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Jones
File

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

AF 70-1
PDR

August 20, 1996

MEMORANDUM FOR: David L. Morrison, Director
Office of Nuclear Regulatory Research

FROM: David L. Meyer, Chief
Rules Review and Directives Branch
Division of Freedom of Information
and Publications Services
Office of Administration

SUBJECT: OFFICE CONCURRENCE ON DIRECT FINAL RULEMAKING PLAN ENTITLED "MEDICAL USE OF CAPSULES CONTAINING ONE MICROCURIE OF CARBON-14"

The Office of Administration concurs on the final rulemaking plan that amends Part 35. We find the rulemaking plan adequate, and will provide support during preparation of the direct final rule.

If you have any questions, please contact Alice Katoski, 415-6862, or Mike Lesar on 415-7163.

Attachment: As stated

072

RULEMAKING PLAN

Lead Office: Office of Nuclear Regulatory Research

Staff Contact: S. Jones, RES/RPHEB

Concurrences:

David L. Morrison 8/13/96
D. Morrison, RES Date

C. Paperiello, NMSS Date

R. Bangart, OSP Date

W. Olmstead, OGC Date

pl - L Meyer 8/16/96
D. Meyer, ADM Date

Approval:

J. Taylor, EDO Date

RULEMAKING PLAN

10 CFR PART 35

MEDICAL USE OF CAPSULES CONTAINING ONE MICROCURIE OF CARBON-14 (PRM-35-12)

Regulatory Issues

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 (μCi) 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 10% 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 non-invasively 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.

In another letter on November 30, 1994, the petitioner stated:

> .... [The test is 95% 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.

Tri-Med based its benefits calculation on a 100% substitution of the ^{14}C-urea breath test (at an average cost of $100) for the endoscopy (at an average cost of $1,000). Applied to approximately 600,000 new ulcer cases with the potential for H. pylori infection each year, this substitution generates a cost reduction to patients on the order of $500 million per year. It assumes that the lower cost and greater availability of an unregulated breath test would not generate an increase in the number of tests for H. pylori but would induce a complete substitution of test procedures.

The NRC's benefit calculation (discussed in the "Preliminary Regulatory Analysis" section of this plan) is based on the assumption that permitting non authorized users (e.g., family physicians or gastrointestinal specialists) to administer ^{14}C-urea tests would avoid referring patients to authorized users (e.g., physicians specializing in nuclear medicine) for the same test. The cost savings are estimated to be approximately $15 million per year from not referring 400,000 patients to authorized users. Patient savings would result from averted travel expenses (transportation and personal time) and administrative costs (e.g., completion of new patient paperwork, reviewing health history, maintaining medical records).

The petitioner states that the reason for requesting the exemption is: "Currently, the test must be supplied only to facilities licensed to receive ^{14}C. This requirement makes the test prohibitively expensive for the great majority of doctors."

Existing NRC regulations permit physicians who are "authorized users," who meet certain training and experience requirements to ensure the safe medical use of radioactive material, to receive and use this product. Granting the petition would permit physicians who are not authorized users to receive and use this product.

The regulatory issue is: Should NRC permit physicians who are not authorized users to receive and use capsules containing one microcurie of carbon-14 for medical use?

Current Regulations

Part 32 permits manufacturers of radioactive drugs containing byproduct material to distribute radioactive drugs, including this product, to persons authorized to receive them pursuant to Part 35.

Part 35 permits authorized users, or individuals working under the supervision of an authorized user, to receive and use radioactive drugs containing byproduct material, including this product, for medical use. An "authorized user" is defined in § 35.2 and the requirements for training and experience for authorized users are specified in Subpart J of Part 35.

Part 30 provides the provisions for "exempt concentrations" and "exempt quantities." However, the regulation in § 30.14, "Exempt Concentrations," states that the exemption does not apply to the transfer of byproduct material contained in any food, beverage, cosmetic, drug, or other commodity or product designed for ingestion or inhalation by, or application to, a human being. Further, the regulations in § 30.18, "Exempt Quantities," set forth the provisions for exempt quantities. The exempt quantity for ^{14}C is 100 μCi. However, § 30.18 excludes Part 35 (i.e., a person is not exempt from Part 35 requirements if this person uses exempt quantities of byproduct material for medical use) because this exemption does not apply to human use.

Recommended Course of Action

The staff recommends proceeding with a direct final rule to grant the petition (see "Basis for the recommendation for a direct final rule" of this plan). The staff recommends amending Part 35 to allow physicians who are not authorized users to receive and use capsules containing ^{14}C-urea and to exempt these physicians from the requirement to have a Part 35 license.

