MATERIALS LICENSE

Amendment No. 73

Pursuant to the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974 (Public Law 93-438), and Title 10, Code of Federal Regulations, Chapter I, Parts 30, 31, 32, 33, 34, 35, 36, 39, 40, and 70, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, possess, and transfer byproduct, source, and special nuclear material designated below; to use such material for the purpose(s) and at the place(s) designated below; to deliver or transfer such material to persons authorized to receive it in accordance with the regulations of the applicable Part(s). This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954, as amended, and is subject to all applicable rules, regulations, and orders of the Nuclear Regulatory Commission now or hereafter in effect and to any conditions specified below.

301576

Licensee	
1. Borgess Medical Center	In accordance with letter dated July 5, 1996 3. License Number 21-12275-02 is amended in its entirety to read as follows:
2. 1521 Gull Road Kalamazoo, MI 49001	4. Expiration Date July 31, 2000
	5. Docket or Reference No. 030-02115

6. Byproduct, Source, and/or Special Nuclear Material	7. Chemical and/or Physical Form	8. Maximum Amount that Licensee May Possess at Any One Time Under This License
A. Any byproduct material identified in 10 CFR 35.100	A. Any radiopharmaceutical identified in 10 CFR 35.100	A. As needed
B. Any byproduct material identified in 10 CFR 35.200	B. Any radiopharmaceutical identified in 10 CFR 35.200	B. As needed
C. Any byproduct material identified in 10 CFR 35.300	C. Any radiopharmaceutical identified in 10 CFR 35.300	C. As needed
D. Any byproduct material identified in 10 CFR 35.400	D. Any brachytherapy sources identified in 10 CFR 35.400	D. As needed
E. Any byproduct material identified in 10 CFR 31.11	E. Prepackaged Kits	E. As needed
F. Phosphorus-32	F. IsoStent, Inc. ion-implanted Palmaz-Schatz Balloon-Expandable IsoStent with Delivery System.	F. See item 9.F.

210109

0/1

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number
21-12275-02

Docket or Reference Number
030-02115

Amendment No. 73

9. Authorized Use:

A. Medical use described in 10 CFR 35.100.

B. Medical use described in 10 CFR 35.200.

C. Medical use described in 10 CFR 35.300.

D. Medical use described in 10 CFR 35.400.

E. In vitro studies.

F. For use in IsoStent, Inc. Palmaz-Schatz Balloon-Expandable IsoStent under the Investigational Device Exemption (IDE) granted by the FDA for the conduct of human clinical trials as described in letter dated July 5, 1996, and subsequent phases of the IDE process associated with the device which are approved by the FDA.

CONDITIONS

10. Location of use: 1521 Gull Road, Kalamazoo, Michigan.

11. Radiation Safety Officer: Tim TenCate

12. Licensed material listed in Item 6 above is only authorized for use by, or under the supervision of, the following individuals for the materials and uses indicated:

Authorized Users	Material and Use
A. Gary L. Bowman, M.D.	10 CFR 35.100, 35.200 and 31.11.
B. John W. Copenhaver, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
C. J. Alex Gardner, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
D. Leonard A. Brunette, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
E. Arthur Gregory Laurell, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
F. James R. Dolan, M.D.	10 CFR 35.100, 35.200, 35.300, 35.400, 35.500 and Item 6.F.
G. Geoffrey A. Wardwell, M.D.	10 CFR 35.100 and 35.200.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number: 21-12275-02
Docket or Reference Number: 030-02115
Amendment No. 73

Authorized Users		Material and Use
H.	N. Warn Courtney, M.D.	10 CFR 35.100, 35.200, 35.300, 31.11 and Item 6.F.
I.	Richard R. McConnell, M.D.	10 CFR 35.100, 35.200, 35.300 (excluding iodine-131 for thyroid carcinoma), 35.500, 31.11 and Item 6.F.
J.	Edwardo R. Crotte, M.D.	10 CFR 35.100, 35.200 and 31.11.
K.	David Tague, M.D.	10 CFR 35.100, 35.200 and 31.11.
L.	L. Enrique Leguizamon, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
M.	Thomas McCormick, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
N.	John E. Francis, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
O.	Kenzo Kawamura, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
P.	Dennis P. Burke, M.D.	10 CFR 35.100, 35.200 and 31.11.
Q.	William B. Campbell, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
R.	Umakant S. Doctor, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
S.	Yoo Sup Hwang, M.D.	10 CFR 35.400.
T.	Khlid Altaf Mian, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
U.	Evalt Ayerdi, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
V.	Stephen L. Peck, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number
21-12275-02
Docket or Reference Number
030-02115
Amendment No. 73

Authorized Users	Material and Use
W. Robert J. LaPenna, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
X. Benjamin A. Perry, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
Y. Robert H. Jongeward, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
Z. George J. Balogh, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
AA. Robert B. Davis, M.D.	10 CFR 35.100, 35.200, 35.300, and Item 6.F.
BB. Katherine Gadwood, M.D.	10 CFR 35.100, 35.200 (excluding generators) and 31.11.
CC. Charles Gregory Hodgman, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
DD. Janos Gellert, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
EE. John A. Azevedo, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
FF. Sharma Saith, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
GG. Steven P. Soper, M.D.	10 CFR 31.11.
HH. Bruce D. Goethe, M.D.	10 CFR 35.100, 35.200 and 31.11.
II. Patrick A. Sorek, M.D.	10 CFR 35.100, 35.200 and 31.11.
JJ. Susan J. Phelps, M.D.	10 CFR 35.100, 35.200 and 31.11.
KK. David Lynn Keedy, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
LL. Douglas J. Wunderly, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
MM. Jonathan Levi, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number
21-12275-02

Docket or Reference Number
030-02115

Amendment No. 73

Authorized Users	Material and Use
NN. Jim Chul Kim, M.D.	10 CFR 35.300, 35.400 and Item 6.F.
OO. Heung (Henry) Shik Shin, M.D.	10 CFR 35.300, 35.400 and Item 6.F.
PP. David G. Brachman, M.D.	10 CFR 35.300, 35.400 and Item 6.F.
QQ. Marc Bernstein, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
RR. Anthony King, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
SS. Alicia Williams, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
TT. Antonio P. Carrillo, M.D.	10 CFR 35.100 and 35.200 (limited to cardiovascular clinical procedures).
UU. Ramon Raneses, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
VV. Joel H. Reinoehl, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
WW. Thomas Winn, M.D.	10 CFR 35.100, 35.200, 35.300 and Item 6.F.

13. The licensee will establish and implement model procedure for radiation safety during implant therapy that was published in Appendix Q to Regulatory Guide 10.8, Revision 2.

14. The licensee shall maintain records of information important to safe and effective decommissioning at the address in Condition 10. per provisions of 10 CFR 30.35(g) until this license is terminated by the Commission.

15. In addition to the possession limits in Item 8, the licensee shall further restrict the possession of licensed material to quantities below the minimum limit specified in 10 CFR 30.35(d) for establishing decommissioning financial assurance.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License Number
21-12275-02

Docket or Reference Number
030-02115

Amendment No. 73

16. Except as specifically provided otherwise in this license, the licensee shall conduct its program in accordance with the statements, representations, and procedures contained in the documents, including any enclosures, listed below, except for minor changes in the medical use radiation safety procedures as provided in 10 CFR 35.31. The Nuclear Regulatory Commission's regulations shall govern unless the statements, representations, and procedures in the licensee's application and correspondence are more restrictive than the regulations.

A. Application dated March 20, 1990; and

B. Letters dated May 25, 1990 (with attachments), July 3, 1990 (with enclosures), October 17, 1990 (with attachments), December 11, 1995, and July 5, 1996.

FOR THE U.S. NUCLEAR REGULATORY COMMISSION

Date 9/30/96

By Kevin G. Null
Nuclear Materials Licensing Branch, Region III

COPY

BETWEEN:

LICENSE FEE MANAGEMENT BRANCH, ARM
AND
REGIONAL LICENSING SECTIONS

(FOR LFMS USE)
INFORMATION FROM LTS

PROGRAM CODE: 02120
STATUS CODE: 0
FEE CATEGORY: 7C
EXP. DATE: 20000731
FEE COMMENTS:
DECOM FIN ASSUR REQDT N

RECEIVED
JUL 22 1996
REGION III

R9
MS-19

LICENSE FEE TRANSMITTAL

A. REGION

1. APPLICATION ATTACHED
APPLICANT/LICENSEE: BORGESS MEDICAL CENTER
RECEIVED DATE: 960710
DOCKET NO: 3002115
CONTROL NO.: 301576
LICENSE NO.: 21-12275-02
ACTION TYPE: AMENDMENT

please expedite

2. FEE ATTACHED
AMOUNT: 440
CHECK NO.: 7905583803

3. COMMENTS

SIGNED D. Hensey
DATE 7-15-96

B. LICENSE FEE MANAGEMENT BRANCH (CHECK WHEN MILESTONE 03 IS ENTERED /__/)

1. FEE CATEGORY AND AMOUNT: 7C $440

2. CORRECT FEE PAID. APPLICATION MAY BE PROCESSED FOR:
AMENDMENT ✓
RENEWAL
LICENSE

3. OTHER

SIGNED SC
DATE 7/15/96

Log Jul 11 III
Remitter
Check No. 7905583803
Amount $440
Fee Category 7C
Type of Fee AMD
Date Check Rec'd 7/15/96
Date Completed
By: SC

Borgess Medical Center
1521 Gull Road
Kalamazoo, Michigan 49001-1640
Telephone 616-226-7000

Member of
Sisters of St. Joseph
Health System, Inc.
Ann Arbor, Michigan

BORGESS
Medical Center

July 5, 1996

UNITED STATES NUCLEAR REGULATORY COMMISSION
Region III, Medical Licensing Section
801 Warrenville Road
Lisle, IL 60532

ATTN: John Madeira

Re: Urgent Amendment Request License No. 21-12275-02 P-32 Coronary Artery Stents

We respectfully request that this license amendment be expedited. Tracy King, our physics consultant, discussed this matter with you on July 3, 1996. In accordance with your conversation, we are faxing this amendment letter so that you may assign it for review while the fee division performs their review.

The FDA has issued approval for this procedure in human clinical trials. The program is due to start on August 5 , 1996. We hope that you can assist us in getting this program approved in time as it will be of great benefit to our patients.

We ask for permission to order, receive, and implant Palmaz-Schatz Balloon-Expandable IsoStent with Delivery System. The stents are manufactured by IsoStent, Inc and contain approximately 1 uCi of P-32. These stents are shipped by the manufacturer in radiation shields which the stent remains in until its placement in a coronary artery. The P-32 stents are placed within the coronary artery by a physician who will be trained in accordance with manufacturer's instructions and the outline enclosed for your review. These are not temporary implants. The P-32 betas will provide local radiation only to the tissue surrounding the stent and is expected to prevent the artery from re-stenosising.

We have enclosed the FDA's conditional approval of this use. We will forward the final approval letter to you.

We have enclosed the following list of documents for your review:

Item 5-7	Radioactive Material and Use
Item 8.1	Personnel Training Program for P-32 Stent Placement
Item 9.1	Equipment List P-32 Stent Program
Item 9.4	Personnel Monitoring P-32 Stent Program
Item 10.4	Rules for Safe Use of P-32 Stents
Item 10.5	Emergency Procedures for Loss of P-32 Stent
Item 10.11	Keeping an Inventory of P-32 Stents
Item 10.15	Radiation Safety Procedures for P-32 Coronary Artery Stents
Item 12.1	Quality Management Program P-32 Stent Program

Our ordering, package receipt, and waste disposal procedures will be followed as they exist in our current license.

We have also enclosed information supplied by IsoStent, Inc. which you may find useful as reference material.

The $440 amendment fee is enclosed for a human use license category 7C amendment.

Again, we respectfully request your assistance in expediting this amendment request.

Cordially,

Gary Beaulac
Vice-President, Ambulatory Services
Borgess Medical Center

Borgess Medical Center
21-12275-02 amendment request
1996

P-32 Stent Program Only
RADIOACTIVE MATERIAL AND USE

Item 5 *Byproduct Material*	*Item 6* *Amount*	*Purpose*
P-32 "Palmaz-Schatz Expandable IsoStent" (coronary artery stent)	Each stent contains less than 10 uCi of P-32. Typically each stent contains 1 uCi of P-32.	Maintain patency of Balloon-stented coronary arteries

RADIATION SAFETY PROGRAM RESPONSIBILITY

Item 7.1
Authorized Users ***Materials***

These physicians have been selected as users for the P-32 stent program. The P-32 stent placement program will be supervised by one or more of these physicians listed below.

James R. Dolan, M.D.
N. Warn Courtney, M.D.
Richard R. McConnell, M.D.
Robert B. Davis, M.D.
Jim Chul Kim, M.D.
Heung (Henry) Shik Shin, M.D.
David G. Brachman, M.D.
Thomas Winn, M.D. previous request sent to add to license, previously listed on License No. 21-13125 for Groups 35.100, 35.200, and 35.300

These physicians have experience with therapeutic agents such as P-32 and are currently authorized for usage of P-32 in Group 35.300 on our license.

Item 7.3 ***No change***

Radiation Safety Officer

Tim Tencate

PERSONNEL TRAINING PROGRAM
for P-32 Stent Placement

Item 8.1

Personnel

Only personnel who have been trained as listed below will be allowed to participate directly in the placement procedure of P-32 stents.

Training Frequency

1. Before participating in a P-32 stent placement
2. During annual refresher training.
3. Whenever there is a significant change in duties, regulations, or in the terms of the license relating to this procedure

Instruction Topics

1. Applicable regulations and license conditions.
2. Physical appearance of the P-32 stent and proper handling procedures
3. Potential hazards associated with the P-32 stents.
4. Appropriate radiation safety procedures.
5. The licensee's in-house work rules.
6. Each individual's obligation to report unsafe conditions to the Radiation Safety Officer.
7. Appropriate response to emergencies or unsafe conditions.
8. Appropriate response if a stent is lost.
9. Locations where the license has been posted or made available, notices, copies of pertinent regulations, and copies of the license and license conditions, as required by 10CFR19.

Documentation will be kept on hand for review of the list of topics covered, the date of the instruction, and the names of those participating.

The method of instruction will be verbal and written.

Borgess Medical Center
21-12275-02 Amendment Request
1996

P-32 Stent Program Only
EQUIPMENT LIST

Item 9.1

Survey Meters

We will use a GM meter with a probe possessing a thin-end window or a beta window to perform surveys relating to the receipt, usage, and disposal of the P-32 stents.

The meter(s) will be calibrated according to our existing license conditions concerning survey meter operational check, use, and calibration.

Shielding Material

The P-32 stents are contained in a beta shielding material during transport and until placement occurs. When additional shielding is required lucite or plastic material will be utilized We will not use lead shielding in order to minimize bremsstrahlung production.

Dose Calibrator

We will not assay the P-32 stents in a dose calibrator since their activity is less than 10 uCi and is generally 1 (one) uCi per stent. We will verify that the shipping documents accompanying the stents show agreement of the activity per stent and the number of stents with the quantity and activity ordered.

Personnel Protective Equipment

Gloves will be worn by all personnel who handle the P-32 stents.
A radiation shield surrounds the stent during shipment and is kept in place until the stent is positioned for placement in the coronary artery.

P-32 Stent Program Only

PERSONNEL MONITORING PROGRAM

Item 9.4

The personnel directly participating in the P-32 Stent Placement procedure will be issued whole body film badges. The physician who is placing the stent will be issued a ring badge.

All other aspects of our personnel monitoring program as authorized by our current license will be followed.

RULES FOR THE SAFE USE OF P-32 STENTS

The P-32 stents are supplied by the manufacturer Iso-Stent in a radiation shield. The stents are not removed from the radiation shield until it is placed directly into the patient's vessel. Therefore, we have developed Rules for Safe Use of P-32 Stents. These rules will apply only to the P-32 Stent procedure.

1. Do not examine the stent itself outside of the radiation shield at any time.

2. Do not remove the radiation shield from over the stent at any time before the delivery catheter is advanced into the body.

3. If the radiation shield accidentally comes loose and the distal end of the delivery system becomes unshielded, slide the shield back over the stent's location and tighten the Tuohy-Borst fitting on the shield to lock the shield down.

