

In the preamble of the proposed rule, the NRC stated that, because the capsules present an insignificant radiological risk to the public and the environment, the NRC believes the capsules could be distributed for "in vivo" diagnostic use to persons exempt from licensing. This change makes the drug more widely available and reduces costs to patients, insurers, and the health care industry.

The NRC received seven public comment letters on the proposed rule: three from industry, three from State agencies, and one from a physician associated with a university medical facility. Four commenters supported the rule, one opposed the rule, and two provided comments but did not explicitly state whether they supported or opposed the rule. Public comments and NRC's responses are presented below.

Comment 1: Under the proposed distribution, the NRC should not be forbidding research use of this drug by the same physicians who may use it clinically. Research use also should be permitted under this exemption because the radiological risk for using C-14 capsules is insignificant.

Response: The NRC did not change the final rule in response to this comment. A common rule entitled "Federal Policy for the Protection of Human Subjects; Notices and Rules" was promulgated by 16 Federal agencies on June 18, 1991 (56 FR 28002) and was intended to ensure the protection of human research subjects. This rule was adopted to implement a recommendation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research which was established on November 9, 1978, by Public Law 95-622. The Federal Policy requires that Federal agencies that conduct, fund, support, or regulate research involving human subjects ensure adequate protection of the rights of the human subjects. The Federal policy represents a societal determination that any research (including research involving radioactive material) must provide for the following minimal protections for the human subjects: (1) that the research is approved by an Institutional Review Board (IRB) and (2) that the human subject gives informed consent to participate in the research. Further, these protections must be provided regardless of whether or not there is any risk of consequences (including radiological consequences). This view is supported by the fact that during the public comment period of the common rule, a commenter suggested that all minimal risk research be exempt from the regulations; however, the final rule did not adopt this comment.

NRC did not participate in the promulgation of the common rule. Subsequently, the NRC adopted 10 CFR 35.6 that requires a licensee who conducts research involving human subjects using byproduct material to obtain informed consent from the human subjects and obtain prior approval by an IRB. Although the NRC did not adopt the common rule, the intention is to follow the essential requirements of the common rule. Because the common rule does not provide an exemption for research involving minimal risk, the Commission has determined that such research use should not be exempt from

Comment 2: Two commenters expressed concerns that the proposed rule language, "not exceeding one microcurie," appeared to indicate that the upper limit of the radioactivity in a capsule is exactly one microcurie of C-14. Both stated that it is not possible to make the capsules to exactly one microcurie because of statistical deviations during the manufacturing process.

Response: The NRC agrees with the commenters. The proposed rule did not intend to limit the radioactivity of C-14 to exactly one microcurie. The final rule language has been modified to read "capsules containing one microcurie C-14 urea (allowing for nominal variation that may occur during the manufacturing process)."

Comment 3: One commenter stated that, when the total amount of energy released from complete decay of a radionuclide is considered, one microcurie of C-14 has the largest energy release, because of its long half-life, when compared to one microcurie of Tc-99m or I-131. The commenter concluded that, given the insignificant radiation risk from the diagnostic use of C-14 urea, the radiation risk from the diagnostic use of Tc-99m or I-131 also would be insignificant.

Response: Carbon-14 emits low energy radiation with no radiation, low energy radiation cannot penetrate very far into tissue. On the other hand, both Tc-99m and I-131 emit radiation, which is more penetrating than the weak radiation. Furthermore, the total energy of C-14 is released slowly over tens of thousands of years, but the total energy of Tc-99m and I-131 is released much faster, i.e., within several days and tens of days, respectively. Thus, the radiation risk to an individual from one microcurie of C-14 is insignificant because of the long half-life and low energy emitted. This is not the case for I-131 or Tc-99m which are both short lived emitters and which would deposit most of the total energy in the individual.

Comment 4: Because of the small quantity of radioactive material in C-14 capsules, this product may be disposed of in the general trash. To avoid unnecessary concern for health risks in the disposal of the product, labels should contain a statement that the product may be disposed of in the general trash.

Response: In the final rule, the label requirements include a statement that the product may be disposed of in ordinary trash.

Comment 5: The Commenter agrees that the widespread use of this product will require uniform regulations and that Agreement States will need to make appropriate regulatory provisions to enable persons to receive the drug for "in vivo" diagnostic use. To avoid confusing licensees and users, these changes to NRC and Agreement State regulations should be made simultaneously. The commenter urges that the NRC take action to expedite the Agreement State regulatory changes.

Response: The NRC has urged the Agreement States to adopt compatible changes in their regulations expeditiously. However, under NRC's Adequacy and Compatibility Policy, Agreement States have up to three years to change their regulations for amendments or program requirements that are items of compatibility.

Comment 6: The NRC should address this rule in its ongoing effort to revise 10 CFR Part 35 in its entirety. The commenter believes that (1) this rule represents a piecemeal effort to respond to a narrow issue and (2) the issue of reduced regulation for medical use of C-14 capsules is applicable to the same extent for virtually the entire range of diagnostic radioisotopes.

Response: If this rule is combined with the overall 10 CFR Part 35 revision, the C-14 capsules would only be available to authorized user physicians during the revision period. Thus, the NRC decided to proceed with this rule now because the benefits of making this capsule available to anyone, including primary-care physicians, outweigh the benefits of addressing this issue in the overall revision of 10 CFR Part 35.

Comment 7: An appropriate function of the regulatory regime is to assure that personnel handling and administering radioactive drugs meet certain basic training and qualification requirements. The proposed exemption would impose no training or qualification requirements on users.

Response: The amount of radiation safety training needed for personnel depends on the level of radiation risk associated with the radioactive drug. Because C-14 capsules present

insignificant radiation risk, radiation safety training for personnel handling and administering the capsule is not necessary, and thus, not required.

Comment 8: If the NRC promulgates the proposed rule in its present form, the exemption will divest the Agreement States of any authority to regulate this product under a general or specific license. Had the NRC instead simply proposed a general license, Agreement State agencies would retain the authority to adopt the general license or continue to require specific licensing.

Response: In the draft rulemaking plan, the NRC suggested using the general license approach. The NRC received nine comment letters from Agreement States on the draft rulemaking plan; three suggested that an exemption approach would be more appropriate because it would be less costly to the Agreement States and their licensees than the general license approach.

Based on these comments, the NRC chose the exemption approach in the final rule plan as more cost-effective than a general license approach. The final rulemaking plan was revised accordingly and was provided to the Agreement States. No Agreement States expressed opposition to the NRC on the exemption approach.

Among the seven public comment letters received on the proposed rule, two were from Agreement States and one from a non Agreement State. All three supported the proposed rule.

Comment 9: The environmental assessment fails to consider the fact that another equally noninvasive, but nonradiological, diagnostic procedure (such as C-13 test) is available and provides a comparable alternative to the C-14 test. The apparent assumption underlying the environmental assessment is that in the absence of the C-14 test, the only alternative for the detection of H. pylori is invasive gastroendoscopy.

Response: Because the C-14 urea capsules are already available to authorized user physicians, the only regulatory issue in this rulemaking is whether the C-14 method should be made available to individuals who are not authorized users. The purpose of the environmental assessment is to consider and document whether the subject rule is expected to have any significant impact to the environment. In this environment assessment, the NRC has determined that the environmental impact is expected to be insignificant because of the extremely low radiological hazards associated with the use of capsules containing one microcurie C-14 urea. The presence of an additional non-invasive alternative procedures does not affect NRC's determination of no significant environmental impact.

Comment 10: NRC's policy in the past has been not to exempt byproduct material that is ingested. Any change in this policy would be a significant departure from existing NRC regulations.