A new section would be added to 10 CFR Part 35, Subpart D--Uptake, Distribution, and Excretion, to read:

> **§ 35.110 Authorization for use of capsules containing one microcurie of ^{14}C-urea**
>
> **Any physician, as defined in § 35.2, is authorized to receive and use capsules containing one microcurie of ^{14}C-urea and is exempt from the requirements for a license set forth in this part. However, this authorization does not relieve physicians from complying with FDA, other Federal, or State requirements for use of this material.**

This amendment, if adopted, would permit physicians who are not authorized users to: (1) receive capsules containing one microcurie of ^{14}C-urea from Tri-Med or any another distributor, and (2) use capsules containing one microcurie of ^{14}C-urea for medical use without an NRC Part 35 license.

Preliminary Regulatory Analysis

Assessment of Likely Impacts on Licensees

This rulemaking would not result in any additional regulatory burden to NRC medical use licensees. Authorized users will continue to be authorized to receive and use this product for medical use. However, after FDA approval, it is assumed that among 600,000 ^{14}C-urea breadth tests each year, one-third of the tests (200,000) would be performed by authorized users and two-thirds (400,000) would be performed by physicians who are not authorized users.

Alternatives

The following two alternatives have been considered:

Alternative 1 - Deny the petition; and

Alternative 2 - Allow any physician to receive and use capsules containing one microcurie of ^{14}C urea.

Alternative 1 - Deny the petition

This alternative would maintain the status quo by continuing to permit only authorized users to receive and use capsules containing one microcurie of ^{14}C.

This alternative is not recommended because it would prohibit physicians who are not authorized users to receive and use the product even though the radiological impact is the same, i.e., the dose received by workers and the general public from a ^{14}C test is not determined by who administers the test. This alternative would effectively require physicians who are not authorized users to refer their patients to authorized users for these tests. This would cause patients to pay extra travel expenses and administrative costs. Although a physician could become an authorized user by meeting NRC's training and experience requirements and obtain a Part 35 license, NRC expects that few non authorized users would obtain a Part 35 specific license for the use of this one product.

Alternative 2 - Allow any physician to receive and use of capsules containing one microcurie of ^{14}C urea

This alternative would grant the petition by authorizing any physician to receive and use capsules containing one microcurie ^{14}C urea without being named as an authorized user on a Part 35 license.

If it is assumed that the number of tests administered is determined by the incidence of suspected ulcer cases, and not who administers the test, then to the extent that assumption is valid there is no radiological impact from this alternative. The environmental impact from the tests (assuming 600,000 per year) would be the same whether these tests are administered by authorized users or non authorized users.

If the number of tests per year increases as a consequence of permitting non authorized users to administer the tests, the radiological impact would still be minimal. Assuming an increase of 400,000 tests per year as a result of adopting this alternative, the collective dose to the U.S. population would be less than 0.04 person-rem per year (assumes the 0.4 curie of ^{14}C contained in the 400,000 capsules is released to the environment). The dose for a health care worker who administers 800 capsules per year (4 capsules/day x 200 days/yr) would be less than 0.1 mrem per year. A patient would receive 0.38 to 0.18 mrem per capsule depending on whether this patient is infected with the bacteria. Under accident conditions, assuming 150 capsules were released into the facility by a fire (150 microcuries of ^{14}C), members of public evacuating the area would receive a dose of less than 0.0002 mrem. Under

another accident condition, assuming rupture of a capsule that causes skin contamination of a worker or a patient for 1 hour prior to washing, the skin dose would be about 6 mrad.

This alternative would result in a significant cost saving to patients. If the alternative is adopted, physicians who are not authorized users would be allowed to receive and use the product for testing. Thus, it would no longer be necessary for them to refer the patients to authorized users for ^{14}C-urea tests. The cost savings are estimated to be approximately $15 million per year from not referring patients to authorized users. Patients' savings would result from averted travel expenses (transportation and personal time) and administrative costs (e.g., completion of new patient paperwork, reviewing health history, maintaining medical records).

This estimate is based on the following:

To estimate both benefit and impact, it is assumed that 400,000 ^{14}C-urea breath tests will be administered each year by non authorized users, and that these tests would otherwise not have been administered in the absence of this rule.

The benefit accrues to the patient from obviating the need to see a second physician (an authorized user) for administration of the test.

Patient savings from averted travel expenses
(Transportation and personal time to see authorized user for administration of test):

Assumed round trip of 20 miles to an authorized user
Personal time is valued at $25.00/hour

400,000 trips/year x (20 miles/trip x $0.25/mile
+ 0.5 hours/trip x $25.00/hour) = $7.0 million

Patient savings from averted administrative expenses
(Administrative costs incurred with medical referral):

$19.00/patient x 400,000 patients/year = $7.6 million

The $19.00 (administrative cost/patient) is based on 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. (American Medical Association, 1995). The patient who is referred to an authorized user (e.g., nuclear medicine specialist) for the ^{14}C-urea breath test would most likely be a new patient for the authorized user.