4. Make sure to advance the delivery system forward into the body following loosening of the shield Tuohy-Borst.

5. If the stent delivery system has been advanced into the body, but for any reason the stent cannot be delivered, pull back the stent delivery catheter until the stent is inside the radiation shield, lock down the shield by tightening the shield Tuohy-Borst, return the device to its package, and return the opened package to the RSO for storage and disposal.

6. It the stent comes off of the catheter due to stent embolization, the physician should retrieve the stent using forceps or other remote retrieval devices when possible.

7. Once the stent is retrieved, it should be placed inside of the radiation shield if possible. If the radiation shield cannot be used, contact the RSO for a disposal container.

8. All personnel should avoid any direct handling of the bare stent with their fingers if possible. When direct handling is absolutely necessary, the use of surgical gloves should reduce the direct contact rate.

9. Wear disposable gloves at all times while handling the P-32 stent.

10. Either after each procedure or before leaving the area, monitor your hands and clothing for contamination in a low background area.

11. Use the radiation shields provided by the manufacturer until you are ready to complete placement directly into the patient's vessel. If the patient's condition does not allow the full use of the radiation shield until placement, the radiation shield will be used as long as possible and holding of the stent by personnel will then be minimized.

12. Do not eat, drink, smoke, or apply cosmetics in an area where P-32 stents are stored or when they are being used.

13. Do not store food, drink, or personal effects in areas where P-32 stents are stored and where they used.

14. The radiation shield and any other packaging material associated with the P-32 stent must be returned to the Nuclear Medicine Department for analysis before they can be disposed of. Place all of this material in a plastic bag or other container provided for this purpose.

15. Transport the P-32 stents from the receipt location (Nuclear Medicine Hot Lab) to the placment location only in a covered container.

16. Before transport, make a visual count of the number of stents to be transported in the container. Upon arrival at the placement location, make a visual count of the number of stents. If the number differs, implement the Emergency P-32 Stent Loss Procedure. Record these numbers on the P-32 Stent log.

17. Survey the placement room after P-32 placement is completed and after the patient has left, to ensure that no P-32 stent has been left behind. Record these results on the P-32 Stent log.

18. Store P-32 stents only in the original radiation shield and in original packaging material or other covered container. P-32 stents will only be stored in the Nuclear Medicine Hot Lab.

Item 10.5

EMERGENCY PROCEDURES FOR LOSS OF P-32 STENT

1. NOTIFY: Notify persons nearby that a stent is lost.

2. Do not allow anyone to leave the area until their clothing has been searched and they have been surveyed with a GM meter. Pay particular attention to cuffs, pockets, shoe bottoms, or anyother place where a stent may be trapped.

3. Do not allow additional personnel into the area.

4. Do not allow any items to be removed from the room until they have been visually searched and surveyed.

5. Begin a systematic survey of the area to ensure that no area is missed.

6. Contact the RSO for assistance.

7. Repeat the above searches and surveys until the source is found.

8. If necessary, retrieve all items and personnel who may have left the room between the time source was lost and its loss was noticed. If the source is still not located, track the paths of these personnel and items since the time they left the room and perform searches and surveys.

9. If the source is not located through all of the above measures, a report must be filed with the RSO who will determine the additional reporting requirements. The report must contain the sequence of events that allowed the loss of a stent and the actions taken to prevent recurrence.

KEEPING AN INVENTORY OF P-32 STENTS

Item 10.11

We will adopt Appendix M.4 "Keeping an Inventory of Implant Sources" that was published in Appendix M.4 to Regulatory Guide 10.8, Revision 2.

MODEL PROCEDURE

1. Use a locking installed cabinet or safe to store all implant sources.

2. Make a list of names of those individuals you allow to handle implant sources and have them initial beside their names.

3. N/A For long-lived sources, draw a map of the storage drawer and indicate the activity of the source at each storage point. For short-lived sources that you store in the manufacturer's shipping container, indicate the area in the safe where you put the container. Also, be sure to add the sources to the inventory log.

4. Post the map and the list of individuals whom you permit to handle the sources in the storage area or on the inventory log.

5. Each time you remove a source, make a record of the number and activity of sources removed, the room number of use or patient's name, and the time and date they were removed from storage; initial the record.

6. Each time you return sources to storage, immediately count them to ensure that every source removed has been returned. Then make a record of the number and activity of sources returned, the room number of use or patient's name, and the time and date they were returned to storage; initial the record.

7. If you ever perceive a discrepancy between the record and the number of sources in use and in storage, notify the RSO immediately.

~~See Exhibit 15 for a sample form you may want to use.~~

P-32 STENT LOG

Only the following individuals may handle these sources:

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Signed RSO_____ Date _____

Received on_____

_____ P-32 stents of ____ uCi per stent

			Number of P-32 stents						
Date	Time	Patient	in storage	removed	transported	implanted	returned	in storage	Initials

Post -placement Survey of patient: _____ mR/hr at 1 meter

Post-placement survey of room: _____ mR/hr maximum at any location

Survey of personnel directly involved in placement:

		_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	

Background radiation level: _____ mR/hr

Survey Meter used: Manufacturer: _____
Probe type: _____
Range used: _____ mR/hr

Signed RSO: _____

Borgess Medical Center
21-12275-02 Amendment Request
1996

RADIATION SAFETY PROCEDURES FOR P-32 CORONARY ARTERY STENTS

Item 10.15

The P-32 Palmaz-Schatz Balloon Expandable IsoStent has been approved by the FDA for human clinical trials to be permanently placed in coronary arteries. Each stent will contain typically 1 uCi of P-32 (never more than 10 uCi) and is prepared by the manufacturer.

Due to the low activity and the beta-emitting properties of P-32, these patients will not be a source of radiation to nursing personnel or the public. Therefore, we will not implement the Radiation Safety Procedures for Temporary Implant Therapies.

These stents are placed within a coronary artery, therefore, there is no chance that a source could dislodge from within the patient's body and become a hazard to nursing personnel. Therefore, we will not instruct nursing personnel in the appearance or proper handling of a loose P-32 stent.

The patient will be surveyed using a GM meter with an end-window or beta window probe. This survey will be conducted after the placement of the stent is completed. If the results are less than 5 mR/hr at 1 meter, the attending physician will be notified that the patient may be released whenever their clinical condition allows.

Any patient measuring over 5mR/hr at 1 meter will not be discharged from the hospital. Please note, this is not a possible scenario due to the low amount of beta emitting material in the stent. However, we note that this is a requirement of 10CFR35 and will operate in accordance with it.

Borgess Medical Center
21-12275-02 amendment request
1996

Item 12.1

P-32 Stent Program Only

Quality Management Program

We will follow our existing Quality Management Program for the use of the P-32 stents.

The written directive for P-32 stent placement will contain the following information.

Patient name	_____
Patient id number, if available	_____
Radioisotope and form	"Permanent placement of P-32 Palmaz-Schatz Balloon-Expandable IsoStent"
Indication	"permanent placement to help maintain the patency of stented coronary arteries"
Placement site	_____ (artery)
Activity per stent	_____
Date of placement	_____
Signature of authorized user for P-32 stents	_____
Date of signature	_____

Reference Material for P-32 IsoStent

Appendix 5.1

Training Guidelines for Radiation Safety

The P32 IsoStents to be used for the IRIS Phase I feasibility study will have between 0.5 and 1 μCi of phosphorous-32 embedded beneath the surface of the stent metal. Each stent will be crimped onto a balloon angioplasty catheter, covered with a sheath and a 1 inch diameter clear plastic radiation shield will be locked over the distal section of the catheter containing the stent.

During the phase I trial only NRC broad scope license institutions may participate. As a result specific radiation training and handling requirements will vary for each institution.

This appendix is written to provide a basic set of safety guidelines for the Radiation Safety Officer (RSO) to use in training each investigator.

1. **Device Tracking**

   Each radioisotope stent must be tracked from the time it arrives at the institution until the patient is discharged. Each RSO should instruct the investigator as to the appropriate institutional protocols for radioactive source tracking.

   Each radioisotope stent must be stored under lock and key with restricted access. The RSO should instruct the investigator as to the appropriate institutional protocols for such device storage, removal for use, and return to storage of unopened packages.

   The RSO should instruct the investigator as the appropriate institutional protocols for the return of stent packages which have been opened. The RSO is responsible for the disposal of the opened but unused stent according to standard procedures for 1 μCi of P32.

2. **Device Handling**

   The Directions for Use which describe the handling methods for the stent delivery system will be included in each stent package. The RSO should go over the section below which specifically refers to the steps associated with the radiation shield.

   Verify the position of the sheath over the stent. Inject saline through the sheath to purge the system and to facilitate sheath withdrawal. Push the distal end of the radiation shield into the Tuohy-Borst adapter fitted to the guiding catheter, then tighten the Tuohy-Borst to secure the radiation shield. Next, loosen the Tuohy-Borst on the radiation shield and advance the rhomboid stent/balloon assembly over the 0.014" exchange wire into the guiding catheter and then to the site of the previously dilated lesion. After advancement of the stent delivery system remove the lock-out device from the back-end of the stent delivery system and loosen its Tuohy-Borst valve.

The RSO should instruct the investigator to take the following precautions during the procedure.

- Make sure to advance the delivery system forward into the body following loosening of the shield Tuohy-Borst
- Do not remove the radiation shield from over the stent at any time before the delivery catheter is advanced into the body. If the radiation shield accidentally comes loose and the distal end of the delivery system becomes unshielded, slide the shield back over the stent's location and tighten the Tuohy-Borst fitting on the shield to lock the shield down.
- Do not examine the stent itself outside of the radiation shield at any time.
- If the stent delivery system has been advanced into the body, but for any reason the stent cannot be delivered, pull back the stent delivery catheter until the stent is inside the radiation shield, lock down the shield by tightening the shield Tuohy-Borst, return the device to its package, and return the opened package to the RSO for disposal.
- If the stent comes off of the catheter due to stent embolization, the investigator should retrieve the stent using standard techniques. Once the stent is retrieved, it should be placed inside of the radiation shield if possible, and if not the RSO should be contacted to provide an appropriate disposal container. The investigator and other cath lab personnel should avoid any direct handling of the bare stent with their fingers if possible. If not possible, the wearing of surgical gloves should reduce the direct contact dose rate for a 1 μCi P32 stent to less than 100 mrem per minute.

3. Radiation Principals

The RSO should provide some instruction to the investigators as to basics of radioisotope emissions. This should include the following:

- The units of radioactivity (e.g. microCuries, Rads, cGy)
- The aspects of natural radioactivity (e.g. beta vs. gamma, half-life, average and peak particle/photon energy)
- The specific attributes of phosphorous-32
- Dose to tissue for the P32 stent. This information will be provided by IsoStent and is contained in the submitted paper (See Appendix 5.4 of this Supplement).

It is anticipated that the entire training as described above should take several hours to complete.

APPENDIX L3

RADIATION SAFETY CONSIDERATIONS FOR HEALTH CARE WORKERS FROM A P-S ISOSTENT

The first clinical trial for the radioisotope stent will use a JJIS, Palmaz-Schatz stent with a maximum radioactivity level of 1.0 microCurie of the isotope phosphorous-32 (P-32). The purpose of this Appendix is to provide a comparison of radiation activities and doses from this device as compared other sources of radiation with regard to safety of the health care workers involved in the procedure.

The following facts illustrate the extraordinarily low level of radiation associated with the 1.0 microCurie radioisotope stents.

1. Since the stent comes with a radiation shield that reduces the emitted radiation to a value approximately equal to background radiation, no health care worker will be exposed to any radiation hazard what-so-ever.

2. Stray radiation to the cath lab personnel from the fluoroscopy during any balloon angioplasty or stent implantation procedure will certainly be more that a 1,000 times greater than the radiation dose received from the P-32 stent.

3. The Nuclear Regulatory Commission allowed "safe dose" for workers in the field (such as the implanting physician) is an annual P-32 ingestion of 600 microCuries. Thus the physician could (theoretically) eat 600 P-32 radioisotope stents each year and stay within the NRC limits. Of course that is absurd, but it gives a feeling for how safe these ultra-low radiation levels are from the stent.

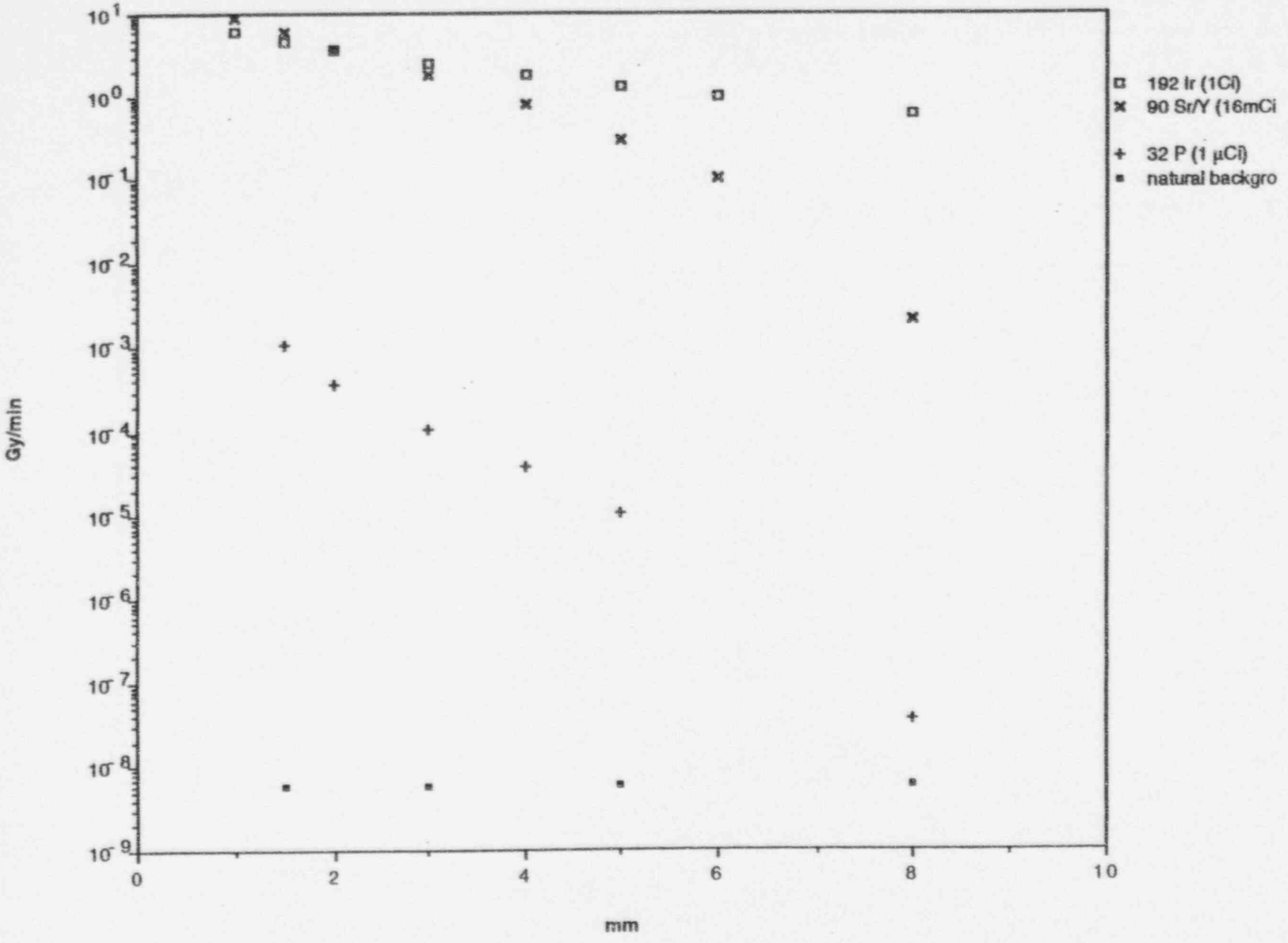
4. If a stent is ever lost, its activity level becomes undetectable as compared to background at approximately five months after it is manufactured. It therefore poses no possibility of a long term hazard as could be the case for long-lived isotopes.

5. A physician could hold the stent in his hand or sit on it for a year (or longer) and it would pose no hazard to his health.