Response: This change is a departure from existing NRC regulations. In the statement of consideration for the proposed rule, under the heading "Current NRC Regulations on Exemptions From Licensing," the NRC stated that, although two broad material exemptions (30.14, "Exempt concentrations," and 30.18, "Exempt quantities") exclude the transfer of byproduct material contained in any product designed for ingestion or inhalation by a human being, the C-14 capsules manufactured or prepared as a radioactive drug can be distributed to persons exempt from licensing for "in vivo" diagnostic use because the capsules present an insignificant radiological risk to the public and the environment. This exemption only applies to the diagnostic use of capsules containing one microcurie C-14 manufactured or prepared as a radioactive drug to make a clear distinction between this radioactive drug that is intended for ingestion by humans and other uses of C-14 urea and byproduct material distributed under 30.14 and 30.18.

Comment 11: The ACMUI's (Advisory Committee on Medical Uses of Radioisotopes) conclusions that either an exemption or general license is appropriate for the C-14 product do not address the fundamental aspects of nuclear safety. Its judgment was based partially on the assumptions: (1) the product may only be dispensed by prescription, (2) the product is approved by the Food and Drug Administration, and (3) the office/facility using the product will be subject to Clinical Laboratory Improvement Amendment (CLIA) regulation.

Response: The transcript from the ACMUI meeting shows the Committee did include radiation safety in its considerations and did not consider it to be an issue. Further, as stated in the supplemental material supporting the proposed rule, there are no nuclear safety issues associated with the use of the C-14 capsules for clinical diagnostic testing. Therefore, use of either an exemption or general license is appropriate.

Comment 12: The exemption approach does not provide the NRC with flexibility to impose a limitation on the amount of C-14 capsules any physician can possess in an office. In the event there is a recall of the product, or a large amount of product becomes unusable, the NRC will have no control over the disposal of the product.

Response: It is not necessary to impose a possession limit on the amount of C-14 capsules because the radiation risk is insignificant. The earth's atmosphere contains an inventory of naturally occurring C-14 of about 3.8 million curies which is in addition to the huge inventory of about 240 million curies in the world's oceans. The small amount of C-14 released into the atmosphere from the use of this test would mix with the global inventory and would have no impact on public health. The current world inventory of naturally occurring C-14 results in an average dose to the public of about 1.25 mrem per year, and the release of 0.6 curies of C-14 from the total of 600,000 tests assumed to be administered annually would result in an additional average annual dose of 2×10^{-7} mrem. In the event that a recall is necessary, the manufacturer may use the same process for recalling any other non-radioactive drugs. If C-14 urea capsules are returned to the manufacturers, they will be disposed of in accordance with the manufacturer's possession license. A user, however, can dispose the C-14 urea capsules as ordinary trash. Medical users of the C-14 urea test would be unlikely to acquire significant quantities of capsules because they can be ordered within a few days. Thus, even under a recall, the impact of disposing of C-14 urea capsules into landfills by the user would also be insignificant.

Comment 13: It is essential that end users be adequately informed of the product's radioactive characteristics, so that some form of storage, use, and disposal precautions can be followed. Thus, the labeling must be conspicuously and prominently placed. The commenter suggested the following: (1) the phrase "conspicuously and prominently" in front of the proposed labeling "bears the words Radioactive Material" should be added, and (2) the NRC should require that the radioactive material legend, "Radioactive Material," be included on promotional brochures.

Response: Because the radiation risk from C-14 capsules is insignificant, regulatory control of the use, storage, and disposal of the drug for purpose of radiation safety is not necessary. In fact, the label accompanying C-14 capsules is required to indicate that the capsules may be disposed of by users as ordinary trash. Paragraph(a)(6) of 32.21 requires that applicants submit copies of prototype labels and brochures for NRC approval. The NRC will ensure that the labels meet the requirements of 32.21a before they are approved. Since paragraph (a) of 32.21a specifies that the label must be durable and legible, the use of an additional phrase such as "conspicuously and prominently" is unnecessary. Promotional brochures are for information only; nothing will prevent manufacturers from indicating on the promotional brochures that C-14 is a radioactive material.

III. Summary of the Final Amendments

Final Amendment to 10 CFR Part 32

The regulations in 10 CFR Part 32 are amended to add new 32.21 and 32.21a, to provide requirements for a specific license to manufacture, prepare, process, produce, package, repackage, or transfer for commercial distribution, capsules containing one microcurie of C-14 urea, as a radioactive drug, to be distributed to any person for "in vivo" diagnostic use. These requirements are consistent with the existing requirements on other items under the

heading "Exemptions" in 10 CFR Part 30. The amendment includes a reminder that licensees distributing the radioactive drug to persons exempt from licensing would not be relieved from other applicable Federal (e.g., FDA) or State requirements governing the manufacture and distribution of drugs.

The amendment requires that the manufacture or preparation of capsules containing one microcurie of C-14 urea be prepared by persons who meet the current NRC regulations to manufacture and commercially distribute radioactive drugs. The NRC believes regulatory control is needed to provide high confidence that the drug contains one microcurie of C-14 urea and does not contain any other radioactive contaminants.

Final Amendment to 10 CFR Part 30

The NRC has determined that the drug in capsule form presents no significant radiological safety or environmental risk, and that it is not necessary to regulate the use of this drug for its radioactive component. Therefore, the NRC can not justify requiring physicians, or any other person, to meet NRC training and experience criteria directed at the safe use of radioactive drugs, or to become an "authorized user." Hence, the capsules can be distributed to any person. However, other Federal or State agencies may limit the receipt and use of the capsules in accordance with their own requirements.

The regulations in 10 CFR Part 30 are amended to add a new 30.21, to permit any person to receive, possess, use, transfer, own, or acquire for "in vivo" diagnostic use, capsules containing one microcurie of C-14 urea without a license. The final regulation includes a reminder that persons receiving the capsules would not be relieved from other Federal or State law governing drugs. Further, in accordance with the NRC's provisions for research involving human subjects (10 CFR 35.6), the exemption permitting receipt and use of the capsules for "in vivo" diagnostic use does not extend to use of the capsules for research involving human subjects. Any person desiring to use the capsules for human research would still be required to submit an application for a specific license under Part 35. The phrase "in vivo diagnostic use" was selected to describe the activity authorized in 30.21 to differentiate it from the term "medical use" because:

- (1) "Medical use" limits administration to authorized users; use of this drug would not be so limited; and
- (2) "Medical use" includes the administration of the drug to a human research subject, which would be prohibited by this rulemaking.

Effects of the Final Amendments

The final amendments make the drug available to any person, for "in vivo" diagnostic use, without need for an NRC or Agreement State license. Because the receipt and use of the drug are exempt from NRC licensing, Agreement States need to make appropriate provisions in their regulations to recognize the exempt distribution of the drug, for "in vivo" diagnostic use. Thus, after the manufacture and distribution of the drug, the NRC and the Agreement States will not regulate the use of the drug as long as its use is for "in vivo" diagnostic use. This means that, under NRC and Agreement State regulations, primary-care physicians do not need to be "authorized users" in order to administer the drug, and do not need to refer their patients to nuclear medicine physicians. This should result in cost savings to patients. Other Federal and State organizations with responsibilities for regulating drugs will determine and regulate who can receive and use the drug for "in vivo" diagnostic use. NRC will continue to regulate the use of the drug for research involving human subjects under a specific Part 35 license.

IV. Description of the Final Amendments

The final amendments are the same as the proposed amendments except for two minor changes. Public comments suggested that the phrase "carbon-14 urea capsules not exceeding one microcurie" used in the proposed rule may be interpreted as an exact limit of one microcurie per capsule (See Comment 2 under the heading "Public Comment and NRC Responses"). The final rule has been modified and the phrase "capsules containing one microcurie carbon-14 urea (allowing for nominal variation that may occur during the manufacturing process)" is used. Another public comment suggested that labels should contain a statement that the product may be disposed of in the general trash. In the final rule, the label requirements include such a statement.

Manufacturer and Distributors

A new section is added to 10 CFR Part 32 to permit the distribution of the capsules to persons who are exempt from licensing.

32.21 Radioactive drug: Manufacture, preparation, or transfer for commercial distribution of capsules containing one microcurie carbon-14 urea each for "in vivo" diagnostic use for humans to persons exempt from licensing; Requirements for a license

Paragraph (a)

This paragraph establishes the requirements for approval of a license application to manufacture, prepare, process, produce, package, repackage, or transfer for commercial distribution, capsules containing one microcurie carbon-14 urea each for "in vivo" diagnostic use, to persons exempt from licensing.