Comments from the Advisory Committee on the Medical Uses of Isotopes (ACMUI)

This petition was discussed with the ACMUI at the October 1995 meeting. The ACMUI indicated that it endorsed the wide availability of this diagnostic test to physicians without requiring a Part 35 license.

Comments from the Public

The "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 and 2 opposing) were received.

The two letters opposing the petition made the following two comments: (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.

The staff disagrees with both comments. The radiological risk would be the same if it is assumed that the number of tests administered is determined by the incidence of suspected ulcer cases, and not who administers the test. If the number of tests per year increases as a consequence of permitting non authorized users to administer the tests, the radiological impact would still be minimal. Assuming an increase of 400,000 tests per year as a result of adopting this alternative, the collective dose to the U.S. population would be less than 0.04 person-rem per year (assuming the 0.4 curie of ^{14}C contained in the 400,000 capsules is released to the environment). This presents a risk so small compared to the annual collective dose to the U.S. population from naturally occurring ^{14}C of over 300,000 person-rem (an average individual dose of 1.25 mrem per year) that it is insignificant, particularly in view of the benefits noted above. Thus, this proposed medical use of capsules containing one microcurie of long-lived ^{14}C in urea would have no significant impact to the public or the environment.

Basis for the Recommended Course of Action

Basis for the recommendation to grant the petition:

(1) Public health and safety risks as well as the environmental impacts are minimal;

(2) The preliminary cost/benefit analysis indicates that, if the proposed amendment were adopted, the increase in radiological risk would be extremely low but the cost saving would be significant;

(3) The petition has been endorsed by the ACMUI;

(4) The majority of public comment letters supported the petition and the two opposing comments have been addressed.

Basis for the recommendation for a direct final rule:

(1) The direct final rule (versus a proposed rule/final rule) is the most expedient means for NRC to grant the petition. The product could be approved by the Food and Drug Administration (FDA) by the end of this year. If this is so, only proceeding with a direct final rule could permit use of the capsules by any physician concurrent with FDA approval. The proposed rule/final rule approach would add about six months to the rulemaking schedule, with concomitant loss of the benefits to be provided though this rulemaking.

(2) The two opposing comments received in response to the "Notice of receipt of petition for rulemaking" will be addressed in the direct final rule.

(3) In accordance with usual procedures, the staff will prepare a companion proposed rule, to be published at the same time as the direct final rule, in the event any significant opposing comments are received.

Agreement State Implementation

This action would not affect the Agreement States because the current Subpart D (i.e., §§ 35.100 and 35.120) is not an item of compatibility. Therefore, the new section, § 35.110, would not be an item of compatibility.

Supporting Documents

A regulatory analysis and an environmental assessment will be provided for this rulemaking.

Resources

The estimated staff resources for the rulemaking are 0.3 FTE,

Lead Office Staff and Staff from Supporting Offices

Lead Office (RES) - Sam Jones

NMSS - Donn Beth Howe
OGC - Marjorie Rothschild
OSP - Lloyd Bolling
ADM - Mike Lesar

Steering Groups/Working Group

There is no need for a steering group for this rulemaking. The Working Group is identified above.

Enhanced Public Participation

This rulemaking will be placed on the electronic bulletin board at FedWorld and will also be published in the Federal Register.

EDO or Commission Issuance.

Because the amendment represents a significant policy issue, it is recommended that the Commission issue the rule.

Schedule

Rulemaking Plan (RP):

Send RP to office for conc	08/14/96
Send revised RP to OSP for AS review (45 days) & to EDO/Comm for info	08/30/96
Send RP to EDO/Comm	10/18/96

Direct Final Rule (DFR)*:
(Assuming RES staff will start work on DFR after sending RP to AS for review)

Send DFR to office for conc	11/01/96
Send DFR to EDO	11/22/96
Send DFR to Comm	11/25/96
Receive Comm approval	11/13/96
Publish DFR in FR; submit ltrs (non-major rule) to Congress/GAO	12/27/96

* Including a companion proposed rule.

CHARLES S. ROBB
VIRGINIA

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United States Senate

WASHINGTON, DC 20510-4603

COMMITTEES
ARMED SERVICES
FOREIGN RELATIONS
INTELLIGENCE
JOINT ECONOMIC COMMITTEE
Vice Chairman
Democratic Policy Committee

AF 70-1
PDR

August 19, 1996

Mr. Dennis K. Rathbun
Director
Nuclear Regulatory Commission
Office of Congressional Affairs
Washington, DC 20555

Dear Mr. Rathbun:

Enclosed is correspondence I received in reference to a matter involving your agency. Your assistance with the requests and concerns expressed in this case would be greatly appreciated.