Figure L3 is a chart providing comparative dose rate vs. distance in tissue information for natural background radiation, I192 afterloaders, Sr90/Y90 afterloaders (Novoste), and the 1 μCi P32 stent. It should be noted that the P32 stent dose rate is already near background at a distance of only 8 mm from the device.

FIGURE L3

dose rate vs distance from 'therapy' sources



APPENDIX L6

POTENTIAL FOR P32 LEECHING OUT OF THE STENT

A potential area of concern with a radioisotope stent is in the permanence of the radioisotope's attachment to the stent. The possibility that a significant amount of the P32 atoms will leech out of the stent must be addressed.

From a theoretical standpoint, for P32 atoms to leech out, the P32 atoms must diffuse first from their location inside of the metallic structure to the surface of the stent. The diffusion of impurities in materials results from random motion of the atomic constituents, and particles diffuse in the direction of decreasing concentration gradient. However, the diffusion of impurities in semiconductors and in metals is significant only when the temperature is very high (~1000° C) and is practically zero at room or body temperature. Therefore, since no mechanism other than diffusion could result in P32 atom migration inside the metallic lattice, one can consider the P32 impurities as permanently embedded into the material with no leeching except for the very first monolayer of the substrate.

In vitro experiments carried out both at the Forschungzentrum Karlsruhe and at facilities at Hopital Notre-Dame in Montreal, Canada indicate that leeching is limited to less than 1% for a P32 ion implanted Palmaz-Schatz stent, an amount consistent with that contained in the first monolayer. Otherwise, the P32 atoms will not leech out unless the stent is chemically dissolved into the blood stream or the soft tissues. This is not likely to occur, since the biocompatibility of the stainless steel has been demonstrated thoroughly in the past.

In addition, as a result of the experiments at the Forschungzentrum Karlsruhe, an optimal post implant washing procedure has been developed which removes approximately 70% of the P32 that can leech out. This results in a potential leeching out in the body of much less than 1% of the total stent activity. This would be less than 10 nanocuries for a 1 microcurie stent and is insignificant compared to the natural radioactivity of the human body.

Appendix 6

Description and Data from Stent Washing Tests

Although the P32 ion implanted into stents is almost entirely embedded below the surface, there is a single layer of phosphorous atoms (approximately 1% of the total activity) on the surface which contains the only P32 which can ever be washed off the stent. Although essentially all of the P32 is on the outer surface of the stent which is embedded in the arterial wall and not subject to the potential washing effects of the blood, it is important to test a worst case scenario where both the outside and inside of the stent are washed.

Between December 1995 and February 1996 washing experiments were conducted at the Forschungszentrum Karlsruhe (Fzk), the German research center where the stents are ion implanted. The object of these experiments was to develop a stent washing process which would remove most of the P32 that could possibly come off the stent.

In these experiments 10 half Palmaz-Schatz stents were ion implanted with an average activity of 11 μCi . This is more than ten times the activity that will be implanted per mm of length in the IRIS trial.

Early experiments showed that the best technique for removing leachable P32 from the stent surface was to ultrasonically wash the stents in 0.9% NaCl solution at 42° C for 15 minutes. These experiments also showed that the washout amount was independent of stent P32 activity and of whether the stents were expanded.

The table below shows for three of the stents which were first ultrasonically washed as described above and then washed in a NaCl solution for 65 days including 38 hours in which ultrasonic washing was used to attempt to maximize washout. The washout during the NaCl wash and the total amount washed out in 65 days are shown. It should be noted here that in an artery, a stent would become encapsulated by tissue in far less than 65 days.

Stent No.	Initial 15 min. NaCl solution washout (%)	65 day washout (%) after initial 15 min.	Total 65 day washout (%) in NaCl Solution	% of the total 65 day wash out removed by the initial 15 minute NaCl wash
K 5.13	0.9	0.20	1.10	82
K 5.15	0.7	0.23	0.93	75
K 5.17	1.5	0.37	1.87	80
Average Values				79

* The total 65 day washout includes the initial 15 minute NaCl washout amount.

It should be noted that although there was some variation on the total amount washed out, the post wash amount was always significantly less than 1% and the NaCl ultrasonic wash took out at least 75 % of the removable P32.

Even a less effective washing step using Alcohol instead of NaCl kept the post wash washout below 1%. This is seen in the table below.

Stent No.	Alcohol Solution washout (%)	Post Alcohol washout (%)	Total 65 day washout (%)	% of 65 day wash out removed by Alcohol wash
K 5.14	0.9	0.32	1.82	49
K 5.16	0.2	0.72	0.92	10
K 5.18	0.2	0.52	0.77	26
Average Values				28

Here it is seen why the NaCl wash is preferred. Not only is it more effective but it is more consistent in its removal of washable P32 from the stent surface.

The table that follows shows the NaCl wash results from the most recent batch of full Palmaz-Schatz stents where the activities range from 7.0 μCi to 30.7 μCi.

Stent No.	Stent Activity (μCi)	NaCl Solution washout (%)
K 8.1	7.0	0.39
K 8.2	22.5	0.50
K 8.3	22.1	0.37
K 8.4	18.2	0.37
K 8.5	19.8	0.44
K 8.6	17.6	0.40
K 8.7	8.8	0.42
K 8.9	11.1	0.67
K 8.11	9.0	0.60
K 8.12	30.4	0.37
K 8.13	30.7	0.29
K 8.14	10.3	0.70
K 8.16	11.1	0.40

It is clear from this lot of full stents, that the stent activity is not a factor in the % removed during NaCl washing. To keep the maximum body washout below 1% of the total activity we have set a quality standard for the IRIS trial, to not accept any stent where the NaCl wash removes more than 2% of the total activity. This is based on the initial test results where 15 minutes of NaCl ultrasonic washing removed more than 70% of the total activity that could ever come off the stent.

It should be noted, that the measurements for long term washout following the NaCl wash provided ultrasonic wash cycles where the wash solution was in contact with the outer surface of the stent (where the P32 is embedded). This is clearly a very worst case as implanted stents are embedded in the arterial wall where the outer surface is not exposed

to blood flow. What is more, the entire stent should become encapsulated with tissue within a few days of implant, even further reducing the probability of P32 wash out.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 28 1996

Ms. A. Jill Schweiger
Vice President, Regulatory and Clinical Affairs
IsoStent, Incorporated
957 P Industrial Road
San Carlos, California 94070

Re: IDE Number G960087
Palmaz-Schatz™ Balloon-Expandable IsoStent™ with Delivery System
Indications for Use: The device is intended to help maintain the patency of stented coronary arteries.
Dated: April 30, 1996
Received: May 1, 1996
HCFA Reimbursement Category: B3

Dear Ms. Schweiger:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. Your application is conditionally approved, and you may begin your investigation, using a revised informed consent document and a revised study protocol which corrects deficiency number 1-R. This investigation may be conducted at an institution after you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA.

Your investigation is limited to three institutions and thirty subjects.

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

1. Please address the following issues regarding the clinical protocol:

   a. With respect to study objective A, please identify specific safety and efficacy endpoints with definitions for "acute or subacute effects." FDA suggests that you include the following: subacute thrombosis, myocardial infarction, revascularization, death and neutropenia secondary to ticlopidine. Also, how is restenosis to be defined? The case report

forms should be structured to capture the appropriate information for each of the endpoints.

b. For study objective B, what specific radiation safety training will be provided to the Principal Investigator (PI) and the catheterization laboratory staff? Will the devices be implanted by the PI only? How much previous experience with implantation of Palmaz-Schatz stents is required? What specific radiation safety information will be given to the patients?

c. The study inclusion criteria do not include clinical symptoms or syndromes. The case report forms (CRFs) suggest that patients with unstable coronary artery disease syndromes such as unstable angina and evolving myocardial infarction be included in this Phase I safety study. The potential synergy of increased thrombogenicity due to delayed endothelialization in the presence of unstable plaques with thrombus is unknown. Since the safety of radioactive stents has not been demonstrated in any patient population, FDA believes that the Phase I safety study be completed in patients with stable coronary artery syndromes to minimize patient risk. FDA also believes that stenting should be limited to 1 coronary artery per patient. Sequential stents covering a lesion length of up to 26-28 mm is acceptable. In the event of an unexpected increase in thrombogenicity and subacute thrombosis, stenting of 2 coronary arteries may place patients at undue risk. Please revise your protocol accordingly.

d. Please justify inclusion of patients with only a 50 percent diameter coronary artery stenosis. Must these patients also present with clinical symptoms in order to qualify for inclusion? Also, given that FDA's Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices defines success as a >20 percent change in luminal diameter with a final diameter stenosis <50 percent, how will acute procedural success be documented in these patients? This definition would require an initial minimum diameter stenosis of 70 percent in order for a procedure to be characterized as a success.

e. Please add contrast hypersensitivity as an exclusion criterion. What level of renal insufficiency will be excluded to minimize risk for contrast induced renal failure?

f. Although less than 10 nanocuries of P32 are expected to leech out of the stent based on the data in Appendix L6, lactating women should be excluded. Please revise exclusion criterion (n) to read "Pregnant, lactating and women of childbearing potential .....".

g. Section 2.2.G states that patients will complete evaluations at the following intervals: pre-procedure, immediately post-procedure, and at 1, 6, and 12 months post-procedure. Appendix A indicates that patients will have white counts checked at 2, 4, and 6 weeks post-procedure. Please include in the protocol a flow diagram and table indicating all time points and studies that patients will complete during follow-up. Since the safety and efficacy of radioactive stents is unknown, FDA believes that long-term follow-up at yearly intervals is required in these patients until the IDE is closed.

h. Section 2.3.D indicates that ticlopidine will be administered for 6 weeks post-procedure to minimize the risk of acute and subacute thrombosis. If the risk period for acute and subacute thrombosis exists for up to 6 weeks (45 days), why is the safety data for these endpoints being collected at 30 days? Please clarify this discrepancy.

i. In Appendix A-Section 6, please identify the primary study endpoints (clinical and technical) and provide appropriate definitions.

j. In Appendix A-Section 7, please enclose the autopsy protocol. Also, the consent form should be modified to state that an autopsy will be requested in the event of patient death for examination of the heart.

k. In Section 8, Appendix A, please identify the criteria to be used to determine that there are no unanticipated adverse device effects within the first 30 days following the 30 procedures. For example, are you going to compare the incidence of subacute

thrombosis, myocardial infarction, revascularization, and death in this patient group to similar data for nonradioactive Palmaz-Schatz stents?

1. The labeling indicates that a cardiac surgery team will be on standby during stent implantation. Please modify the protocol to include this requirement. Further, please provide documentation that surgical standby is available at each participating medical center.

m. The labeling indicates that MRI is contraindicated for 8 weeks after stent implantation. Please specify this in the patient consent form.

n. FDA suggests that the inclusion and exclusion criteria be incorporated in the form entitled "Case Summary Form" (Appendix C2) to facilitate patient evaluation and completion of the form. Please list ticlopidine as a discharge medication. The section on Site Description(s)/Coronary list the vessel types as native and gratt. Please clarity this discrepancy since the protocol includes native vessels only.

o. Please modify the CRFs to include follow-up for ticlopidine induced neutropenia.

p. The protocol indicates that IVUS measurements will be made at the time of cardiac catheterization. Please modify the CRFs to include this data and the measurements to be derived from the data.

q. In Appendix C4, anginal pain is classified using the CCS scale. Please modify the protocol and all CRFs to ensure that this classification is used in a consistent manner.

2. The following modifications should be made in the patient consent form:

a. The language in the patient consent form is too technical and complex for the average lay person. Medical and scientific terms are used without any definitions or explanations. Please simplify the language so that it can be understood by a person with an 8th grade education.

b. FDA suggest that the consent form be organized in the following sections: Introduction, Purpose of Study, Description of Procedures, Follow-up, Risk, and Potential Benefits.

c. Please clearly specify the following items: (i) this study involves research; (ii) radioactive stents have not been previously used in humans and the purpose of the study is to determine the safety of these devices in humans for the first time and; (iii) the use of radioactive stents may involve risks to the patient which are currently unforeseeable.

d. The number of subjects participating in the study should be stated in accordance with CFR Part 50.25.

e. The information provided in Tables 1, 2, and 3 is uninterpretable as presented to the average lay person. This information should be explained in simple text form. The risk section should also include known information on the possibility of radiation induced coronary artery damage such as long-term fibrosis and aneurysm formation.

3 Please address the following issues regarding the P32 isotope and the engineering of the device:

a. You have stated that a washing process removes most of the P32 not fully embedded. Please explain your validation process of 1 percent removable activity. Also, how is the amount of removable activity routinely monitored?

b. The source activity is measured by "traceable" means. However, no information is provided regarding how the activity is determined. Please clarify how the source activity is determined.

c. A Monte Carlo calculation was done to estimate the dose from the implanted P32 isotope in the stent. Please provide experimental verification of this calculation.

d. Please explain how the local institution will independently validate the stent's activity before use (see page 18, last paragraph).

e. The criteria for uniformity of activity distribution over the stent surface is ±20 percent. Please clarify if this uniformity is along the length of the stent or on the surface (or at 0.1 micron depth).

f. There is no mention of correction due to absorption within the implant layer of the stent. Considering that the ions are implanted at a depth of 0.1 micron, please discuss what effect this absorption will have on the dose levels predicted by the Monte Carlo calculation.

g. Please specify the thickness of the plastic safety shield and clarify whether the shield actually comes in contact with the stent.

The following additional deficiencies were noted during the review of your application and must be addressed before any expansion of the study can be considered:

1. Since one of the Principal Investigators and the "independent" angiographic core laboratory are located at the same institution, please explain how this does not represent a conflict of interest? What safeguards are used to ensure "independent" function of the core laboratory? Further, since this core laboratory analyzes data for multiple clinical studies, what safeguards are used to ensure appropriate data set management? For example, what steps will be taken to ensure that your data set includes data for your patients only? In addition, please provide the operating manual for the core laboratory.

2. Please address the following concerns regarding the device labeling:

   a. Labeling for the device should follow the format outlined in the Device Labeling Guidance (enclosed). Please revise your labeling as appropriate.

   b. Please modify the labeling to incorporate the revised inclusion and exclusion criteria.

   c. FDA suggests that you consider giving each patient a device identification card similar to pacemaker patients indicating that they have a radioactive stent and MRI is contraindicated for 8 weeks post-implantation.

e. The criteria for uniformity of activity distribution over the stent surface is ±20 percent. Please clarify if this uniformity is along the length of the stent or on the surface (or at 0.1 micron depth).

f. There is no mention of correction due to absorption within the implant layer of the stent. Considering that the ions are implanted at a depth of 0.1 micron, please discuss what effect this absorption will have on the dose levels predicted by the Monte Carlo calculation.

g. Please specify the thickness of the plastic safety shield and clarify whether the shield actually comes in contact with the stent.

The following additional deficiencies were noted during the review of your application and must be addressed before any expansion of the study can be considered:

1. Since one of the Principal Investigators and the "independent" angiographic core laboratory are located at the same institution, please explain how this does not represent a conflict of interest? What safeguards are used to ensure "independent" function of the core laboratory? Further, since this core laboratory analyzes data for multiple clinical studies, what safeguards are used to ensure appropriate data set management? For example, what steps will be taken to ensure that your data set includes data for your patients only? In addition, please provide the operating manual for the core laboratory.

2. Please address the following concerns regarding the device labeling:

   a. Labeling for the device should follow the format outlined in the Device Labeling Guidance (enclosed). Please revise your labeling as appropriate.

   b. Please modify the labeling to incorporate the revised inclusion and exclusion criteria.

   c. FDA suggests that you consider giving each patient a device identification card similar to pacemaker patients indicating that they have a radioactive stent and MRI is contraindicated for 8 weeks post-implantation.

3. Information presented in Table 1 (and in Appendix L1, etc.) suggests that as the 3.0 mm stent expands its length increases to 15.1 mm. Please explain how this is possible or verify that this is simply a typographical mistake.