Paragraph (a)(1)

This paragraph limits issuance of an "exempt distribution license" for distribution of the capsules to persons exempt from licensing to only those who possess either a NRC or Agreement State "specific license" for possession and use of byproduct material.

Paragraph (a)(2)

To assure that the capsules contain one microcurie of carbon-14 and present no other radiological risks, this paragraph requires that the persons manufacturing and/or commercially distributing the capsules for "in vivo" diagnostic use must also meet the requirements of 32.72(a)(2). Specifically,

these persons must be:

- (1) Registered with or licensed by the FDA as a drug manufacturer; or
- (2) Registered with or licensed by a state agency as a drug manufacturer; or
- (3) Licensed as a pharmacy by a State Board of Pharmacy; or
- (4) Operating as a nuclear pharmacy within a Federal medical institution.

Paragraph (a)(3)

This paragraph requires applicants to provide evidence that each carbon-14 urea capsule contains one microcurie. The NRC's evaluation that the capsules would not result in significant radiation risks was based on the capsules containing one microcurie of carbon-14 urea. Therefore, applicants must demonstrate that the activity of each carbon-14 capsule contains one microcurie, allowing for nominal variation that may occur during the manufacturing process.

Paragraph (a)(4)

This paragraph prohibits carbon-14 urea from being contained in any food, beverage, cosmetic, drug or other commodity designed for ingestion or inhalation by, or topical application to, a human being except for the capsules as described in this section, because exempt distribution of this drug has only been evaluated for "in vivo" diagnostic use in the form of a capsule containing one microcurie of carbon-14 urea. There is no prohibition against the capsule being combined with food or beverage at the time of administration so that the capsule can be ingested by the patient.

Paragraph (a)(5)

Because the exempt distribution of this drug has only been evaluated for "in vivo" diagnostic use in the form of a capsule containing one microcurie of carbon-14 urea, this paragraph prohibits incorporation of the capsules into any manufactured or assembled commodity, product, or device intended for commercial distribution. Further, although the drug is being distributed to persons exempt from licensing, this paragraph requires the carbon-14 urea to be identified as radioactive because the drug is being used for its radioactive content; therefore, the end user must be provided with information that the drug contains a radioactive material.

Paragraph (a)(6)

As with any product approved for distribution to persons exempt from licensing, this paragraph requires persons who apply for a license to manufacture or commercially distribute these capsules to submit copies of prototype labels or brochures for NRC approval. This will allow the NRC to confirm that the labels or brochures meet the requirements of 32.21a(a) and (b).

Paragraph (b)

This paragraph declares that the regulations do not relieve licensees or applicants from complying with applicable FDA, other Federal, and State requirements governing the manufacture and distribution of drugs.

Section 32.21a Same: Conditions of license

This section establishes the conditions required for a licensee to commercially distribute the capsules to persons exempt from licensing.

Paragraph (a)

To inform the end user of the identity of the radioisotope, the physical and chemical form, and the dosage of radioactivity, this paragraph establishes that the immediate container of each capsule or capsules must bear a durable, legible label that:

- (1) Identifies the radioisotope, the physical and chemical form of the radioisotope, the quantity of radioactivity contained in each container at a specific date; and
- (2) Bears the words "Radioactive Material."

The date requirement is consistent with labeling requirements for other radioactive drugs with a half life of greater than 100 days.

Paragraph (b)

This paragraph establishes that, consistent with the intended use of the capsules, the label affixed to the immediate container, or an accompanying brochure, must:

- (1) State that the contents are exempt from NRC or Agreement State licensing requirements;
- (2) Bear the words "Radioactive Material. For "In Vivo" Diagnostic Use Only. This Material Is Not To Be Used for Research Involving Human Subjects, and Must Not Be Introduced into Foods, Beverages, Cosmetics, or Other Drugs or Medicinals, or into Products Manufactured for Commercial Distribution. This Product May Be Disposed of in Ordinary Trash."

The intent of the requirement set out in Paragraph (b)(2) is to make clear that the capsule must remain in the form of a capsule and is not to be combined with one of the listed items such as food or beverages which would result in a radioactive product other than in the form of a capsule for commercial distribution. There is no prohibition against the capsule being combined with food or beverage at the time of administration so that the capsule can be ingested by the patient. This label also informs the user that this product may be disposed of in ordinary trash.

"In vivo" diagnostic use by persons exempt from licensing

A new section is added to 10 CFR Part 30 to exempt any person from NRC or the Agreement State regulations to receive the drug for "in vivo" diagnostic use for humans.

Section 30.21 Radioactive drug: Capsules containing one microcurie of carbon-14 urea for "in vivo" diagnostic use for humans

Paragraph (a)

This paragraph provides an exemption to any person from the requirements for a license to receive, possess, use, transfer, own, or acquire capsules containing one microcurie of carbon-14 urea for "in vivo" diagnostic purposes. It should be noted that the "transfer" in this paragraph does not include "transfer for commercial distribution," which is covered in paragraph (c) of this section.

Paragraph (b)

This paragraph establishes that persons who desire to use the drug for research involving humans subjects must apply for and receive a specific Part 35 license. Such a license would ensure the protection of the rights of the human subjects by requiring that the research be approved by an IRB and that the human subjects give their informed consent to participate in the research.

Paragraph (c)

This paragraph specifies that a specific license is needed to manufacture, prepare, process, produce, package, repackage or transfer such capsules for commercial distribution.

Paragraph (d)

This paragraph declares that the regulations do not relieve end users from complying with applicable FDA, other Federal, or State requirements governing the receipt, administration, and use of drugs.

V. Agreement State Compatibility

Under the Atomic Energy Act, certain regulatory functions are reserved to the NRC. Among these are the distribution of products to persons exempt from licensing, as discussed in 10 CFR Part 150. Hence, amendments related to the manufacture and commercial distribution of the capsules (10 CFR Part 32) is a Division 4 item of compatibility (Category NRC under the new adequacy and compatibility policy). However, amendments related to possession and use (10 CFR Part 30) are a Division 1 item of compatibility (Category B under the new adequacy and compatibility policy) because of the need for nationwide consistency in the use of products which are widely distributed. Therefore, the Agreement States will need to make appropriate provisions in their regulations to allow any person to receive capsules containing one microcurie of carbon-14 urea for "in vivo" diagnostic use in humans without need for a license.

VI. Finding of No Significant Environmental Impact: Availability

The Commission has determined under the National Environmental Policy Act of 1969, as amended, and the Commission's regulations in Subpart A of 10 CFR Part 51, that the final rule is not a major Federal action significantly affecting the quality of the human environment; therefore, an environmental impact statement is not required. The final rule establishes requirements for the manufacture and commercial distribution of carbon-14 urea capsules to persons exempt from licensing and establishes regulations to permit any person to receive the capsules without an NRC license. The Commission believes that the radioactive component of this drug presents no significant radiation risk and, therefore, regulatory control of the "in vivo" diagnostic use of the capsules for radiation safety is not necessary. It is expected that this final rule will not cause any significant increase in radiation exposure to the public or radiation release to the environment beyond the exposures or releases resulting from the use of the carbon-14 capsules under the current regulations. Also, it is expected that there will be no non-radiological impacts. One public comment on the draft environmental assessment has been received (See Comment 9 under the heading "Proposed Rule, Public Comments, and NRC Responses").

The environmental assessment and finding of no significant impact on which this determination is based is available for inspection at the NRC Public Document Room, 2120 L Street NW. (Lower Level), Washington, DC. Single copies of the environmental assessment and the finding of no significant impact are available from Dr. Anthony N. Tse, Office of Nuclear Regulatory Research, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, telephone (301) 415-6233 or e-mail at ANT@nrc.gov.