It would be very helpful if you would reply in duplicate and return the enclosure. In your reply, please reference Tri-Med Specialties, Inc.

Your correspondence should be mailed to my office at the address indicated above.

Again, thank you for your assistance.

Sincerely,

Chuck Robb

Charles S. Robb

CSR/sds

Enclosure

Washington Office:
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and Constitution Avenue, NE
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[illegible]shington, DC 20510
(202) 224-4024

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(540) 985-0103

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PHONE (804) 977-8711 FAX (804) 977-8760

July 24, 1996

Honorable Charles S. Robb
154 Russell Senate Office Bldg.
Washington, DC 20510

Dear Senator Robb,

I work with Tri-Med Specialties, Inc. a medical research and development company in Charlottesville. Several of my colleagues and I would like to meet with you to discuss a problem we have encountered with the Nuclear Regulatory Commission.

Tri-Med has developed a new medical diagnostic test, the Carbon 14 Urea Breath Test (PYtest), to diagnose a bacterial infection (Helicobacter pylori) which has been proven to cause stomach ulcers and possibly gastric cancer. To perform this very simple test, the patient swallows a capsule and 10 minutes later blows up a balloon. The breath sample is then analyzed to determine if the patient has the bacterial infection. An antibiotic combination can then be administered to destroy the bacteria. The medical savings from this new method of treating ulcers is tremendous. A New Drug Application for this test is currently pending with the FDA. It was filed on May 12, 1995. It is anticipated that approval will be granted by the end of 1996.

Due to the small amount of radioactivity in the capsule (less than that found in a smoke detector) this test is regulated by the NRC. In order for a physician to administer the test they must have a license with the NRC. This license costs approximately $4000 a year with untold hidden administrative costs. We feel our test will be sold for approximately $50.00. The cost of the license will restrict many physicians from performing the test.

For this reason, Tri-Med Specialties, Inc., on August 23, 1994, filed a petition with the NRC for either a rule change or an exemption from licensing for the ^{14}C-urea Breath Test (PYtest). An announcement of the petition filed with the NRC was published in the Federal Register on December 2, 1994 along with a request for comments. The comment period extended until February 10, 1995. It is our understanding that 304 comments were received; 302 in favor and 2 opposed. On October 18, 1995 the petition was discussed at the ACMUI(Advisory Committee for the Medical Use of Isotopes). It seemed, at that meeting that the committee came to a consensus that a special exemption for the test should be granted under the conditions that final approval from the FDA is granted and that the drug is prescribed by a

physician. The committee recommended the exemption route versus a rule change because it would be the most expeditious and the easiest means of resolving this issue.

When this process was begun, we were advised by the NRC that the entire process would take approximately one year. In December of 1995 in a conversation with John Glenn, (Branch Chief for the NRC) I was told the final ruling would take place as early as July, 1996 or no later than December.1996. Last week, I again spoke with John Glenn to get an update on the progress of our application. Mr. Glenn informed me that the application was not yet close to a ruling. I asked him to explain to me the steps remaining in the process. Following is a list of those steps.

1. Finish the "rule plan" He stated this should take about another month.
2. The plan is then sent to the NRC- specifically to the 5 commissioners (these 5 people are appointed by the President)
3. If the commissioners approve the rule plan, the rule is then sent to the 29 agreement states for their approval. They have 45 days to respond. If any of the states suggest a change, the rule plan has to be revised and re-approved by the commissioners.
4. Once the rule plan is approved they actually write the rule (we know from past experience that this can take 6 months) The rule is then published in the Federal Register. There is a set 75 day comment period.
5. If there are no negative comments they can then make the decision to accept the rule. (note that even ONE negative comment can stop the whole process)

I was also told by Mr. Glenn that this application is not considered a priority because the NRC is not preventing physicians who have a license with the NRC from obtaining the test. Therefore the NRC is not prohibiting patients from receiving the test by delaying or not granting the waiver.

Looking at the steps listed above it is obvious that a ruling will not be made by the end of 1996

It has already been 2 years since the submission of our application and a final ruling is nowhere in sight. The NRC advisory committee recommended approval of this application almost a year ago. Both the NRC Advisory Committee and the FDA Advisory Panel Committee (February 96) have concluded that this is a safe test.

We currently have a meeting scheduled with the FDA at 9:30 am on August 1st. Another meeting is also scheduled on Capitol Hill at 2:30 PM on August 1st. Each of these meetings should take approximately 1 ½ hours. If you have any time available on July 31st or August 1 we would greatly appreciate the opportunity to meet with you to discuss the situation. If you have any questions please feel free to contact me at 804-977-8711.

Sincerely,

Susie Hoffman

Susie R. Hoffman RN BSN
Product Development Coordinator