4. FDA recommends that Nuclear Regulatory Commission (NRC) be contacted for advice regarding NRC, state, and local authority licensure of the PALMAZ-SCHATZ™ Balloon-Expandable IsoStent™ for the clinical study that you are proposing. Attachment C of the Intravascular Brachytheraphy Guidance Document (enclosed) specifies the appropriate NRC contact.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

We would like to point out that FDA approval of your IDE application does not imply that this investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597.

We have enclosed the guidance document entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Also enclosed is the guidance document "Investigators' Responsibilities for a Significant Risk Device Investigation" which you should provide to participating investigators.

If you have questions, please contact H. Semih Oktay, Ph.D., at (301) 443-8243.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

From: James Smith (JAS4)
To: NCD2.CH2.ERM
Date: Tuesday, July 16, 1996 4:13 pm
Subject:

Dixie-

The following is the text that was included in the FDA Guidance.

NRC Regulations and Requirements Relating to Brachytherapy Treatment of Restenosis

Currently, 10 CFR Part 35, Medical Use of Byproduct Material does not permit the use of brachytherapy sources for intravascular uses. Therefore, these treatments currently could only be performed under a broad scope license or at a facility with a limited specific license which has received an exemption from the requirements of 10 CFR 35.400, Use of Sources for Brachytherapy.

Many broad scope licensees are authorized to use isotopes with atomic numbers 3-83 for medical research, diagnosis and therapeutic uses in individual quantities not to exceed 1 curie. These licensees would be authorized to perform medical research into brachytherapy treatment of restenosis, provided that the licensee complies with the requirements of 10 CFR 35.6, Provisions for Research Involving Human Subjects. These licensees should be reminded that, for any research not conducted, funded, supported, or regulated by a Federal Agency that has adopted the Federal Policy, the licensee must apply, in accordance with 10 CFR 35.6, for a specific amendment before conducting research involving human subjects. Additionally, some broad scope licenses are written to restrict the use of brachytherapy sources to the treatment of cancer; therefore, use of the sources for treatment of restenosis would require an amendment to the license. Broad scope licensees should review the authorizations for the use of brachytherapy sources on their licenses.

Limited specific licensees seeking authorization to perform these procedures must apply for an exemption from the requirements of 10 CFR 35.400, Use of Sources for Brachytherapy. This application must address the training and experience of the individuals involved in treatment delivery. Individuals performing these treatments must either meet the training and experience requirements of 10 CFR 35.940, Training for Use of Brachytherapy Sources, or be supervised by such an individual. It is anticipated that due to the complexity of these procedures, a team approach will be used, which would include a radiation oncologists, a cardiologist, a medical physicist, and possibly a cardiac surgeon.

In addition to the requirements regarding brachytherapy found in 10 CFR Part 35, licensees wishing to use remote afterloading brachytherapy units may need to address additional requirements found in Policy and Guidance Directive FC 86-4., Information for Licensing Remote Afterloading Devices . These requirements include establishing provisions to perform emergency surgical procedures for the removal of dislodged sources within the patient and the presence of an authorized user physician, radiation safety officer, or medical physicist during the treatment of the patient.

From: James Smith (JAS4)
To: NCD2.CH2.ERM
Date: Tuesday, July 16, 1996 4:22 pm
Subject: P-32 stent use

Dixie-

I spoke with Sally Merchant, and she doesn't believe that the exemption could be processed by August 1.

Jim

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

June 4, 1996

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

FROM: Patricia G. Norry, Director
Office of Administration

SUBJECT: PETITION FOR RULEMAKING (PRM-35-14) FILED BY ISOSTENT, INC.

Attached for your review is a petition for rulemaking (PRM-35-14) filed with the Commission by IsoStent, Inc. Please determine whether this petition qualifies for special handling by the staff as a fast-track petition for rulemaking as specified in 10 CFR 2.802(e). Also attached is Section 11.7 of the NRC Regulations Handbook (NUREG/BR-0053) that contains information to assist in this determination.

If your office determines that PRM-35-14 should not be handled as a fast-track petition, please provide your comments and concurrence on the attached draft notice for the Federal Register and let us know the name of the staff member you designate as task leader for action on the petition by June 7, 1996.

If you have any questions about this petition, please have a member of your staff contact Michael T. Lesar, 415-7163, or Betty K. Golden, 415-6863, of the Division of Freedom of Information and Publications Services.

Attachments:
1. PRM-35-13
2. Section 11.7 of the NRC Regulations Handbook
3. Draft Federal Register Notice

IsoStent, Inc.

May 9, 1996

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

Attn.: Chief, Docketing and Service Branch

re: **Petition for Rulemaking**

Dear Mr. Secretary:

Pursuant to Part 2.802 of Title 10 of the Code of Federal Regulations, IsoStent, Inc. respectfully requests that the Nuclear Regulatory Commission amend its current regulations under Part 35 in order to address an innovative approach for the treatment of stenotic arteries and vessels with low-activity, beta-emitting stents. Preliminary data indicates that stents combined with a low-activity, beta-emitting source (less than 3 microCuries per millimeter of length) may significantly reduce restenosis (renarrowing) of the vessel following therapeutic intervention. It is estimated that "the total societal costs of restenosis in the United States alone is somewhere between 800 million and 2 billion dollars a year," (refer to "Discoveries in Radiation for Restenosis," presented at Emory University, January 11-12, 1996).

Since radioactive stents could have a significant beneficial impact, not only on the healthcare system, but on the quality of life of patients who suffer from this condition, we believe that it is important to ensure that they are appropriately classified and regulated. We have reviewed the existing categories pertaining to the medical uses of byproduct materials and have determined that a new category is necessary to address permanently implanted radioisotope intraluminal stents. These stents would have less than 3 microCuries of beta-emitting isotope (e.g. Phosphorous 32) per millimeter of length. Thus, standard coronary stents, 15 millimeters in length would contain less than 20 microCuries (740 kBq) of beta-emitting isotope. However, longer and larger diameter stents will be required for other anatomical sites, but all of these will contain less than 3 microCuries of beta-emitting isotope per millimeter of length.

357 Industrial Road • San Carlos, California 94070
Tel: (415) 593-2567 • Fax (415) 593-4479

The existing regulations do not include Phosphorous 32 and Strontium 89 as a sealed source for medical therapeutic use; therefore, these devices would be regulated under Title 10, Subpart G, section 35.400 "Use of sources for brachytherapy." These sources are used for traditional brachytherapy and require expert knowledge of dwell time and dose calculations, as well as, extensive radiobiology, radiation physics, and radiation protection. We believe that this category is not appropriate to control low-activity, beta-emitting stents for the following reasons:

1) Training and Competency Requirements

1.1) Low-activity, beta-emitting stents differ significantly from those sources that are used for traditional brachytherapy. Traditional brachytherapy sources have higher activity and require significant dose calculations; thus, to be used safely, the traditional brachytherapy sources require extensive knowledge in radiobiology, radiation physics, and radiation protection. The low-activity beta-emitting stents do not require this same level of radiation expertise, because they have significantly lower radioactivity levels and are permanently implanted devices that do not require any calculation of dose or dwell time.

1.2) Under the current regulations, any procedure using a source defined under section 35.400 would require the supervision of a certified radiation oncologist. Stents are currently prescribed and implanted by physicians trained in cardiovascular specialties, and once given required training in the proper handling of these low dose-rate, beta-emitting sources, could safely and effectively implant radioactive stents. Access to low-activity, beta-emitting stents should be allowed to those physicians who are already certified for stent implantation specialties. Requiring the additional oversight of a radiation oncologist for these stent applications, could potentially limit the accessibility of this technology and add significant cost to each procedure which would unnecessarily burden the medical system.

2) Safety Requirements

Low-activity, beta-emitting stents can be shielded with approximately one centimeter of plastic material and have shorter half-lives of less than two months, as compared with other sources. Thus, as shielded, these materials should not pose a significant hazard to the public or medical staff. Also note that the radioactive stent remains within the shield until it is passed into the patient by means of a stent delivery catheter. Once in the patient, these beta emitters are shielded by the patient's tissues, and because of the shorter half-lives, do not represent a significant long term risk to the public or medical personnel. A precedent for the release of patients with such short half-life sources has been set with sources such as Iodine 125 seeds which have a 60 day half-life and 10^3 to 10^4 times higher activity per seed, as well as, the more penetrating photon radiation.

3) Facility Licensing Requirements

Access to low-activity, beta-emitting stents should be allowed to non-broad scope licensed medical facilities. Under current regulations, radioisotope stents could only be utilized by facilities with a broad scope license. There are a large number of medical facilities that currently implant stents, that do not meet these licensing requirements. Maintaining these licensing requirements could also limit the accessibility of this technology.

Based upon these issues, this petition specifically requests:

1) an amendment to 10 C.F.R. § 35 to include a new section for "permanently implanted intraluminal stents." These are to include Phosphorous 32 and Strontium 89 radioisotope stents. And as the proposed title implies, these sources are to be implanted in the patient's vessels and arteries and be capable of being left permanently. These "sealed sources" will have removable contamination that will be less than 1% of the total device activity. The total device activity will be less than 3 microCuries of beta-emitting isotope per millimeter of stent length; and,

2) a new category of training and experience should be created which requires that the stents be placed in the patient by a licensed physician who:

2.1) is certified either:

2.1) by the American Board of Radiology in diagnostic radiology with additional specialization in intravascular radiology; or

2.2) by the American Board of Internal Medicine with special competence in cardiology; and

2.2) who has received 8 hours of classroom and laboratory training in the basic handling of beta-emitting sources.

I appreciate your prompt review and consideration of our petition. Also, since this technology has a potentially large benefit to patients, as well as, the healthcare system, we would like to request that our petition be considered for an expedited review. If you have any questions or require any additional information, please feel free to contact me at 415-593-2555.

Sincerely,

Jill Schweiger,
Vice President,
Regulatory & Clinical Affairs

EMORY UNIVERSITY
SCHOOL OF MEDICINE

The Robert W. Woodruff Health Sciences Center

DISCOVERIES IN RADIATION FOR RESTENOSIS

Presented by

THE ANDREAS GRUENTZIG CARDIOVASCULAR CENTER
AND
THE DEPARTMENT OF RADIATION ONCOLOGY OF
EMORY UNIVERSITY SCHOOL OF MEDICINE

Course Directors

SPENCER B. KING, III, M.D. - RON WAKSMAN, M.D. - IAN CROCKER, M.D.

Selected Literature

J.W. MARRIOTT HOTEL
AT LENOX
Atlanta, Georgia

JANUARY 11-12, 1996

Andreas Gruentzig Cardiovascular Center and the
Department of Radiation Oncology of Emory University
Presents

DISCOVERIES IN RADIATION FOR RESTENOSIS

The first international workshop devoted to this exciting new field

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at
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ATLANTA, GEORGIA

- Mechanisms of Restenosis
- Basic Radiobiology
- Physics of Radiation
- Radiation for Restenosis in Animal Models
- Stents and Radiation
- Endovascular Radiation in Peripheral Vascular System
- Endovascular Radiation in Human Coronary Arteries
- Industry Demonstration of New Devices
- Economic and Regulatory Issues

11.7 Petitions eligible for "fast-track" processing.

(a) Occasionally, the NRC receives a petition for rulemaking that requests an amendment to the regulations that is obviously meritorious. In order to expedite the rulemaking process, these petitions for rulemaking may be published initially for public comment as a proposed rule. This "fast-track" procedure eliminates the usual step of publishing a notice of receipt of a petition for rulemaking and inviting public comment on the petition when this additional procedural step is unnecessary. "Fast-track" petitions are processed by the staff according to the procedures specified in this section and 11.9 of this handbook. The "fast-track" procedure may not be used for the expeditious denial of a petition for rulemaking.

(b) Following a determination that a petition for rulemaking meets the threshold requirements for a petition, RRDB assigns the petition to the appropriate staff office to determine whether the petition is eligible for "fast-track" processing. The staff office assigns a contact person to handle the petition. The staff office makes the "fast-track" determination within 10 working days.

(c) The NRC may consider a petition eligible for "fast-track" processing if it --

(1) Proposes action granting or recognizing an exemption from requirements in 10 CFR Chapter I or granting relief from restrictions while not imposing additional burdens upon or increasing the risks to the health and safety of any segment of industry or the public;

(2) Proposes action involving interpretive rules, rules of agency organization, procedure, or practice, and rules for the orderly conduct of Commission business;

(3) Proposes action involving an amendment to 10 CFR Chapter I that is corrective or of a minor or non-policy nature and that does not substantially modify existing regulations;

(4) Proposes action involving --

(i) A minor safety, safeguards, or environmental issue;

(ii) An increase in NRC efficiency; or

(iii) A reduction in the regulatory burden on licensees.

(5) Proposes action involving a request already under consideration in an ongoing rulemaking proceeding (Note, however, that NRC consideration of a request already included in an ongoing rulemaking depends on the status of the rulemaking proceeding); or

(6) Proposes other action that is clearly meritorious and will not adversely affect the rights of other licensees or persons.

(d) The NRC normally will not consider a petition eligible for "fast-track" processing if the proposed action will --

(1) Require the preparation of an Environmental Impact Statement;

(2) Impose new or increased reporting, application, or recordkeeping requirements subject to clearance by the Office of Management and Budget;

(3) Have a significant economic impact on a substantial number of small entities (see discussion of Regulatory Flexibility Act requirements in sections 3.19 and 5.19 of this handbook),

(4) Have a significant impact on NRC staff and resource commitments; or

(5) Result in denial of the petition for rulemaking.

[7590-01-P]

NUCLEAR REGULATORY COMMISSION

10 CFR Part 35

[Docket No. PRM-35-14]

IsoStent, Inc.,
Receipt of a Petition for Rulemaking

AGENCY: Nuclear Regulatory Commission.

ACTION: Petition for rulemaking; Notice of receipt.

SUMMARY: The Nuclear Regulatory Commission (NRC) has received and requests public comment on a petition for rulemaking filed by IsoStent, Inc. The petition has been docketed by the Commission and assigned Docket No. PRM-35-14. The petitioner requests that the NRC amend its regulations by adding a new section to address permanently implanted intraluminal stents, including phosphorus-32 and strontium-89 radioisotope stents. These stents would be permanently implanted in the patient's vessels and arteries. The petitioner also requests that the NRC add a new section to specify training and experience requirements for qualified physicians responsible for placing radioisotope stents in patients. The petitioner believes the suggested amendments would address an innovative approach for the treatment of stenotic arteries and vessels with low-activity, beta-emitting stents.

DATE: Submit comments by (75 days after date of publication). Comments received after this date will be considered if it is practical to do so, but assurance of consideration cannot be

given except to those comments received on or before this date.

ADDRESSES: For a copy of the petition, write: Rules Review Section, Rules Review and Directives Branch, Division of Freedom of Information and Publications Services, Office of Administration, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001.

Submit comments to: Secretary, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001. Attention: Docketing and Services Branch.

Deliver comments to 11555 Rockville Pike, Rockville, Maryland, between 7:45 am and 4:15 pm on Federal workdays.

For information on sending comments by electronic format, see "Electronic Access," under the Supplementary Information section of this notice.

FOR FURTHER INFORMATION CONTACT: Michael T. Lesar, Office of Administration, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001. Telephone: 301-415-7163 or Toll Free: 800-368-5642, or E-mail MTL@NRC.GOV.

SUPPLEMENTARY INFORMATION:

Receipt of Petition for Rulemaking

The NRC received the IsoStent, Inc., petition for rulemaking on May 10, 1996. The petition is dated May 9, 1996, and was docketed as PRM-35-14 on May 20, 1996.

Background

The petitioner states that preliminary data indicates that stents, combined with a low-activity, beta-emitting source (less than 3 microcuries per millimeter of length), may significantly reduce restenosis of the vessel following therapeutic intervention. The petitioner refers to a source that estimates total societal costs of restenosis in the United States is somewhere between $800 million and $2 billion a year.

The petitioner states that it is important to ensure that the stents are appropriately classified and regulated because radioactive stents could significantly benefit the healthcare system and the quality of life of patients suffering from restenosis of the vessel following therapeutic intervention. The petitioner believes, after reviewing existing NRC regulations pertaining to the medical uses of byproduct materials, that a new section is necessary to address permanently implanted radioisotope intraluminal stents. The petitioner states that standard coronary stents, 15 millimeters in length, would contain less than 20 microcuries (740 kBq) of beta-emitting isotope, and longer and larger diameter stents for other anatomical sites would contain less than 3 microcuries of beta-emitting isotope per millimeter of length.