VII. Paperwork Reduction Act Statement

This final rule amends information collection requirements that are subject to the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 et seq.). These requirements were approved by the Office of Management and Budget, approval numbers 3150-0001, 3150-0017, and 3150-0120.

The public reporting burden for this collection of information is estimated to average 16 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments on any aspect of this collection of information, including suggestions for reducing the burden, to the Information and Records Management Branch (T-6 F33), U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, or by Internet electronic mail at BJS1@NRC.GOV; and to the Desk Officer, Office of Information and Regulatory Affairs, NEOB-10202, (3150-0001, 3150-0017, and 3150-0120), Office of Management and Budget, Washington, DC 20503.

Public Protection Notification

The NRC may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VIII. Regulatory Analysis

The NRC has prepared a regulatory analysis for the final rule. The analysis examines the benefits and impacts considered by the NRC. No public comments on the draft regulatory analysis have been received during the public comment period. The regulatory analysis is available for inspection at the NRC Public Document Room, 2120 L Street NW. (Lower Level), Washington, DC. Single copies of the regulatory analysis are available from Dr. Anthony N. Tse, Office of Nuclear Regulatory Research, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001, telephone (301) 415-6233 or e-mail at ANT@nrc.gov.

IX. Regulatory Flexibility Certification

As required by the Regulatory Flexibility Act of 1980, 5 U.S.C. 605(b), the Commission certifies that this rule does not have a significant economic impact upon a substantial number of small entities. The final rule permits physicians and other health care providers to use an additional diagnostic test without having to obtain an NRC license, thus, would provide cost savings to patients, insurers, and the health care industry. The final rule does not impose any additional obligations on entities that may fall within the definition of "small entities" as set forth in Section 601(3) of the Regulatory Flexibility Act; or within the definition of "small business" as found in Section 3 of the Small Business Act, 15 U.S.C. 632; or within the size standards adopted by the NRC on April 11, 1995 (60 FR 18344).

X. Small Business Regulatory Enforcement Fairness Act

In accordance with the Small Business Regulatory Enforcement Fairness Act of 1996, the NRC has determined that this action is not "a major" rule and has verified this determination with the Office of Information and Regulatory Affairs, Office of Management and Budget.

XI. Backfit Analysis

The NRC has determined that the backfit rule, 10 CFR 50.109, does not apply to this rule, and therefore, a backfit analysis is not required because these amendments do not involve any provisions that would impose backfits as defined in 10 CFR 50.109(a)(1).

XII. List of Subjects

10 CFR Part 30

Byproduct material, Criminal penalties, Government contracts, Intergovernmental relations, Isotopes, Nuclear materials, Radiation protection, Reporting and record keeping requirements.

10 CFR Part 32

Byproduct material, Criminal penalties, Labeling, Nuclear materials, Radiation protection, Reporting and recordkeeping requirements.

For the reasons set out in the preamble and under the authority of the Atomic energy Act of 1954, as amended, the Energy Reorganization Act of 1974, as amended, and 5 U.S.C. 552 and 553, the NRC is adopting the following amendments to 10 CFR Parts 30 and 32.

PART 30--RULES OF GENERAL APPLICABILITY TO DOMESTIC LICENSING OF BYPRODUCT MATERIAL

1. The authority citation for Part 30 continues to read as follows:

AUTHORITY: Secs. 81, 82, 161, 182, 183, 186, 68 Stat. 935, 948, 953, 954, 955, as amended, sec. 234, 83 Stat. 444, as amended (42 U.S.C. 2111, 2112, 2201, 2232, 2233, 2236, 2282); secs. 201, as amended, 202, 206, 88 Stat. 1242, as amended, 1244, 1246 (42 U.S.C. 5841, 5842, 5846).

Section 30.7 also issued under Pub. L. 95-601, sec.10, 92 Stat. 2951 as amended by Pub. L. 102-486, sec. 2902, 106 Stat. 3123, (42 U.S.C. 5851). Section 30.34(b) also issued under sec. 184, 68 Stat. 954, as amended (42 U.S.C. 2234). Section 30.61 also issued under sec. 187, 68 Stat. 955 (42 U.S.C. 2237).

2. In 30.8, paragraph (b) is revised to read as follows:

30.8 Information collection requirements: OMB approval.

(b) The approved information collection requirements contained in this part appear in 30.9, 30.11, 30.15, 30.18, 30.19, 30.20, 30.21, 30.32, 30.34, 30.35, 30.36, 30.37, 30.38, 30.41, 30.50, 30.51, 30.55, appendices A and C to this part.

3. A new 30.21 is added under the undesignated center heading "Exemptions" to read as follows:

30.21 Radioactive drug: Capsules containing one microcurie of carbon-14 urea for "in vivo" diagnostic use for humans.

(a) Except as provided in paragraphs (b) and (c) of this section, any person is exempt from the requirements for a license set forth in Section 81 of the Act and from the regulations in this part and Part 35 of this chapter provided that such person receives, possesses, uses, transfers, owns, or acquires capsules containing one microcurie carbon-14 urea (allowing for nominal variation that may occur during the manufacturing process) each, for "in vivo" diagnostic use for humans.

(b) Any person who desires to use the capsules for research involving human subjects shall apply for and receive a specific license pursuant to Part 35 of this chapter.

(c) Any person who desires to manufacture, prepare, process, produce, package, repackage, or transfer for commercial distribution such capsules shall apply for and receive a specific license pursuant to 32.21 of this chapter.

(d) Nothing in this section relieves persons from complying with applicable FDA, other Federal, and State requirements governing receipt, administration, and use of drugs.

PART 32--SPECIFIC DOMESTIC LICENSES TO MANUFACTURE OR TRANSFER CERTAIN ITEMS CONTAINING BYPRODUCT MATERIAL

4. The authority citation for Part 32 continues to read as follows:

AUTHORITY: Secs. 81, 161, 182, 183, 68 Stat. 935, 948, 953, 954, as amended (42 U.S.C. 2111, 2201, 2232, 2233); sec. 201, 88 Stat. 1242, as amended (42 U.S.C. 5841).

5. In 32.8, paragraph (b) is revised to read as follows:

32.8 Information collection requirements: OMB approval.

(b) The approved information collection requirements contained in this part appear in 32.11, 32.12, 32.14, 32.15, 32.16, 32.17, 32.18, 32.19, 32.20, 32.21, 32.21a, 32.22, 32.23, 32.25, 32.26, 32.27, 32.29, 32.51, 32.51a, 32.52, 32.53, 32.54, 32.55, 32.56, 32.57, 32.58, 32.61, 32.62, 32.71, 32.72, 32.74, and 32.210.

6. A new 32.21 is added to read as follows:

32.21 Radioactive drug: Manufacture, preparation, or transfer for commercial distribution of capsules containing one microcurie carbon-14 urea each for "in vivo" diagnostic use for humans to persons exempt from licensing; Requirements for a license.

(a) An application for a specific license to manufacture, prepare, process, produce, package, repackage, or transfer for commercial distribution capsules containing one microcurie carbon-14 urea (allowing for nominal variation that may occur during the manufacturing process) each for "in vivo" diagnostic use, to persons exempt from licensing under 30.21 of this chapter or the equivalent regulations of an Agreement State will be approved if:

(1) The applicant satisfies the general requirements specified in 30.33 of this chapter, provided that the requirements of 30.33(a)(2) and (3) of this chapter do not apply to an application for a license to transfer byproduct material manufactured, prepared, processed, produced, packaged, or repackaged pursuant to a license issued by an Agreement State;

(2) The applicant meets the requirements under 32.72(a)(2) of this Part;

(3) The applicant provides evidence that each capsule contains one microcurie carbon-14 urea (allowing for nominal variation that may occur during the manufacturing process);

(4) The carbon-14 urea is not contained in any food, beverage, cosmetic, drug (except as described in this section) or other commodity designed for ingestion or inhalation by, or topical application to, a human being;

(5) The carbon-14 urea is in the form of a capsule, identified as radioactive, and to be used for its radioactive properties, but is not incorporated into any

manufactured or assembled commodity, product, or device intended for commercial distribution; and

(6) The applicant submits copies of prototype labels and brochures and the NRC approves these labels and brochures.

(b) Nothing in this section relieves the licensee from complying with applicable FDA, other Federal, and State requirements governing drugs.

7. A new 32.21a is added to read as follows:

32.21a Same: Conditions of license.

Each license issued under 32.21 of this Part is subject to the following conditions:

(a) The immediate container of the capsule(s) must bear a durable, legible label which:

- (1) Identifies the radioisotope, the physical and chemical form, the quantity of radioactivity of each capsule at a specific date; and
- (2) Bears the words "Radioactive Material."

(b) In addition to the labeling information required by paragraph (a) of this section, the label affixed to the immediate container, or an accompanying brochure also must:

- (1) State that the contents are exempt from NRC or Agreement State licensing requirements; and
- (2) Bear the words "Radioactive Material. For "In Vivo" Diagnostic Use Only. This Material Is Not To Be Used for Research Involving Human Subjects and Must Not Be Introduced into Foods, Beverages, Cosmetics, or Other Drugs or Medicinals, or into Products Manufactured for Commercial Distribution. This Material May Be Disposed of in Ordinary Trash."

Dated at Rockville, Maryland this _____ day of _____, 1997.

For the Nuclear Regulatory Commission.

John C. Hoyle,
Secretary of the Commission.

REGULATORY ANALYSIS
FOR FINAL RULEMAKING
"EXEMPT DISTRIBUTION AND USE OF A RADIOACTIVE DRUG
CONTAINING ONE MICROCURIE OF CARBON 14 UREA"
10 CFR PARTS 30 AND 32

1. Background

1.1 Statement of the Problem

On October 6, 1994, the Commission docketed a petition for rulemaking (Docket No. PRM-35-12) from Tri-Med Specialties, Inc (Tri-Med). In a letter dated August 23, 1994, Tri-Med petitioned the NRC to amend its regulations "to allow for the general licensing and/or exemption for the commercial distribution by licensed pharmaceutical manufacturers of a capsule containing one micro-Curie (Ci) of ^{14}C -urea for in vivo diagnostic testing." The purpose of this diagnostic test is to detect the presence of the bacterium *Helicobacter pylori* (*H. pylori*), a cause of peptic ulcers.

"Peptic ulcer disease is a chronic inflammatory condition of the stomach and duodenum that affects as many as ten percent of people in the United States at some time in their lives. The disease has relatively low mortality, but it results in substantial human suffering and high economic costs." (Source: Article included as an appendix to the petition, from JAMA, July 6, 1994-Vol 272, No. 1, "H. pylori in Peptic Ulcer Disease-NIH Consensus Conference").

In the petition dated August 23, 1994, the petitioner stated the following:

Recent medical research has found that peptic ulcers are commonly caused by a bacterium called *H. pylori*. This bacterium lives in the stomach of most ulcer sufferers. By treating ulcer patients with antibiotics, doctors can now cure most ulcer problems.

It is therefore necessary to detect the presence of *H. pylori* bacteria in ulcer patients so that the new treatment can be given appropriately. In the past, this was done by a gastroenterologist who took biopsy samples of the stomach lining at endoscopy, a procedure which was uncomfortable and expensive (\$1000).

With the new test, *H. pylori* can be detected noninvasively using a ^{14}C -urea tracer. ^{14}C -urea is broken down by *H. pylori* to form labeled CO_2 which is expired in the breath. To do the test, a doctor asks the patient to swallow the capsule with 30 mls of water. After 15 minutes the patient blows 2 liters of breath into a collection bag (a mylar balloon) which is mailed to a testing laboratory. If ^{14}C - CO_2 more than twice background is present in the breath

sample, then the patient must be infected with *H. pylori*.

1.2 Current NRC Regulations

In 10 CFR Part 32, "Specific Domestic Licenses To Manufacture or Transfer Certain Items Containing Byproduct Materials," 32.72, "Manufacture, preparation, or transfer for commercial distribution of radioactive drugs containing byproduct material for medical use under Part 35," provides for commercial distribution of radioactive drugs containing byproduct material for use by persons authorized pursuant to Part 35. Thus, the regulations currently would permit Part 32 licensees to commercially distribute capsules containing 1 Ci of ^{14}C -urea to persons authorized pursuant to Part 35.

In 10 CFR Part 35, "Medical Use of Byproduct Material," sets forth radiation safety requirements, including requirements for the training and experience of authorized user physicians to assure the safe possession and use of radioactive drugs containing byproduct material.

Existing exemptions for use of byproduct material in 30.14, "Exemption concentrations" and 32.18, "Manufacture, distribution and transfer of exempt quantities of byproduct material: Requirements for license," do not permit the exempt transfer of byproduct material contained in any food, beverage, cosmetic, drug, or any product designed for ingestion or inhalation by, or application to, a human being.

Therefore, under current regulations, the ^{14}C -urea capsules must be used under a Part 35 license.

1.3 Earlier NRC Actions

Following the receipt of the petition, a "Notice of receipt of petition for rulemaking" was published for public comment in the Federal Register on December 2, 1994 (59 FR 61831). A total of 315 public comment letters were received. Of these, 313 supported the petition (they were mostly form letters) and two letters opposed the petition. The two letters opposing the petition stated that (1) the product should not receive an exempt status because the uncontrolled distribution and application of this product could lead to significant risk to the public and (2) medical uses should be restricted to short-lived isotopes because of disposal problems presented by long-lived isotopes.

This petition was discussed with NRC's Advisory Committee on the Medical Uses of Isotopes (ACMUI) at the October 1995 meeting. The ACMUI indicated that it endorsed the wide availability of this diagnostic test and that the radioactive drug could be used under a general license or an exemption, whichever the NRC may determine to be procedurally easier.

A rulemaking plan was prepared. After receiving comments from Agreement States on the draft rulemaking plan, the Commission approved a final rulemaking plan to develop a proposed rule to amend 10 CFR Parts 30 and 32 allowing the distribution of the Carbon-14 capsules as an exempt material to any person.

1.4 Proposed Rule and Public Comments

The proposed rule was published in the Federal Register (62 FR 32552, June 16, 1997) for a 30-day public comment period. The NRC received seven public comment letters. Four commenters supported the rule, one opposed the rule, and two provided comments without explicitly stating whether they support or oppose the rule. A summary of public comments and NRC's responses are presented in the preamble of the Federal Register notice. Except a minor change in wording, the final amendments are the same as the proposed amendments. No comments related to the draft Regulatory Guide has been received.

2. Objective

The objective of the rulemaking is to amend 10 CFR Part 32 to permit the manufacture and commercial distribution of ^{14}C -urea capsules to any person (including physicians who are not "authorized users" under Part 35) and to amend 10 CFR Part 30 to permit any person, without an NRC license, to receive and use the capsules for in vivo diagnostic use for humans.

3. Alternatives

Three alternatives have been considered in the regulatory analysis: deny the petition, i.e., maintain the status quo, permit the distribution of the capsules to persons exempt from licensing, and permit the distribution of the capsules to general licensees.

Under the first alternative, only physicians who are authorized users under Part 35 would be allowed to possess and administer the ^{14}C -urea test. Any physician could apply to become an authorized user. However, the NRC expects few physicians would apply for a Part 35 license for the sole purpose of using the capsules because of the requirement for training and experience and the associated costs of obtaining and maintaining a Part 35 license. Alternatively, physicians who are not authorized users can continue to refer their patients to physicians who are authorized users to undergo the diagnostic test. However this would not relieve the current expense, inconvenience, and delay encountered in an otherwise straight-forward procedure.

Under the second alternative, 10 CFR Parts 32 and 30 would be amended. 10 CFR Part 32 would be amended to permit the manufacture and commercial distribution of ^{14}C -urea capsules to any person (including physicians who are not "authorized users" under Part 35); 10 CFR Part 30 would be amended to permit the manufacture and commercial distribution of the capsules to any person, for in vivo diagnostic use for humans. The NRC has determined that the radioactive component of this drug presents a minimal radiation risk and, therefore, regulatory control of the capsules is not necessary.