Petitioner's Suggested Amendments

The petitioner requests that the NRC amend its regulations by adding a new section that would be applicable to permanently

implanted intraluminal stents. The new section would govern stents that include phosphorus-32 and strontium-89 radioisotope sealed sources. These sealed sources would have removable contamination of less than 1 percent of the total device activity. The petitioner further requests a new section be created on training and experience requiring the stents to be placed in the patient by a licensed physician who--

(1) Is certified either by the American Board of Radiology in diagnostic radiology with additional specialization in intravascular radiology or by the American Board of Internal Medicine with special competence in cardiology; and

(2) Has received 8 hours of classroom and laboratory training in the basic handling of beta-emitting sources.

Discussion of the Petition

The petitioner states that the existing regulations do not include phosphorus-32 and strontium-89 as sealed sources for medical therapeutic use. Therefore, the petitioner believes that these sources would be regulated under sources used for traditional brachytherapy. The petitioner believes this category is not appropriate to control low-activity, beta-emitting stents for the following reasons:

1. Training and Competency Requirements.

Low-activity, beta-emitting stents differ significantly from those sources that are used for traditional brachytherapy. Traditional brachytherapy sources have higher activity and

require significant dose calculations. To be used safely, traditional brachytherapy sources require extensive knowledge in radiobiology, radiation physics, and radiation protection. Low-activity beta-emitting stents do not require this same level of radiation expertise because they have significantly lower radioactivity levels and are permanently implanted devices that do not require any calculation of dose or dwell time.

Under current NRC regulations, any procedure using a source defined under § 35.400 would require the supervision of a certified radiation oncologist. Stents are currently prescribed and implanted by physicians trained in cardiovascular specialties. Once given required training in the proper handling of these low dose-rate, beta-emitting sources, these physicians could safely and effectively implant radioactive stents. Access to low-activity, beta-emitting stents should be allowed to those physicians who are already certified for stent implantation specialties. Requiring the additional oversight of a radiation oncologist for these stent applications could potentially limit the accessibility of this technology and add significant cost to each procedure. Such a requirement would unnecessarily burden the medical system.

2. Safety Requirements.

Low-activity, beta-emitting stents can be shielded with approximately 1 centimeter of plastic material and have half-lives of less than two months, and, when shielded, should not pose a significant hazard to the public or medical staff. The

radioactive stent remains within the shield until it is passed into the patient by means of a stent delivery catheter. Once in the patient, these beta-emitters are shielded by the patient's tissues, and because of their shorter half-lives, do not represent a significant long-term risk to the public or to medical personnel. A precedent for the release of patients with such short half-life sources has been set with sources such as iodine-125 seeds having a 60-day half-life and 10^3 to 10^4 times higher activity per seed, as well as with the more penetrating photon radiation.

3. Facility Licensing Requirements.

Medical facilities without a broad-scope license also should have access to low-activity, beta-emitting stents, as do facilities with a broad-scope license under current regulations. There are a large number of medical facilities that currently implant stents, but do not meet these licensing requirements. Therefore, maintaining these requirements also could limit the accessibility of this technology.

The petitioner believes that these suggested changes would have a potentially large benefit to patients and the healthcare system.

Electronic Access

Comments may be submi d electronically in either ASCII text or WordPerfect format (version 5.1 or later) by calling the NRC Electronic Bulletin Board (BBS) on FedWorld. The bulletin

board may be accessed using a personal computer, a modem, and one of the commonly available communications software packages, or directly via Internet. Background documents on the petition for rulemaking also are available, as practical, for downloading and viewing on the bulletin board.

If using a personal computer and modem, the NRC rulemaking subsystem on FedWorld can be accessed directly by dialing the toll free number 800-303-9672. Communication software parameters should be set as follows: parity to none, data bits to 8, and stop bits to 1 (N,8,1). Using ANSI or VT-100 terminal emulation, the NRC rulemaking subsystem can then be accessed by selecting the "Rules Menu" option from the "NRC Main Menu." Users will find the "FedWorld Online User's Guides" particularly helpful. Many NRC subsystems and data bases also have a "Help/Information Center" option that is tailored to the particular subsystem.

The NRC subsystem on FedWorld also can be accessed by a direct-dial telephone number for the main FedWorld BBS, 703-321-3339, or by using Telnet via Internet: fedworld.gov. If using 703-321-3339 to contact FedWorld, the NRC subsystem will be accessed from the main FedWorld menu by selecting the "Regulatory, Government Administration and State Systems," then selecting "Regulatory Information Mall." At that point, a menu will be displayed that has an option "U.S. Nuclear Regulatory Commission" that will take the user to the NRC online main menu. The NRC online area also can be accessed directly by typing "/go nrc" at a FedWorld command line. If NRC is accessed from

FedWorld's main menu, the user may return to FedWorld by selecting the "Return to FedWorld" option from the NRC online main menu. However, if NRC is accessed at FedWorld by using NRC's toll-free number, the user will have full access to all NRC systems, but will not have access to the main FedWorld system.

If FedWorld is contacted using Telnet, the user will see the NRC area and menus, including the Rules Menu. Although the user will be able to download documents and leave messages, he or she will not be able to write comments or upload files (comments). If FedWorld is contacted using FTP, all files can be accessed and downloaded, but uploads are not allowed. Only a list of files will be shown without descriptions (normal Gopher look). An index file listing all files within a subdirectory, with descriptions, is available. There is a 15-minute time limit for FTP access.

Although FedWorld also can be accessed through the World Wide Web, like FTP, that mode only provides access for downloading files and does not display the NRC Rules Menu.

For more information on NRC bulletin boards, call Mr. Arthur Davis, Systems Integration and Development Branch, NRC, Washington, DC 20555-0001, telephone 301-415-5780; E-mail AXD3@nrc.gov.

Single copies of this petition for rulemaking may be obtained by written request or telefax (301-415-5144) from the Rules Review and Directives Branch, Division of Freedom of Information and Publications Services, Office of Administration,

Mail Stop T6-D59, U.S. Nuclear Regulatory Commission, Washington DC 20555-0001. Certain documents related to this petition for rulemaking, including comments received, may be examined at the NRC Public Document Room, 2120 L Street NW. (Lower Level), Washington, DC. These same documents also may be viewed and downloaded electronically via the Electronic Bulletin Board established by NRC for this petition for rulemaking as indicated above.

Dated at Rockville, Maryland, this day of 1996.

For the Nuclear Regulatory Commission.

John C. Hoyle,
Secretary of the Commission.

DRAFT Version 1.3a

Intravascular Brachytherapy - Guidance for Data to be Submitted to the Food and Drug Administration in Support of Investigational Device Exemption (IDE) Applications

Prepared by:

Interventional Cardiology Devices Group
Division of Cardiovascular, Respiratory, and Neurological Devices
Office of Device Evaluation

May 24, 1996

U.S. Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health

Specific IDE Requirements

1. Identify yourself, your center and other centers involved.

2. Identify the radioactive isotope and the method which will be used to deliver the radiation. Also, specify the manufacturer(s) of the source and delivery system.

3. Provide a **Report of Prior Investigations** (bench, animal and clinical) conducted with the system you intend to use in your investigation.

   a. Bench Testing

   Much of the bench testing may have already been conducted by the manufacturer. A list of the types of bench testing which FDA believes is appropriate to qualify brachytherapy systems is provided in Attachment A. Clinical investigators should forward this list to the manufacturer. The manufacturer may provide this information directly to the investigator for inclusion in the IDE application. Alternatively, the manufacturer may provide the investigator a letter which allows the investigator to reference appropriate files within the Agency where this bench testing is contained. This letter should clearly specify the file numbers (or master file) and pages where these test data can be found and should be included in the IDE application.

   b. Animal Testing

   Describe any animal tests conducted using the radiation source and delivery system you intend to use in your investigation. Work done by others may be referenced; however differences in components and/or experimental methodologies should be noted and an explanation provided as to how such data are applicable to your study. (Attachment B contains a comprehensive intravascular brachytherapy bibliography). Also, state whether the animal testing was done in compliance with Good Laboratory Practices (GLPs). These regulations are contained in 21 CFR part 58 *Good Laboratory Practices for Nonclinical Laboratory Studies* and may be obtained from DSMA.

   c. Clinical Experience

   Provide all clinical data available using the radiation source and delivery system you intend to use in your investigation. Similar to the animal test results, work done by others may be referenced but a justification is needed for how this data is applicable if the radiation source, delivery system and/or methods used were different from those proposed in your study.

4. Provide a copy of your **Investigational Plan**. Included in your plan should be the following:

   a. **Purpose** should clearly define:
      - Name and intended use of the device
      - Objectives of the investigation
      - Duration of the investigation

d. **Description of the device**

- List each component of the source/delivery system.
- State the principal and mode of operation, including a description of how the source is centered, if applicable.
- If not centered, address the consequences to dose distribution within the lesion and vessel.
- Specify the therapeutic dose(s) which will be delivered to the lesion and provide a rationale for the choice of this dose(s).
- Specify the dose prescription point(s) in the lesion and the dose expected to be delivered to the closest point in the intima and furthest point in the adventitia. Discuss this dose(s) in light of the potential for tissue damage, i.e., necrosis, aneurysms, etc.
- Specify the source strength, delivered dose, and distance for each dose specification.
- Describe how the therapeutic dose to the lesion and the spatial distribution of this dose are estimated.
- Describe how this dose and dose distribution are validated.
- Describe quality assurance (QA) and radiation safety procedures which will be followed at your center, e.g., NRC or state license requirements for reactor-produced isotopes. Otherwise provide similar procedures for non-NRC sources, as appropriate.
- Specify the applicability of any national, state and/or local regulations regarding the use of radioactive substances, and your compliance with these regulations. (See Attachment C)

e. **Monitoring Procedures**

- Name and address of the study monitor
- Description of the monitoring procedure

5. Manufacturing Information

Provide information regarding the manufacture, processing, packaging, transport and storage of all components which will be used in your study. The manufacturer can provide this information to you directly for inclusion in the IDE application. Alternatively, a letter granting Agency access to this information may be provided.

6. Investigator Agreement

a. a sample of the investigator's agreement

b. name, address, and fax number of all investigators who have signed the investigator agreement

c. certification that no investigators will be included in the study until the investigator agreement is signed

d. specification of the cardiologist, interventional radiologist, radiation oncologist, medical (radiation) physicist, and others as appropriate.

Attachment A. Bench Testing

1. Characterization of Radiation source
   - radiation type (alpha, beta, gamma, x-ray)
   - radiation half-life, average and maximum energy (MeV) as appropriate
   - activity of the source (curie or Bq)
   - source configuration (encapsulation, plating, etc.)
   - source uniformity (linear activity)
   - dose distribution map (iso-dose curves providing three-dimensional representation of the dose)
   - plot of absorbed dose rate vs. distance in a properly selected medium
   - algorithms used to calculate the dose, including attenuation by the medium in which the irradiation is performed
   - method of radiation source calibration, including accuracy and precision
   - a description of the software used to calculate doses and dose distribution (note that good software developing practices should be utilized as described in "Reviewers Guidance for Computer-Controlled Medical Devices Undergoing 510(k) Review").
   - a description of the testing done to ensure that the calculated dose distribution is validated
2. Biocompatibility of blood-contacting materials used in the delivery system (if applicable)
3. Mechanical Integrity of components used in the delivery system (if applicable)
4. Sterility of the source and delivery system

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112.* King SB, Waksmann R, Crocker I: Discoveries in Radiation for Restenosis. Emory University School of Medicine, Atlanta, GA, 1996, 142 pages.

Abs: Collects the 44 abstracts from the "first international workshop devoted to this exciting new field" presented by the Andreas Gruentzig and Cardiovascular Center and the Department of Radiation Oncology of the Emory University School of Medicine held at the JW Marriott Hotel. Atlanta, GA, January 11-12, 1996. There were 12 corporate sponsors and 35 faculty including Ralph Shuping and Bram Zuckerman. Topics included Incidence and mechanisms of restenosis; Radiobiology, pathology and Physics; Radiation for restenosis in animal models; Stents and radiation; Peripheral vascular disease; Clinical trials with endovascular radiation in coronary arteries; Industry approach; Economic and regulatory issues.

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Attachment C. NRC Regulations and Requirements Relating to Brachytherapy Treatment of Restenosis

Currently, 10 CFR Part 35, *Medical Use of Byproduct Material* does not permit the use of brachytherapy sources for intravascular uses. Therefore, these treatments currently could only be performed under a broad scope license or at a facility with a limited specific license which has received an exemption from the requirements of 10 CFR 35.400, *Use of Sources for Brachytherapy.*

Broad Scope License

Many broad scope licensees are authorized to use isotopes with atomic numbers 3-83 for medical research, diagnosis and therapeutic uses in individual quantities not to exceed 1 curie. These licensees would be authorized to perform medical research into brachytherapy treatment of restenosis, provided that the licensee complies with the requirements of 10 CFR 35.6, Provisions for Research Involving Human Subjects. These licensees should be reminded that, for any research not conducted, funded, supported, or regulated by a Federal Agency that has adopted the Federal Policy, the licensee must apply, in accordance with 10 CFR 35.6, for a specific amendment before conducting research involving human subjects. Additionally, some broad scope licenses are written to restrict the use of brachytherapy sources to the treatment of cancer; therefore, use of the sources for treatment of restenosis would require an amendment to the license. Broad scope licensees should review the authorizations for the use of brachytherapy sources on their licenses.

Limited Specific License

Limited specific licensees seeking authorization to perform these procedures must apply for an exemption from the requirements of 10 CFR 35.400, *Use of Sources for Brachytherapy*. This application must address the training and experience of the individuals involved in treatment delivery. Individuals performing these treatments must either meet the training and experience requirements of 10 CFR 35.940, *Training for Use of Brachytherapy Sources*, or be supervised by such an individual. It is anticipated that due to the complexity of these procedures, a team approach will be used, which would include a radiation oncologist, a cardiologist, an interventional radiologist, a medical physicist, etc.

Licensing Remote Afterloading Devices

In addition to the requirements regarding brachytherapy found in 10 CFR Part 35, licensees wishing to use remote afterloading brachytherapy units may need to address additional requirements found in *Policy and Guidance Directive FC 86-4., Information for Licensing Remote Afterloading Devices.* These requirements include establishing provisions to perform emergency surgical procedures for the removal of dislodged sources within the patient and the presence of an authorized user physician, radiation safety officer, or medical physicist during the treatment of the patient.

Specific questions relating to NRC regulations and requirements may be referred to James Smith, 301-415-7904

Revision history -- Brachytherapy Guidance

3/11/96 - bibliography development, John, Ralph, Dan

3/15/96 - initial draft to Brachy Team, Tara Ryan

3/25/96 - draft v 1.2 to Susan Alpert

3/26/96 - draft v 1.2 to SCVIR, ACR, ASTRO and ABS

5/3/96 - draft v 1.3 reflecting NRC's attachment C and all comments received

5/9/96 - draft v 1.3 distributed

Intravascular Brachytherapy Team

Name	E-mail	Phone	Mail
Andrew Green	{AMG}	301-443-8243	HFZ-450
Anne Roberts	{ACR}	301-443-8320	HFZ-450
Brad Astor	{BCA}	301-443-8243	HFZ-450
Bram Zuckerman	{BDZ}	301-443-8243	HFZ-450
Dan Spyker	{DXS}	301-443-8320	HFZ-450
Dorothy Abel	{DBA}	301-443-8262	HFZ-450
Eldon Leutzinger	{Leutz}	301-443-1560	HFD-160
Gerald Sokol	{Sokol}	301-594-2473	HFD-150
John Stuhlmuller*	{JES}	301-443-8609	HFZ-450
Lynette Gabriel	{LAG}	301-443-8243	HFZ-450
Ralph Shuping	{RXS}	301-594-1212	HFZ-470
Semih Oktay	{HSO}	301-443-8243	HFZ-450
Shang Hwnag	{SWH}	301-443-8609	HFZ-450
Subbu Subramanian	{RCS}	301-443-8320	HFZ-450
Tara Ryan	{TXR}	301-443-8243	HFZ-450
Tom Callahan	{TJC}	301-443-8320	HFZ-450
Wolf Sapirstein	{WYS}	301-443-8320	HFZ-450

*fax 301-480-4204, E-mail: {JES}@ FDADR.CDRH.FDA.gov

Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION III
801 WARRENVILLE ROAD
LISLE, ILLINOIS 60532-4351

Matson
96-54

JUL 23 1996

REGIONAL TECHNICAL ASSISTANCE REQUEST FORM

Date: July 19, 1996

To: Don Cool, Director, Division of Industrial and Medical Nuclear Safety, NMSS

From: John Madera, Chief, Nuclear Materials Safety and Safeguards Branch, RIII

Licensee: Borgess Medical Center

License No. 21-12275-02

☐ **Control No.:** 301576 (enclosed)

☐ **Letters dated:** July 5, 1996 (enclosed)

☐ **Problem/Issue:** This limited scope medicial licensee is requesting authorization to use phosphorus-32 for intravascular use as a cardiac stent. Therefore, an exemption from the provisions of 10 CFR35.400 appears to be needed to allow this activity.