Under the third alternative, 10 CFR Part 35 would be amended to permit any physician to receive and use the capsules under a general license. The

health and safety concerns for this alternative are the same as the Alternative 2. However, if this alternative were adopted, there could be a burden to those Agreement States that normally require registration of general license holders. An additional burden could also be imposed on general licensees located in the Agreement State if the State charges a license or registration fee.

4. Value-Impact Analysis

4.1 The Petitioner's Assessment

In the letters dated August 23, 1994 and November 30, 1994, the petitioner stated, respectively:

If exempted, the C-14 breath test could be done by most doctors for less than \$100 cost to the patient. This is a considerable savings over endoscopy and biopsy (\$1000).

... The test is 95 percent accurate and quite inexpensive because of its simplicity. The test would permit doctors to determine easily whether or not ulcer patients have been cured of their infection. By providing the public with an inexpensive, easily accessible diagnostic test, more individuals would be accurately diagnosed and treated for their H. pylori infection. This would save the United States an estimated \$500 million per annum over conventional therapy.

The petitioner estimates annual benefits to be on the order of \$500 million/year. This assumes approximately 600,000 ¹⁴C-urea breath tests/year, at an average cost of \$100, in lieu of performing endoscopy at an average cost of \$1000/test. It assumes that the lower cost and greater availability of an unregulated breath test would result in a complete substitution for endoscopy. Tri-Med's benefit analysis provides a measure of the total benefits associated with the test and does not focus on the incremental benefits of administering the test pursuant to 10 CFR 35.100 regulation (status quo) versus releasing the test to all physicians (NRC licensed and non licensed alike). Implicit in Tri-Med's estimated annual benefits is the presumption that none of these ¹⁴C tests and corresponding savings would accrue if the petition were denied. In reality, under the status quo, the test would be available and administered by physicians or clinics holding a license under NRC's Part 35 or an equivalent Agreement State regulations. Further, Tri-Med's estimate did not allow for the substitution of other non-invasive tests (e.g., serological test for IgG antibodies to H. pylori antigens) for both endoscopy and ¹⁴C-urea tests.

4.2 The NRC's Assessment

(a) Cost Savings Associated with Amendments to 10 CFR Part 30

The value-impact analysis focuses on the incremental benefits of granting relief consistent with Alternative 2 or 3, as specified in Section 3 above. The analysis looks solely at changes relative to the base case or status quo. In this analysis, the comparison is between regulated and unregulated ¹⁴C-urea breath tests, not unregulated ¹⁴C-urea breath tests and endoscopies or other noninvasive tests. For the purposes of this regulatory analysis, the NRC assumes that the same number of breath tests (i.e., 600,000 tests) will be administered regardless of the level of NRC regulatory control. This view is predicated on the belief that each physician's primary motivation is to provide the best possible care to his or her patients. If the breath test is judged preferable to endoscopy, or other procedure, any physician not authorized to use the test will refer his or her patient to authorized users who could perform the test under existing NRC regulations. This appears fully consistent with standard medical practice, whereby patients are referred routinely to laboratories and specialists for a wide array of tests and procedures.

The benefits of adopting the petition accrue as a result of reduced patient cost and reduced health-care cost resulting from the elimination of the need for referrals from a physician who is not an authorized user (e.g., gastrointestinal specialist). There would also be some regulatory savings because the NRC would not have to expend resources reviewing new applications for specific medical use licenses. However, these savings would be small because the NRC expects that few physicians who are not authorized users would apply for a specific NRC license for use of this one product.

The benefit calculation is based on the assumption that as a result of this rulemaking action, a significant portion of the 600,000 patients would receive the ¹⁴C breath test from physicians who are not authorized users (e.g., gastrointestinal specialists). The actual savings would be dependent on the number of tests ultimately administered by physicians who are not authorized users, thereby eliminating the need for a referral to physicians who are authorized users (e.g., nuclear medicine specialists).

The annual savings could be as high as approximately \$20 million if there were a complete shift of the administration of the tests from physicians who are authorized users (i.e., base case) to physicians who are not authorized users.

The basis for this estimate is as follows.

Assuming adoption of the petition eliminates the need for up to 600,000 referrals, patient savings in averted travel expenses (transportation and personal time incurred with medical referral) would be:

Assuming round trip of 20 miles @ \$0.25/mile, and personal time of 0.5/hours/trip valued at \$25.00/hour

$600,000 \text{ trips/year} \times (20 \text{ miles/trip} \times \$0.25/\text{mile} + 0.5 \text{ hours/trip} \times \$25.00/\text{hour}) = \$10.5 \text{ million/year}$

Health Care Savings in averted administrative expenses (administrative costs incurred with medical referral) would be:

$600,000 \text{ patients/year} \times \$19.00/\text{patient} = \$11.4 \text{ million/year}$

Assuming \$19.00 (administrative cost/patient) as the differential between the cost of an office visit to a general family practice physician by an established patient (\$45.90), and the cost to a new patient (\$64.90 per visit) for completion of new patient paperwork, reviewing health history, maintaining medical records, etc. The patient who is referred to an authorized user (e.g., nuclear medicine specialist) for the ¹⁴C-urea breath test would most likely be a new patient for the authorized user.

Total Savings:

\$10.5 million/year + \$11.4 million/year = \$ 21.9 million/year

Alternatively, if only 200,000 or 400,000 of the 600,000 tests were performed by a physician who is not an authorized user, the annual cost savings would be approximately \$7 million per year and \$15 million per year, respectively.

If Alternative 3 were adopted, it would permit any physician to receive and use capsules containing 1 Ci ¹⁴C-urea for human use under a general license. The health and safety concerns for this alternative are the same as Alternative 2. However, the adoption of Alternative 3 could add unnecessary burden to those Agreement States and Agreement State licensees in States that assess licensing or registration fees for general license holders. Alternative 2 also imposes incremental cost burden for manufacturers or commercial distributors of the capsules because they would need to obtain an exempt distribution license. Each application is estimated to take up to 16 hours to prepare. Assuming 3 applicants per year, the total reporting burden would be 48 hours. For recordkeeping burden, assuming each of the 3 applicants in a year would need 2 hours to reprogram its computer to print additional words on the label or brochure, the one-time total recordkeeping burden would be 6 hours. Assuming a labor rate of \$125 per hour, the total burden would be about \$6,750 per year.

There would be costs for the Federal and State governments if Alternative 2 or 3 is adopted. Under both Alternatives 2 or 3, the NRC and some Agreement States would need to amend their regulations to permit the use of the capsules by persons other than physician who are authorized users.

(b)Health and Safety Effects

For the purposes of this regulatory analysis, the NRC assumes that the same number of breath tests (i.e., 600,000 tests) will be administered regardless of the level of NRC regulatory control. This view is predicated on the belief that each physician's primary motivation is to provide the best possible care to his or her patients. In addition, the routine and accidental exposures per carbon-14 urea breath test is not expected to be affected by the level of NRC regulatory control. Thus, radiation exposures to the workers and members of the public would be the same regardless of which alternative is adopted.

The NRC has concluded that the human use of these capsules results in insignificant exposures as depicted below:

Scenario	Maximum Exposed Individual	Routine Exposure
Worker administering ¹⁴ C-urea breath tests	Full-time worker, 8,000 patients/yr	Less than 0.7 mrem/yr
Routine exposure of patients from ¹⁴ C-urea breath tests	Patient tests negative Patient tests positive	0.38 mrem/capsule 0.18 mrem/capsule
Release of 150 Ci of ¹⁴ CO ₂ into administration facility from fire	Member of public in the administration area	Less than 0.0002 mrem
Rupture of a capsule causing skin contamination of worker or patient	Skin (100 cm ²) exposed for one hour prior to washing; 0.075 Ci skin absorption	5.8 mrad skin dose, 0.029 mrem (CEDE)

Furthermore, the NRC concluded that the impacts associated with any releases of ¹⁴C to the surrounding environment are expected to be very small and the expected risks are minimal. The earth's atmosphere contains an inventory of naturally occurring ¹⁴C of about 3.8 million curies (equivalent to the activity in 3.8 trillion breath tests), which is in addition to the huge inventory of about 240 million curies in the world's oceans. The ¹⁴C released into the atmosphere from the use of this test would mix with the global inventory and expose the public and other biotic components of the environment to ¹⁴C intakes from inhalation, drinking water, and all possible food pathways in the same manner as naturally occurring ¹⁴C. The current world inventory of naturally occurring ¹⁴C results in an average dose to the public of about 1.25 mrem/year, and the release of 0.6 curies of ¹⁴C from the total of 600,000 tests assumed to be administered annually would result in an additional average annual dose of 2 X 10⁻⁷ mrem. This is far below the EPA reporting level of 1 mrem/year required under the Clean Air Act for routine exposures to a member of the public, or the 4 mrem/year EPA limit for public drinking water. In a total population of about 260 million people in the U.S., the collective annual dose from the breath tests would be about 0.051 person-rem. In addition, the doses from normal use of breath tests, or from any accidental release of ¹⁴C to the environment also are expected to be very small because the concentration of CO₂ released is very low and it would mix immediately with the atmosphere.

The small doses from naturally occurring ¹⁴C are of little significance to human health and the environment. Potential long-term impacts from widespread releases of the long-lived ¹⁴C (5,730-year radiological half-life) from breath tests were concluded to be insignificant. Assuming that the testing in the U.S. would increase over a period of time to an average of a million tests per year for 50 years, the collective annual dose to the U.S. population would be about 5 person-rem over the next 50 years. This dose is very small when compared to the annual collective dose to the U.S. population from naturally occurring ¹⁴C of over 300,000 person-rem, and about 78,000,000 person-rem from all naturally occurring radiation. Clearly,

an increase of a few person-rem will not significantly change these exposures, and thus there is no expected impact from the widespread use of the breath test on the entire U.S. population.

As a result of this analysis, the NRC concludes that Alternatives 2 and 3 are clearly preferable to the no action alternative. This is because either of the two alternatives will result in significant cost savings with no measurable adverse effect on health and safety. Furthermore, the NRC's recommended option is Alternative 2 because it would avoid the unnecessary cost burden to some Agreement States and their general licensees.

Therefore, by promulgating the final rule, the cost savings would be maximized without any measurable adverse effect on public health and safety.

5. Decision Rationale

Based on the above analysis, the NRC is amending its regulations to permit the manufacture and commercial distribution of Carbon-14 urea capsules to any person (including physicians who are not "authorized users" under Part 35) and permit any person, without an NRC license, to receive and use the capsules for in vivo diagnostic use for humans because the radiological risk from such distribution would be negligible and the savings to patients could be significant.

ENCLOSURE 2
REGULATORY ANALYSIS

Environmental Assessment
For Final Amendments to 10 CFR Parts 30 and 32
"Distribution of a Radioactive Drug Containing One Microcurie of
Carbon-14 Urea as Exempt Material for "In Vivo" Diagnostic Testing"

Statement of the Final Action

The Nuclear Regulatory Commission (NRC) is amending its regulations to allow NRC licensees to distribute a radioactive drug containing one microcurie of carbon-14 urea to any person for "in vivo" diagnostic use. The NRC has determined that the radioactive component of such capsules presents a minimal radiation risk and, therefore, regulatory control of the drug for radiation safety is not necessary. This amendment makes the drug more widely available, thus reducing costs to patients, insurers, and the health care industry. This action is being taken in response to a petition for rulemaking (PRM-35-12) submitted by Tri-Med Specialties, Inc.

Need for the Amendments

The amendments have been developed to grant the petition for rulemaking. The final rule permits manufacturers or commercial distributors to distribute carbon-14 urea capsules as exempt material to any person. The Commission is promulgating this rulemaking because it believes that the radiological risk from such distribution would be negligible and the savings to patients could be significant. In addition, the Commission recognizes that other Federal and State agencies (e.g., Food and Drug Administration and the State Boards of Pharmacy) are responsible for the receipt and use of drugs that do not contain byproduct materials, and would provide necessary oversight for the safe use of these carbon-14 urea capsules as drugs.

Alternatives Considered

Three alternatives have been considered regarding the petition: deny the petition, i.e., maintain the status quo, permit the distribution of the capsules as exempt material, and permit the distribution of the capsules to general licensees.

Under the first alternative, the current situation would continue: only physicians who are authorized users under Part 35 would be allowed to possess and administer the C-14 urea test. Any physician could apply to become an authorized user. However, the NRC expects few physicians would apply for a Part 35 license for the sole purpose of using such capsules because of the requirement for training and experience and the associated costs of obtaining and maintaining a Part 35 license. Alternatively, physicians who are not authorized users can continue to refer their patients to physicians who are authorized users to undergo the diagnostic test. However this would not relieve the current expense, inconvenience, and delay encountered in an otherwise straight-forward procedure.

Under the second alternative, 10 CFR Parts 32 and 30 would be amended. Part 32 would be amended to establish requirements for the manufacture and distribution of C-14 urea capsules to persons exempt from licensing, i.e., any person (including physicians who are not "authorized users" under Part 35); Part 30 would be amended to permit any person to receive, possess, use, transfer, own, or acquire the capsules for in vivo diagnostic use for humans without a license. The NRC has determined that the radioactive component of this drug presents a minimal radiation risk and, therefore, regulatory control of the capsules is not necessary.

Under the third alternative, 10 CFR Part 35 would be amended to permit any physician to receive and use the capsules under a general license. The health and safety concerns for this alternative are the same as the Alternative 2. However, if this alternative were adopted, there could be a burden to those Agreement States that normally require registration of general license holders. An additional burden could also be imposed on general licensees located in the Agreement State if the State charges a license or registration fee.

Based on the Draft Regulatory Analysis prepared for this proposed rule, the Commission concludes that Alternatives 2 and 3 are clearly preferable to the no action alternative. This is because either of the two alternatives will result in significant cost savings with no measurable adverse effect on health and

safety. Furthermore, the NRC's recommended option is Alternative 2 because it avoids the unnecessary cost burden to some Agreement States and their licensees.

Impact on the Public and the Environment

The amendments are expected to have no significant impact on the public and the environment. The NRC assumes that the same number of breath tests will be administered regardless of the level of NRC regulatory control. This view is predicated on the belief that each physician's primary motivation is to provide the best possible care to his or her patients. If the breath test is judged preferable to endoscopy, or other procedure, any physician not authorized to use the test will refer his or her patient to authorized users who could perform the test under existing NRC regulations. Under this assumption, this rulemaking action is expected to result in no change in radiation exposures to the workers and patients when compared with the status quo. Similarly, it is expected that there will be no change in impact to the environment because the Commission assumes that the same number of tests will be administered regardless of which alternative is adopted.

The earth's atmosphere contains an inventory of naturally occurring C-14 of about 3.8 million curies which is in addition to the huge inventory of about 240 million curies in the world's oceans. The small amount of C-14 released into the atmosphere from the use of this test would mix with the global inventory and would have no impact on public health. The current world inventory of naturally occurring C-14 results in an average dose to the public of about 1.25 mrem per year, and the release of 0.6 curies of C-14 from the total of 600,000 tests assumed to be administered annually would result in an additional average annual dose of 2×10^{-7} mrem.

List of Agencies and Persons Consulted and Identification of Sources Used

Following the receipt of the petition for rulemaking, a "Notice of receipt of petition for rulemaking" was published for public comment in the Federal Register on December 2, 1994, (59 FR 61831). A total of 315 public comment letters, 313 supporting (mostly form letters) and 2 opposing letters, were received. This petition was discussed with NRC's Advisory Committee on the Medical Uses of Isotopes (ACMUI) at the October 1995 meeting. Furthermore, the draft rulemaking plan was forwarded to 29 Agreement States for comments.