☐ **Action Required:** Please review the information submitted and determine if RIII can issue the exemption with the current information provided or describe what additional information is needed.

☐ **Recommended Action:** RIII recommends an exemption be granted for the use of phosphorus-32 for intravascular use by physicians who meet the training and experience criteria of 10 CFR 35.940 for brachytherapy procedures.

☐ **Remarks:** The potential medical benefits from this new procedure provides a justification for the exemption and the licensee's radiation safety procedures appear adequate.

Headquarters Reviewer: _____
Regional Reviewer: EVELYN MATSON
Reviewer Code: R9
Reviewer Phone No.: (708)829-9822 EMAIL: ERM
Request Needed by: 8/31/96

Form TAR-10
8/93

NRC FORM 374
(7-94)

U.S. NUCLEAR REGULATORY COMMISSION

MATERIALS LICENSE

Amendment No. 71

Pursuant to the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974 (Public Law 93-438), and Title 10, Code of Federal Regulations, Chapter I, Parts 30, 31, 32, 33, 34, 35, 36, 39, 40, and 70, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, possess, and transfer byproduct, source, and special nuclear material designated below; to use such material for the purpose(s) and at the place(s) designated below; to deliver or transfer such material to persons authorized to receive it in accordance with the regulations of the applicable Part(s). This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954, as amended, and is subject to all applicable rules, regulations, and orders of the Nuclear Regulatory Commission now or hereafter in effect and to any conditions specified below.

399642

Licensee	
1. Borgess Medical Center	In accordance with letter dated December 11, 1995
2. 1521 Gull Road Kalamazoo, MI 49001	3. License Number 21-12275-02 is amended in its entirety to read as follows:
	4. Expiration Date July 31, 1995
	5. Docket or Reference No. 030-02115

6. Byproduct, Source, and/or Special Nuclear Material	7. Chemical and/or Physical Form	8. Maximum Amount that Licensee May Possess at Any One Time Under This License
A. Any byproduct material identified in 10 CFR 35.100	A. Any radiopharmaceutical identified in 10 CFR 35.100	A. As needed
B. Any byproduct material identified in 10 CFR 35.200	B. Any radiopharmaceutical identified in 10 CFR 35.200	B. As needed
C. Any byproduct material identified in 10 CFR 35.300	C. Any radiopharmaceutical identified in 10 CFR 35.300	C. As needed
D. Any byproduct material identified in 10 CFR 35.400	D. Any brachytherapy sources identified in 10 CFR 35.400	D. As needed
E. Any byproduct material identified in 10 CFR 31.11	E. Prepackaged Kits	E. As needed

9. Authorized Use:

A. Medical use described in 10 CFR 35.100.

B. Medical use described in 10 CFR 35.200.

C. Medical use described in 10 CFR 35.300.

COPY

D. Medical use described in 10 CFR 35.400

E. In vitro studies.

CONDITIONS

10. Location of use: 1521 Gull Road, Kalamazoo, Michigan.

11. Radiation Safety Officer: Tim TenCate

12. Licensed material listed in Item 6 above is only authorized for use by, or under the supervision of, the following individuals for the materials and uses indicated:

Authorized Users	Material and Use
A. Gary L. Bowman, M.D.	10 CFR 35.100, 35.200 and 31.11.
B. John W. Copenhaver, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
C. J. Alex Gardner, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
D. Leonard A. Brunette, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
E. Arthur Gregory Laurell, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
F. James R. Dolan, M.D.	10 CFR 35.100, 35.200, 35.300, 35.400 and 35.500.
G. Geoffrey A. Wardwell, M.D.	10 CFR 35.100 and 35.200.
H. N. Warn Courtney, M.D.	10 CFR 35.100, 35.200, 35.300 and 31.11.
I. Richard R. McConnell, M.D.	10 CFR 35.100, 35.200, 35.300 (excluding iodine-131 for thyroid carcinoma), 35.500 and 31.11.
J. Edwardo R. Crotte, M.D.	10 CFR 35.100, 35.200 and 31.11.
K. David Tague, M.D.	10 CFR 35.100, 35.200 and 31.11.
L. L. Enrique Leguizamon, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
M. Thomas McCormick, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.

Authorized Users	Material and Use
N. John E. Francis, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
O. Kenzo Kawamura, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
P. Dennis P. Burke, M.D.	10 CFR 35.100, 35.200 and 31.11.
Q. William B. Campbell, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
R. Umakant S. Doctor, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
S. Yoo Sup Hwang, M.D.	10 CFR 35.400.
T. Khlid Altaf Mian, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
U. Evalt Ayerdi, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
V. Stephen L. Peck, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
W. Robert J. LaPenna, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
X. Benjamin A. Perry, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
Y. Robert H. Jongeward, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
Z. George J. Balogh, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.
AA. Robert B. Davis, M.D.	10 CFR 35.100, 35.200 and 35.300.
BB. Katherine Gadwood, M.D.	10 CFR 35.100, 35.200 (excluding generators) and 31.11.
CC. Charles Gregory Hodgman, M.D.	10 CFR 35.100, 35.200, 35.500 and 31.11.

Authorized Users	Material and Use
DD. Janos Gellert, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
EE. John A. Azevedo, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
FF. Sharma Saith, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
GG. Steven P. Soper, M.D.	10 CFR 31.11.
HH. Bruce D. Goethe, M.D.	10 CFR 35.100, 35.200 and 31.11.
II. Patrick A. Sorek, M.D.	10 CFR 35.100, 35.200 and 31.11.
JJ. Susan J. Phelps, M.D.	10 CFR 35.100, 35.200 and 31.11.
KK. David Lynn Keedy, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
LL. Douglas J. Wunderly, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
MM. Jonathan Levi, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
NN. Jim Chul Kim, M.D.	10 CFR 35.300 and 35.400.
OO. Heung (Henry) Shik Shin, M.D.	10 CFR 35.300 and 35.400.
PP. David G. Brachman, M.D.	10 CFR 35.300 and 35.400.
QQ. Marc Bernstein, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
RR. Anthony King, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
SS. Alicia Williams, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).
TT. Antonio P. Carrillo, M.D.	10 CFR 35.100 and 35.200 (limited to cardiovascular clinical procedures).

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number: 21-12275-02
Docket or Reference number: 030-02115
Amendment No. 71

Authorized Users	Material and Use
UU. Ramon Raneses, M.D.	10 CFR 35.200 (limited to cardiovascular clinical procedures).

13. The licensee will establish and implement model procedure for radiation safety during implant therapy that was published in Appendix Q to Regulatory Guide 10.8, Revision 2.

14. The licensee shall maintain records of information important to safe and effective decommissioning at the address in Condition 10. per provisions of 10 CFR 30.35(g) until this license is terminated by the Commission.

15. In addition to the possession limits in Item 8, the licensee shall further restrict the possession of licensed material to quantities below the minimum limit specified in 10 CFR 30.35(d) for establishing decommissioning financial assurance.

16. Except as specifically provided otherwise in this license, the licensee shall conduct its program in accordance with the statements, representations, and procedures contained in the documents, including any enclosures, listed below, except for minor changes in the medical use radiation safety procedures as provided in 10 CFR 35.31. The Nuclear Regulatory Commission's regulations shall govern unless the statements, representations, and procedures in the licensee's application and correspondence are more restrictive than the regulations.

    A. Application dated March 20, 1990; and

    B. Letters dated May 25, 1990 (with attachments), July 3, 1990 (with enclosures), October 17, 1990 (with attachments), and December 11, 1995.

FOR THE U.S. NUCLEAR REGULATORY COMMISSION

Date 1/3/96

By James Williams
Nuclear Materials Licensing Branch, Region III

COPY

A
030-02115

BORGESS
Medical Center

July 5, 1996

UNITED STATES NUCLEAR REGULATORY COMMISSION
Region III, Medical Licensing Section
801 Warrenville Road
Lisle, IL 60532

ATTN: John Madeira

Re: Urgent Amendment Request License No. 21-12275-02 P-32 Coronary Artery Stents

We respectfully request that this license amendment be expedited. Tracy King, our physics consultant, discussed this matter with you on July 3, 1996. In accordance with your conversation, we are faxing this amendment letter so that you may assign it for review while the fee division performs their review.

The FDA has issued approval for this procedure in human clinical trials. The program is due to start on August 5 , 1996. We hope that you can assist us in getting this program approved in time as it will be of great benefit to our patients.

We ask for permission to order, receive, and implant Palmaz-Schatz Balloon-Expandable IsoStent with Delivery System. The stents are manufactured by IsoStent, Inc and contain approximately 1 uCi of P-32. These stents are shipped by the manufacturer in radiation shields which the stent remains in until its placement in a coronary artery. The P-32 stents are placed within the coronary artery by a physician who will be trained in accordance with manufacturer's instructions and the outline enclosed for your review. These are not temporary implants. The P-32 betas will provide local radiation only to the tissue surrounding the stent and is expected to prevent the artery from re-stenosising.

We have enclosed the FDA's conditional approval of this use. We will forward the final approval letter to you.

We have enclosed the following list of documents for your review:

Item 5-7	Radioactive Material and Use
Item 8.1	Personnel Training Program for P-32 Stent Placement
Item 9.1	Equipment List P-32 Stent Program
Item 9.4	Personnel Monitoring P-32 Stent Program
Item 10.4	Rules for Safe Use of P-32 Stents
Item 10.5	Emergency Procedures for Loss of P-32 Stent
Item 10.11	Keeping an Inventory of P-32 Stents
Item 10.15	Radiation Safety Procedures for P-32 Coronary Artery Stents
Item 12.1	Quality Management Program P-32 Stent Program

Our ordering, package receipt, and waste disposal procedures will be followed as they exist in our current license.

We have also enclosed information supplied by IsoStent, Inc. which you may find useful as reference material.

The $440 amendment fee is enclosed for a human use license category 7C amendment.

Again, we respectfully request your assistance in expediting this amendment request.

Cordially,

Gary Beaulac
Vice-President, Ambulatory Services
Borgess Medical Center

Borgess Medical Center
21-12275-02 amendment request
1996

P-32 Stent Program Only
RADIOACTIVE MATERIAL AND USE

Item 5 *Byproduct Material*	*Item 6* *Amount*	*Purpose*
P-32 "Palmaz-Schatz Expandable IsoStent" (coronary artery stent)	Each stent contains less than 10 uCi of P-32. Typically each stent contains 1 uCi of P-32.	Maintain patency of Balloon-stented coronary arteries

Please add to our existing authorized materials:

RADIATION SAFETY PROGRAM RESPONSIBILITY

Item 7.1
Authorized Users ***Materials***

These physicians have been selected as users for the P-32 stent program. The P-32 stent placement program will be supervised by one or more of these physicians listed below.

James R. Dolan, M.D.
N. Warn Courtney, M.D.
Richard R. McConnell, M.D.
Robert B. Davis, M.D.
Jim Chul Kim, M.D.
Heung (Henry) Shik Shin, M.D.
David G. Brachman, M.D.
Thomas Winn, M.D. previous request sent to add to license, previously listed on License No. 21-13125 for Groups 35.100, 35.200, and 35.300

These physicians have experience with therapeutic agents such as P-32 and are currently authorized for usage of P-32 in Group 35.300 on our license.

Item 7.3 ***No change***

Radiation Safety Officer

Tim Tencate

PERSONNEL TRAINING PROGRAM
for P-32 Stent Placement

Item 8.1

Personnel

Only personnel who have been trained as listed below will be allowed to participate directly in the placement procedure of P-32 stents.

Training Frequency

1. Before participating in a P-32 stent placement
2. During annual refresher training.
3. Whenever there is a significant change in duties, regulations, or in the terms of the license relating to this procedure

Instruction Topics

1. Applicable regulations and license conditions.
2. Physical appearance of the P-32 stent and proper handling procedures
3. Potential hazards associated with the P-32 stents.
4. Appropriate radiation safety procedures.
5. The licensee's in-house work rules.
6. Each individual's obligation to report unsafe conditions to the Radiation Safety Officer.
7. Appropriate response to emergencies or unsafe conditions.
8. Appropriate response if a stent is lost.
9. Locations where the license has been posted or made available, notices, copies of pertinent regulations, and copies of the license and license conditions, as required by 10CFR19.

Documentation will be kept on hand for review of the list of topics covered, the date of the instruction, and the names of those participating.

The method of instruction will be verbal and written.

P-32 Stent Program Only
EQUIPMENT LIST

Item 9.1

Survey Meters

We will use a GM meter with a probe possessing a thin-end window cr a beta window to perform surveys relating to the receipt, usage, and disposal of the P-32 stents.

The meter(s) will be calibrated according to our existing license conditions concerning survey meter operational check, use, and calibration.

Shielding Material

The P-32 stents are contained in a beta shielding material during transport and until placement occurs. When additional shielding is required lucite or plastic material will be utilized We will not use lead shielding in order to minimize bremsstrahlung production.

Dose Calibrator

We will not assay the P-32 stents in a dose calibrator since their activity is less than 10 uCi and is generally 1 (one) uCi per stent. We will verify that the shipping documents accompanying the stents show agreement of the activity per stent and the number of stents with the quantity and activity ordered.

Personnel Protective Equipment

Gloves will be worn by all personnel who handle the P-32 stents.
A radiation shield surrounds the stent during shipment and is kept in place until the stent is positioned for placement in the coronary artery.

P-32 Stent Program Only

PERSONNEL MONITORING PROGRAM

Item 9.4

The personnel directly participating in the P-32 Stent Placement procedure will be issued whole body film badges. The physician who is placing the stent will be issued a ring badge.

All other aspects of our personnel monitoring program as authorized by our current license will be followed.

Item 10.4

RULES FOR THE SAFE USE OF P-32 STENTS

The P-32 stents are supplied by the manufacturer Iso-Stent in a radiation shield. The stents are not removed from the radiation shield until it is placed directly into the patient's vessel. Therefore, we have developed Rules for Safe Use of P-32 Stents. These rules will apply only to the P-32 Stent procedure.

1. Do not examine the stent itself outside of the radiation shield at any time.

2. Do not remove the radiation shield from over the stent at any time before the delivery catheter is advanced into the body.

3. If the radiation shield accidentally comes loose and the distal end of the delivery system becomes unshielded, slide the shield back over the stent's location and tighten the Tuohy-Borst fitting on the shield to lock the shield down.

4. Make sure to advance the delivery system forward into the body following loosening of the shield Tuohy-Borst.

5. If the stent delivery system has been advanced into the body, but for any reason the stent cannot be delivered, pull back the stent delivery catheter until the stent is inside the radiation shield, lock down the shield by tightening the shield Tuohy-Borst, return the device to its package, and return the opened package to the RSO for storage and disposal.

6. It the stent comes off of the catheter due to stent embolization, the physician should retrieve the stent using forceps or other remote retrieval devices when possible.

7. Once the stent is retrieved, it should be placed inside of the radiation shield if possible. If the radiation shield cannot be used, contact the RSO for a disposal container.

8. All personnel should avoid any direct handling of the bare stent with their fingers if possible. When direct handling is absolutely necessary, the use of surgical gloves should reduce the direct contact rate.

9. Wear disposable gloves at all times while handling the P-32 stent.

10. Either after each procedure or before leaving the area, monitor your hands and clothing for contamination in a low background area.

11. Use the radiation shields provided by the manufacturer until you are ready to complete placement directly into the patient's vessel. If the patient's condition does not allow the full use of the radiation shield until placement, the radiation shield will be used as long as possible and holding of the stent by personnel will then be minimized.

12. Do not eat, drink, smoke, or apply cosmetics in an area where P-32 stents are stored or when they are being used.

13. Do not store food, drink, or personal effects in areas where P-32 stents are stored and where they used.

14. The radiation shield and any other packaging material associated with the P-32 stent must be returned to the Nuclear Medicine Department for analysis before they can be disposed of. Place all of this material in a plastic bag or other container provided for this purpose.

15. Transport the P-32 stents from the receipt location (Nuclear Medicine Hot Lab) to the placment location only in a covered container.

16. Before transport, make a visual count of the number of stents to be transported in the container. Upon arrival at the placement location, make a visual count of the number of stents. If the number differs, implement the Emergency P-32 Stent Loss Procedure. Record these numbers on the P-32 Stent log.

17. Survey the placement room after P-32 placement is completed and after the patient has left, to ensure that no P-32 stent has been left behind. Record these results on the P-32 Stent log.

18. Store P-32 stents only in the original radiation shield and in original packaging material or other covered container. P-32 stents will only be stored in the Nuclear Medicine Hot Lab.

Item 10.5

EMERGENCY PROCEDURES FOR LOSS OF P-32 STENT

1. NOTIFY: Notify persons nearby that a stent is lost.

2. Do not allow anyone to leave the area until their clothing has been searched and they have been surveyed with a GM meter. Pay particular attention to cuffs, pockets, shoe bottoms, or anyother place where a stent may be trapped.

3. Do not allow additional personnel into the area.

4. Do not allow any items to be removed from the room until they have been visually searched and surveyed.

5. Begin a systematic survey of the area to ensure that no area is missed.

6. Contact the RSO for assistance.

7. Repeat the above searches and surveys until the source is found.

8. If necessary, retrieve all items and personnel who may have left the room between the time source was lost and its loss was noticed. If the source is still not located, track the paths of these personnel and items since the time they left the room and perform searches and surveys.

9. If the source is not located through all of the above measures, a report must be filed with the RSO who will determine the additional reporting requirements. The report must contain the sequence of events that allowed the loss of a stent and the actions taken to prevent recurrence.

KEEPING AN INVENTORY OF P-32 STENTS

Item 10.11

We will adopt Appendix M.4 "Keeping an Inventory of Implant Sources" that was published in Appendix M.4 to Regulatory Guide 10.8, Revision 2.

MODEL PROCEDURE

1. Use a locking installed cabinet or safe to store all implant sources.

2. Make a list of names of those individuals you allow to handle implant sources and have them initial beside their names.

3. For long-lived sources, draw a map of the storage drawer and indicate the activity of the source at each storage point. For short-lived sources that you store in the manufacturer's shipping container, indicate the area in the safe where you put the container. Also, be sure to add the sources to the inventory log.

N/A

4. Post the map and the list of individuals whom you permit to handle the sources in the storage area or on the inventory log.

5. Each time you remove a source, make a record of the number and activity of sources removed, the room number of use or patient's name, and the time and date they were removed from storage; initial the record.

6. Each time you return sources to storage, immediately count them to ensure that every source removed has been returned. Then make a record of the number and activity of sources returned, the room number of use or patient's name, and the time and date they were returned to storage; initial the record.

7. If you ever perceive a discrepancy between the record and the number of sources in use and in storage, notify the RSO immediately.

~~See Exhibit 15 for a sample form you may want to use.~~

P-32 STENT LOG

Only the following individuals may handle these sources:

_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Signed RSO_____ Date _____

Received on_____

_____ P-32 stents of ____ uCi per stent

Date	Time	Patient	Number of P-32 stents						
			in storage	removed	transported	implanted	returned	in storage	Initials

Post -placement Survey of patient: _____ mR/hr at 1 meter

Post-placement survey of room: _____ mR/hr maximum at any location

Survey of personnel directly involved in placement:

_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____
_____ mR/hr	Name	_____

Background radiation level: _____ mR/hr

Survey Meter used: Manufacturer: _____
Probe type: _____
Range used: _____ mR/hr

Signed RSO: _____

Borgess Medical Center
21-12275-02 Amendment Request
1996

RADIATION SAFETY PROCEDURES FOR P-32 CORONARY ARTERY STENTS

Item 10.15

The P-32 Palmaz-Schatz Balloon Expandable IsoStent has been approved by the FDA for human clinical trials to be permanently placed in coronary arteries. Each stent will contain typically 1 uCi of P-32 (never more than 10 uCi) and is prepared by the manufacturer.

Due to the low activity and the beta-emitting properties of P-32, these patients will not be a source of radiation to nursing personnel or the public. Therefore, we will not implement the Radiation Safety Procedures for Temporary Implant Therapies.

These stents are placed within a coronary artery, therefore, there is no chance that a source could dislodge from within the patient's body and become a hazard to nursing personnel. Therefore, we will not instruct nursing personnel in the appearance or proper handling of a loose P-32 stent.

The patient will be surveyed using a GM meter with an end-window or beta window probe. This survey will be conducted after the placement of the stent is completed. If the results are less than 5 mR/hr at 1 meter, the attending physician will be notified that the patient may be released whenever their clinical condition allows.

Any patient measuring over 5mR/hr at 1 meter will not be discharged from the hospital. Please note, this is not a possible scenario due to the low amount of beta emitting material in the stent. However, we note that this is a requirement of 10CFR35 and will operate in accordance with it.

Borgess Medical Center
21-12275-02 amendment request
1996

Item 12.1

P-32 Stent Program Only

Quality Management Program

We will follow our existing Quality Management Program for the use of the P-32 stents.

The written directive for P-32 stent placement will contain the following information.

Patient name	_____
Patient id number, if available	_____
Radioisotope and form	"Permanent placement of P-32 Palmaz-Schatz Balloon-Expandable IsoStent"
Indication	"permanent placement to help maintain the patency of stented coronary arteries"
Placement site	_____ (artery)
Activity per stent	_____
Date of placement	_____
Signature of authorized user for P-32 stents	_____
Date of signature	_____

Reference Material for P-32 IsoStent

Appendix 5.1

Training Guidelines for Radiation Safety

The P32 IsoStents to be used for the IRIS Phase I feasibility study will have between 0.5 and 1 μCi of phosphorous-32 embedded beneath the surface of the stent metal. Each stent will be crimped onto a balloon angioplasty catheter, covered with a sheath and a 1 inch diameter clear plastic radiation shield will be locked over the distal section of the catheter containing the stent.

During the phase I trial only NRC broad scope license institutions may participate. As a result specific radiation training and handling requirements will vary for each institution.

This appendix is written to provide a basic set of safety guidelines for the Radiation Safety Officer (RSO) to use in training each investigator.

1. Device Tracking

   Each radioisotope stent must be tracked from the time it arrives at the institution until the patient is discharged. Each RSO should instruct the investigator as to the appropriate institutional protocols for radioactive source tracking.

   Each radioisotope stent must be stored under lock and key with restricted access. The RSO should instruct the investigator as to the appropriate institutional protocols for such device storage, removal for use, and return to storage of unopened packages.

   The RSO should instruct the investigator as the appropriate institutional protocols for the return of stent packages which have been opened. The RSO is responsible for the disposal of the opened but unused stent according to standard procedures for 1 μCi of P32.

2. Device Handling

   The Directions for Use which describe the handling methods for the stent delivery system will be included in each stent package. The RSO should go over the section below which specifically refers to the steps associated with the radiation shield.

   Verify the position of the sheath over the stent. Inject saline through the sheath to purge the system and to facilitate sheath withdrawal. Push the distal end of the radiation shield into the Tuohy-Borst adapter fitted to the guiding catheter, then tighten the Tuohy-Borst to secure the radiation shield. Next, loosen the Tuohy-Borst on the radiation shield and advance the shorthod stent/balloon assembly over the 0.014" exchange wire into the guiding catheter and then to the site of the previously dilated lesion. After advancement of the stent delivery system remove the lock-out device from the back-end of the stent delivery system and loosen its Tuohy-Borst valve.

The RSO should instruct the investigator to take the following precautions during the procedure.

- Make sure to advance the delivery system forward into the body following loosening of the shield Tuohy-Borst
- Do not remove the radiation shield from over the stent at any time before the delivery catheter is advanced into the body. If the radiation shield accidentally comes loose and the distal end of the delivery system becomes unshielded, slide the shield back over the stent's location and tighten the Tuohy-Borst fitting on the shield to lock the shield down.
- Do not examine the stent itself outside of the radiation shield at any time.
- If the stent delivery system has been advanced into the body, but for any reason the stent cannot be delivered, pull back the stent delivery catheter until the stent is inside the radiation shield, lock down the shield by tightening the shield Tuohy-Borst, return the device to its package, and return the opened package to the RSO for disposal.
- If the stent comes off of the catheter due to stent embolization, the investigator should retrieve the stent using standard techniques. Once the stent is retrieved, it should be placed inside of the radiation shield if possible, and if not the RSO should be contacted to provide an appropriate disposal container. The investigator and other cath lab personnel should avoid any direct handling of the bare stent with their fingers if possible. If not possible, the wearing of surgical gloves should reduce the direct contact dose rate for a 1 μCi P32 stent to less than 100 mrem per minute.

3. Radiation Principals

The RSO should provide some instruction to the investigators as to basics of radioisotope emissions. This should include the following:

- The units of radioactivity (e.g. microCuries, Rads, cGy)
- The aspects of natural radioactivity (e.g. beta vs. gamma, half-life, average and peak particle/photon energy)
- The specific attributes of phosphorous-32.
- Dose to tissue for the P32 stent. This information will be provided by IsoStent and is contained in the submitted paper (See Appendix 5.4 of this Supplement).

It is anticipated that the entire training as described above should take several hours to complete.

APPENDIX L3

RADIATION SAFETY CONSIDERATIONS FOR HEALTH CARE WORKERS FROM A P-S ISOSTENT

The first clinical trial for the radioisotope stent will use a JJIS, Palmaz-Schatz stent with a maximum radioactivity level of 1.0 microCurie of the isotope phosphorous-32 (P-32). The purpose of this Appendix is to provide a comparison of radiation activities and doses from this device as compared other sources of radiation with regard to safety of the health care workers involved in the procedure.

The following facts illustrate the extraordinarily low level of radiation associated with the 1.0 microCurie radioisotope stents.

1. Since the stent comes with a radiation shield that reduces the emitted radiation to a value approximately equal to background radiation, no health care worker will be exposed to any radiation hazard what-so-ever.

2. Stray radiation to the cath lab personnel from the fluoroscopy during any balloon angioplasty or stent implantation procedure will certainly be more that a 1,000 times greater than the radiation dose received from the P-32 stent.

3. The Nuclear Regulatory Commission allowed "safe dose" for workers in the field (such as the implanting physician) is an annual P-32 ingestion of 600 microCuries. Thus the physician could (theoretically) eat 600 P-32 radioisotope stents each year and stay within the NRC limits. Of course that is absurd, but it gives a feeling for how safe these ultra-low radiation levels are from the stent.

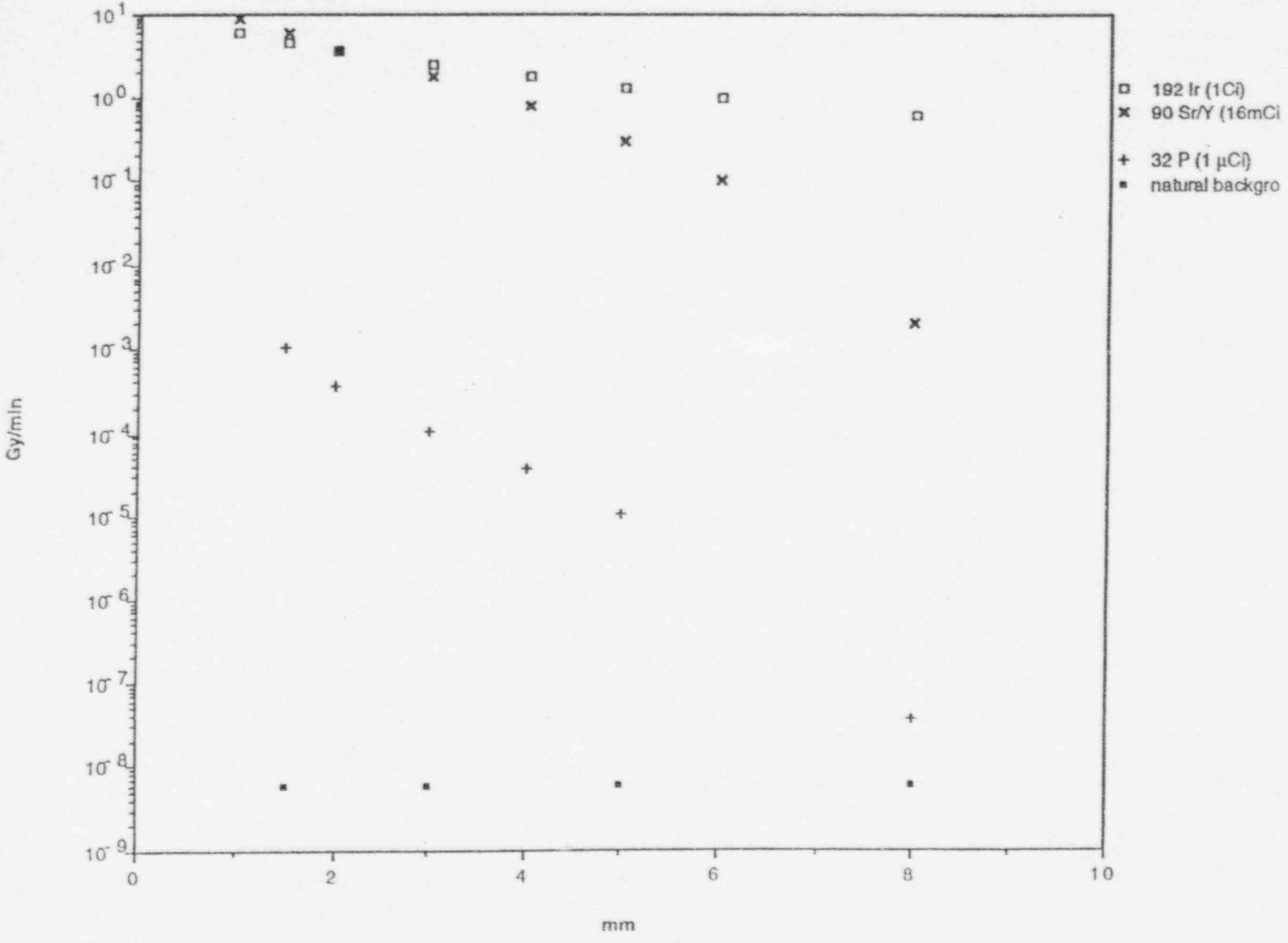
4. If a stent is ever lost, its activity level becomes undetectable as compared to background at approximately five months after it is manufactured. It therefore poses no possibility of a long term hazard as could be the case for long-lived isotopes.

5. A physician could hold the stent in his hand or sit on it for a year (or longer) and it would pose no hazard to his health.

Figure L3 is a chart providing comparative dose rate vs. distance in tissue information for natural background radiation, I192 afterloaders, Sr90/Y90 afterloaders (Novoste), and the 1 μCi P32 stent. It should be noted that the P32 stent dose rate is already near background at a distance of only 8 mm from the device.

FIGURE L3

dose rate vs distance from 'therapy' sources



APPENDIX L6

POTENTIAL FOR P32 LEECHING OUT OF THE STENT

A potential area of concern with a radioisotope stent is in the permanence of the radioisotope's attachment to the stent. The possibility that a significant amount of the P32 atoms will leech out of the stent must be addressed.