A proposed rule was published in the Federal Register (62 FR 32552, June 16, 1997) for a 30-day public comment period. The NRC received seven public comment letters. Four commenters supported the rule, one opposed the rule, and two provided comments without explicitly stating support of or oppose opposition to the rule. A summary of public comments and NRC's responses are presented in the preamble of the Federal Register notice. Except a minor change in wording, the final amendments are the same as the proposed amendments.

One commenter addressed the draft environmental Assessment. The commenter stated that the environmental Assessment fails to consider the fact that another equally non-invasive, but non-radiological, diagnostic procedure (such as C-13 test) is available and provides a comparable alternative to the C-14 test. The apparent commenter apparently concluded that the assumption underlying the environmental assessment is that in the absence of the C-14 test, the only alternative for the detection of H. pylori is invasive gastroendoscopy.

The only regulatory issue in this rulemaking is whether the C-14 method should be made available to physicians who are not authorized users. The purpose of the environmental assessment is to address and document that the subject rule is the expected to have no significant impact to the environment of subject rule . As presented in the regulatory analysis prepared for this rule, the NRC has determined that the environmental impact is expected to be insignificant because of the extremely low radiological hazards associated with the use of capsules containing one microcurie C-14 urea. The earth's atmosphere contains an inventory of naturally occurring C-14 of about 3.8 million curies which is in addition to the huge inventory of about 240 million curies in the world's oceans. The small amount of C-14 released into the atmosphere from the use of this test would mix with the global inventory and would have no impact on public health. The current world inventory of naturally occurring C-14 results in an average dose to the public of about 1.25 mrem per year, and the release of 0.6 curies of C-14 from the total of 600,000 tests assumed to be administered annually would result in an additional average annual dose of 2×10^{-7} mrem.

If the environmental impact had been significant, then the existence of a non-radioactive alternative would have been a factor in assessing the cost - benefit of this rulemaking. However, the impact is not significant. Hence, the regulatory issue in this rulemaking is whether the C-14 method should be made available to physicians who are not authorized users, and not whether there exists a non-radioactive alternative.

Finding of No Significant Impacts

The Commission has determined under the National Environmental Policy Act of 1969, as amended, and the Commission's regulations in Subpart A of 10 CFR Part 51, that the amendments will not be a major Federal action significantly affecting the quality of the human environment, and therefore an environmental impact statement is not required. The final rule amends 10 CFR Part 32 to permit the manufacture and commercial distribution of C-14 urea capsules to any person (including physicians who are not "authorized users" under Part 35) and to amend 10 CFR Part 30 to permit any person, without an NRC license, to receive and use the capsules for in vivo diagnostic use for humans. The Commission believes that the radioactive component of this drug presents a minimal radiation risk and, therefore, regulatory control of the capsules for "in vivo" diagnostic use is not necessary. It is expected that this final rule will not cause any significant increase in radiation exposure to the public or radiation release to the environment beyond the exposures or releases resulting from the use of the carbon-14 capsules under the current regulations.

The Honorable Dan Schaefer, Chairman
Subcommittee on Energy and Power
Committee on Commerce
United States House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

Enclosed for the information of the Subcommittee are copies of a public announcement and a Federal Register notice concerning a final amendment to 10 CFR Parts 30 and 32. This rulemaking is being taken in response to a petition for rulemaking submitted by Tri-Med Specialties, Inc.

The Nuclear Regulatory Commission (NRC) is amending its regulations to allow NRC licensees to distribute a radioactive drug containing one microcurie of carbon-14 urea to any person for "in vivo" diagnostic use. The purpose of this diagnostic test is to detect the presence of the bacterium *Helicobacter pylori* (*H. pylori*), a cause of peptic ulcers. The NRC has determined that the radioactive component of such capsules presents a minimal radiation risk and, therefore, regulatory control of the drug for radiation safety is not necessary. The manufacture and distribution of the capsules will continue to require an NRC license. This amendment makes the drug more widely available, thus reduces costs to patients, insurers, and the health care industry.

Sincerely,
Dennis K. Rathbun, Director
Office of Congressional Affairs

Enclosures: 1. Public Announcement
2. Federal Register Notice

cc: Representative Ralph Hall

The Honorable James M. Inhofe, Chairman
Subcommittee on Clean Air, Wetlands,
Private Property and Nuclear Safety
Committee on Environment and Public Works
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

Enclosed for the information of the Subcommittee are copies of a public announcement and a Federal Register notice concerning a final amendment to 10 CFR Parts 30 and 32. This rulemaking is being taken in response to a petition for rulemaking submitted by Tri-Med Specialties, Inc.

The Nuclear Regulatory Commission (NRC) is amending its regulations to allow NRC licensees to distribute a radioactive drug containing one microcurie of carbon-14 urea to any person for "in vivo" diagnostic use. The purpose of this diagnostic test is to detect the presence of the bacterium *Helicobacter pylori* (*H. pylori*), a cause of peptic ulcers. The NRC has determined that the radioactive component of such capsules presents a minimal radiation risk and, therefore, regulatory control of the drug for radiation safety is not necessary. The manufacture and distribution of the capsules will continue to require an NRC license. This amendment makes the drug more widely available, thus reduces costs to patients, insurers, and the health care industry.

Sincerely,
Dennis K. Rathbun, Director
Office of Congressional Affairs

Enclosures: 1. Public Announcement
2. Federal Register Notice

cc: Senator Bob Graham

Mr. Robert P. Murphy
General Counsel
General Accounting Office
Room 7175
441 G. St., NW
Washington, DC 20548

Dear Mr. Murphy:

Pursuant to Subtitle E of the Small Business Regulatory Enforcement Fairness Act of 1996, 5 U.S.C. 801, the Nuclear Regulatory Commission (NRC) is submitting a final rule regarding distribution of a radioactive drug containing one microcurie of carbon-14 urea to any person for "in vivo" diagnostic use for humans. The purpose of this diagnostic test is to detect the presence of the bacterium *Helicobacter pylori* (*H. pylori*), a cause of peptic ulcers. The

final rule makes the drug more widely available, and reduces costs to patients, insurers, and health care industry. The distribution of the drug in capsule form presents a minimal radiation risk and, therefore, regulatory control of the drug for radiation safety is not necessary. This action is being taken in response to a petition for rulemaking (PRM-35-12) submitted by Tri-Med Specialties, Inc.

We have determined that this rule is not a "major rule" as defined in 5 U.S.C. 804(2). We have confirmed this determination with the Office of Management and Budget.

Enclosed is a copy of the final rule that is being transmitted to the Office of the Federal Register for publication. The Regulatory Flexibility Certification and a statement of the availability of the Regulatory Analysis are included in the final rule.

Sincerely,
Dennis K. Rathbun, Director
Office of Congressional Affairs

Enclosure: Final Rule

The Honorable Al Gore
President of the United
States Senate
Washington, DC 20510
Dear Mr. President:

Pursuant to Subtitle E of the Small Business Regulatory Enforcement Fairness Act of 1996, 5 U.S.C. 801, the Nuclear Regulatory Commission (NRC) is submitting a final rule regarding distribution of a radioactive drug containing one microcurie of carbon-14 urea to any person for "in vivo" diagnostic use for humans. The purpose of this diagnostic test is to detect the presence of the bacterium *Helicobacter pylori* (*H. pylori*), a cause of peptic ulcers. The final rule makes the drug more widely available, and reduces costs to patients, insurers, and health care industry. The distribution of the drug in capsule form presents a minimal radiation risk and, therefore, regulatory control of the drug for radiation safety is not necessary. This action is being taken in response to a petition for rulemaking (PRM-35-12) submitted by Tri-Med Specialties, Inc.

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Sincerely,
Dennis K. Rathbun, Director
Office of Congressional Affairs

Enclosure: Final Rule

The Honorable Newt Gingrich
Speaker of the United States
House of Representatives
Washington, DC 20515
Dear Mr. Speaker:

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Dennis K. Rathbun, Director
Office of Congressional Affairs

Enclosure: Final Rule