From a theoretical standpoint, for P32 atoms to leech out, the P32 atoms must diffuse first from their location inside of the metallic structure to the surface of the stent. The diffusion of impurities in materials results from random motion of the atomic constituents, and particles diffuse in the direction of decreasing concentration gradient. However, the diffusion of impurities in semiconductors and in metals is significant only when the temperature is very high (~1000° C) and is practically zero at room or body temperature. Therefore, since no mechanism other than diffusion could result in P32 atom migration inside the metallic lattice, one can consider the P32 impurities as permanently embedded into the material with no leeching except for the very first monolayer of the substrate.

In vitro experiments carried out both at the Forschungzentrum Karlsruhe and at facilities at Hopital Notre-Dame in Montreal, Canada indicate that leeching is limited to less than 1% for a P32 ion implanted Palmaz-Schatz stent, an amount consistent with that contained in the first monolayer. Otherwise, the P32 atoms will not leech out unless the stent is chemically dissolved into the blood stream or the soft tissues. This is not likely to occur, since the biocompatibility of the stainless steel has been demonstrated thoroughly in the past.

In addition, as a result of the experiments at the Forschungzentrum Karlsruhe, an optimal post implant washing procedure has been developed which removes approximately 70% of the P32 that can leech out. This results in a potential leeching out in the body of much less than 1% of the total stent activity. This would be less than 10 nanocuries for a 1 microcurie stent and is insignificant compared to the natural radioactivity of the human body.

Appendix 6

Description and Data from Stent Washing Tests

Although the P32 ion implanted into stents is almost entirely embedded below the surface, there is a single layer of phosphorous atoms (approximately 1% of the total activity) on the surface which contains the only P32 which can ever be washed off the stent. Although essentially all of the P32 is on the outer surface of the stent which is embedded in the arterial wall and not subject to the potential washing effects of the blood, it is important to test a worst case scenario where both the outside and inside of the stent are washed.

Between December 1995 and February 1996 washing experiments were conducted at the Forschungszentrum Karlsruhe (Fzk), the German research center where the stents are ion implanted. The object of these experiments was to develop a stent washing process which would remove most of the P32 that could possibly come off the stent.

In these experiments 10 half Palmaz-Schatz stents were ion implanted with an average activity of 11 μCi . This is more than ten times the activity that will be implanted per mm of length in the IRIS trial.

Early experiments showed that the best technique for removing leachable P32 from the stent surface was to ultrasonically wash the stents in 0.9% NaCl solution at 42° C for 15 minutes. These experiments also showed that the washout amount was independent of stent P32 activity and of whether the stents were expanded.

The table below shows for three of the stents which were first ultrasonically washed as described above and then washed in a NaCl solution for 65 days including 38 hours in which ultrasonic washing was used to attempt to maximize washout. The washout during the NaCl wash and the total amount washed out in 65 days are shown. It should be noted here that in an artery, a stent would become encapsulated by tissue in far less than 65 days.

Stent No.	Initial 15 min. NaCl solution washout (%)	65 day washout (%) after initial 15 min.	Total 65 day washout (%) in NaCl Solution	% of the total 65 day wash out removed by the initial 15 minute NaCl wash
K 5.13	0.9	0.20	1.10	82
K 5.15	0.7	0.23	0.93	75
K 5.17	1.5	0.37	1.87	80
Average Values				79

* The total 65 day washout includes the initial 15 minute NaCl washout amount.

It should be noted that although there was some variation on the total amount washed out, the post wash amount was always significantly less than 1% and the NaCl ultrasonic wash took out at least 75 % of the removable P32.

Even a less effective washing step using Alcohol instead of NaCl kept the post wash washout below 1%. This is seen in the table below.

Stent No.	Alcohol Solution washout (%)	Post Alcohol washout (%)	Total 65 day washout (%)	% of 65 day wash out removed by Alcohol wash
K 5.14	0.9	0.32	1.82	49
K 5.16	0.2	0.72	0.92	10
K 5.18	0.2	0.52	0.77	26
Average Values				28

Here it is seen why the NaCl wash is preferred. Not only is it more effective but it is more consistent in its removal of washable P32 from the stent surface.

The table that follows shows the NaCl wash results from the most recent batch of full Palmaz-Schatz stents where the activities range from 7.0 μCi to 30.7 μCi.

Stent No.	Stent Activity (μCi)	NaCl Solution washout (%)
K 8.1	7.0	0.39
K 8.2	22.5	0.50
K 8.3	22.1	0.37
K 8.4	18.2	0.37
K 8.5	19.8	0.44
K 8.6	17.6	0.40
K 8.7	8.8	0.42
K 8.9	11.1	0.67
K 8.11	9.0	0.60
K 8.12	30.4	0.37
K 8.13	30.7	0.29
K 8.14	10.3	0.70
K 8.16	11.1	0.40

It is clear from this lot of full stents, that the stent activity is not a factor in the % removed during NaCl washing. To keep the maximum body washout below 1% of the total activity we have set a quality standard for the IRIS trial, to not accept any stent where the NaCl wash removes more than 2% of the total activity. This is based on the initial test results where 15 minutes of NaCl ultrasonic washing removed more than 70% of the total activity that could ever come off the stent.

It should be noted, that the measurements for long term washout following the NaCl wash provided ultrasonic wash cycles where the wash solution was in contact with the outer surface of the stent (where the P32 is embedded). This is clearly a very worst case as implanted stents are embedded in the arterial wall where the outer surface is not exposed

to blood flow. What is more, the entire stent should become encapsulated with tissue within a few days of implant, even further reducing the probability of P32 wash out.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 28 1996

Ms. A. Jill Schweiger
Vice President, Regulatory and Clinical Affairs
IsoStent, Incorporated
957 P Industrial Road
San Carlos, California 94070

Re: IDE Number G960087
Palmaz-Schatz™ Balloon-Expandable IsoStent™ with Delivery System
Indications for Use: The device is intended to help maintain the patency of stented coronary arteries.
Dated: April 30, 1996
Received: May 1, 1996
HCFA Reimbursement Category: B3

Dear Ms. Schweiger:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. Your application is conditionally approved, and you may begin your investigation, using a revised informed consent document and a revised study protocol which corrects deficiency number 1-R. This investigation may be conducted at an institution after you have obtained institutional review board (IRB) approval and submitted certification of IRB approval to FDA.

Your investigation is limited to three institutions and thirty subjects.

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following deficiencies:

1. Please address the following issues regarding the clinical protocol:

   a. With respect to study objective A, please identify specific safety and efficacy endpoints with definitions for "acute or subacute effects." FDA suggests that you include the following: subacute thrombosis, myocardial infarction, revascularization, death and neutropenia secondary to ticlopidine. Also, how is restenosis to be defined? The case report

forms should be structured to capture the appropriate information for each of the endpoints.

b. For study objective B, what specific radiation safety training will be provided to the Principal Investigator (PI) and the catheterization laboratory staff? Will the devices be implanted by the PI only? How much previous experience with implantation of Palmaz-Schatz stents is required? What specific radiation safety information will be given to the patients?

c. The study inclusion criteria do not include clinical symptoms or syndromes. The case report forms (CRFs) suggest that patients with unstable coronary artery disease syndromes such as unstable angina and evolving myocardial infarction be included in this Phase I safety study. The potential synergy of increased thrombogenicity due to delayed endothelialization in the presence of unstable plaques with thrombus is unknown. Since the safety of radioactive stents has not been demonstrated in any patient population, FDA believes that the Phase I safety study be completed in patients with stable coronary artery syndromes to minimize patient risk. FDA also believes that stenting should be limited to 1 coronary artery per patient. Sequential stents covering a lesion length of up to 26-28 mm is acceptable. In the event of an unexpected increase in thrombogenicity and subacute thrombosis, stenting of 2 coronary arteries may place patients at undue risk. Please revise your protocol accordingly.

d. Please justify inclusion of patients with only a 50 percent diameter coronary artery stenosis. Must these patients also present with clinical symptoms in order to qualify for inclusion? Also, given that FDA's Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices defines success as a >20 percent change in luminal diameter with a final diameter stenosis <50 percent, how will acute procedural success be documented in these patients? This definition would require an initial minimum diameter stenosis of 70 percent in order for a procedure to be characterized as a success.

e. Please add contrast hypersensitivity as an exclusion criterion. What level of renal insufficiency will be excluded to minimize risk for contrast induced renal failure?

f. Although less than 10 nanocuries of P32 are expected to leech out of the stent based on the data in Appendix L6, lactating women should be excluded. Please revise exclusion criterion (n) to read "Pregnant, lactating and women of childbearing potential .....".

g. Section 2.2.G states that patients will complete evaluations at the following intervals: pre-procedure, immediately post-procedure, and at 1, 6, and 12 months post-procedure. Appendix A indicates that patients will have white counts checked at 2, 4, and 6 weeks post-procedure. Please include in the protocol a flow diagram and table indicating all time points and studies that patients will complete during follow-up. Since the safety and efficacy of radioactive stents is unknown, FDA believes that long-term follow-up at yearly intervals is required in these patients until the IDE is closed.

h. Section 2.3.D indicates that ticlopidine will be administered for 6 weeks post-procedure to minimize the risk of acute and subacute thrombosis. If the risk period for acute and subacute thrombosis exists for up to 6 weeks (45 days), why is the safety data for these endpoints being collected at 30 days? Please clarify this discrepancy.

i. In Appendix A-Section 6, please identify the primary study endpoints (clinical and technical) and provide appropriate definitions.

j. In Appendix A-Section 7, please enclose the autopsy protocol. Also, the consent form should be modified to state that an autopsy will be requested in the event of patient death for examination of the heart.

k. In Section 8, Appendix A, please identify the criteria to be used to determine that there are no unanticipated adverse device effects within the first 30 days following the 30 procedures. For example, are you going to compare the incidence of subacute

thrombosis, myocardial infarction, revascularization, and death in this patient group to similar data for nonradioactive Palmaz-Schatz stents?

1. The labeling indicates that a cardiac surgery team will be on standby during stent implantation. Please modify the protocol to include this requirement. Further, please provide documentation that surgical standby is available at each participating medical center.

m. The labeling indicates that MRI is contraindicated for 8 weeks after stent implantation. Please specify this in the patient consent form.

n. FDA suggests that the inclusion and exclusion criteria be incorporated in the form entitled "Case Summary Form" (Appendix C2) to facilitate patient evaluation and completion of the form. Please list ticlopidine as a discharge medication. The section on Site Description(s)/Coronary list the vessel types as native and gratt. Please clarity this discrepancy since the protocol includes native vessels only.

o. Please modify the CRFs to include follow-up for ticlopidine induced neutropenia.

p. The protocol indicates that IVUS measurements will be made at the time of cardiac catheterization. Please modify the CRFs to include this data and the measurements to be derived from the data.

q. In Appendix C4, anginal pain is classified using the CCS scale. Please modify the protocol and all CRFs to ensure that this classification is used in a consistent manner.

2. The following modifications should be made in the patient consent form:

a. The language in the patient consent form is too technical and complex for the average lay person. Medical and scientific terms are used without any definitions or explanations. Please simplify the language so that it can be understood by a person with an 8th grade education.

b. FDA suggest that the consent form be organized in the following sections: Introduction, Purpose of Study, Description of Procedures, Follow-up, Risk, and Potential Benefits.

c. Please clearly specify the following items: (i) this study involves research; (ii) radioactive stents have not been previously used in humans and the purpose of the study is to determine the safety of these devices in humans for the first time and; (iii) the use of radioactive stents may involve risks to the patient which are currently unforeseeable.

d. The number of subjects participating in the study should be stated in accordance with CFR Part 50.25.

e. The information provided in Tables 1, 2, and 3 is uninterpretable as presented to the average lay person. This information should be explained in simple text form. The risk section should also include known information on the possibility of radiation induced coronary artery damage such as long-term fibrosis and aneurysm formation.

3. Please address the following issues regarding the P32 isotope and the engineering of the device:

a. You have stated that a washing process removes most of the P32 not fully embedded. Please explain your validation process of 1 percent removable activity. Also, how is the amount of removable activity routinely monitored?

b. The source activity is measured by "traceable" means. However, no information is provided regarding how the activity is determined. Please clarify how the source activity is determined.

c. A Monte Carlo calculation was done to estimate the dose from the implanted P32 isotope in the stent. Please provide experimental verification of this calculation.

d. Please explain how the local institution will independently validate the stent's activity before use (see page 18, last paragraph).

e. The criteria for uniformity of activity distribution over the stent surface is ±20 percent. Please clarify if this uniformity is along the length of the stent or on the surface (or at 0.1 micron depth).

f. There is no mention of correction due to absorption within the implant layer of the stent. Considering that the ions are implanted at a depth of 0.1 micron, please discuss what effect this absorption will have on the dose levels predicted by the Monte Carlo calculation.

g. Please specify the thickness of the plastic safety shield and clarify whether the shield actually comes in contact with the stent.

The following additional deficiencies were noted during the review of your application and must be addressed before any expansion of the study can be considered:

1. Since one of the Principal Investigators and the "independent" angiographic core laboratory are located at the same institution, please explain how this does not represent a conflict of interest? What safeguards are used to ensure "independent" function of the core laboratory? Further, since this core laboratory analyzes data for multiple clinical studies, what safeguards are used to ensure appropriate data set management? For example, what steps will be taken to ensure that your data set includes data for your patients only? In addition, please provide the operating manual for the core laboratory.

2. Please address the following concerns regarding the device labeling:

   a. Labeling for the device should follow the format outlined in the Device Labeling Guidance (enclosed). Please revise your labeling as appropriate.

   b. Please modify the labeling to incorporate the revised inclusion and exclusion criteria.

   c. FDA suggests that you consider giving each patient a device identification card similar to pacemaker patients indicating that they have a radioactive stent and MRI is contraindicated for 8 weeks post-implantation.

3. Information presented in Table 1 (and in Appendix L1, etc.) suggests that as the 3.0 mm stent expands its length increases to 15.1 mm. Please explain how this is possible or verify that this is simply a typographical mistake.

4. FDA recommends that Nuclear Regulatory Commission (NRC) be contacted for advice regarding NRC, state, and local authority licensure of the PALMAZ-SCHATZ™ Balloon-Expandable IsoStent™ for the clinical study that you are proposing. Attachment C of the Intravascular Brachytheraphy Guidance Document (enclosed) specifies the appropriate NRC contact.

This information should be identified as an IDE supplement referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you do not provide this information within 45 days from the date of this letter, we may take steps to propose withdrawal of approval of your IDE application.

We would like to point out that FDA approval of your IDE application does not imply that this investigation will develop sufficient safety and effectiveness data to assure FDA approval of a premarket approval (PMA) application for this device. You may obtain the guideline for the preparation of a PMA application, entitled "Premarket Approval (PMA) Manual," from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597.

We have enclosed the guidance document entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation" to help you understand the functions and duties of a sponsor. Also enclosed is the guidance document "Investigators' Responsibilities for a Significant Risk Device Investigation" which you should provide to participating investigators.

If you have questions, please contact H. Semih Oktay, Ph.D., at (301) 443-8243.

Sincerely yours,

for Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

Borgess Medical Center
1521 Gull Road
Kalamazoo, Michigan 49001-1640
Telephone 616-226-7000

Member of
Sisters of St. Joseph
Health System, Inc.
Ann Arbor, Michigan

R9

August 13, 1996

BORGESS
Medical Center

John Madera
Branch Chief
Nuclear Materials License
U.S. Nuclear Regulatory Commission
Region 3
810 Warrenville Road
Lisle, Illinois 60532-4357

Dear Mr. Madera:

I would like to follow up on our phone conversation that took place last Tuesday and stress to you the importance of getting the amendment to our license changed. As you are aware, Borgess Medical Center is the first medical center in the country to utilize the Isostent, which uses a P-32 isotope. Borgess needs your assistance to expedite the approval process for the amendment to our NRC license, which was submitted to your attention July 5, 1996. (License #21-12275-02) Please, let me know if there is anyone I can contact at the home office in Washington, D.C. to help expedite this process.

This cardiac stent and its application is in the best interest of patient care. We already have one patient candidate for this procedure who is awaiting approval so the procedure can be performed.

I appreciate your consideration and look forward to hearing from you very soon.

Sincerely,

Gary Beaulac
Vice President, Ambulatory Services

GB/jcs

cc: Tim TenCate
Sandy Tolchin, M.D.

RECEIVED
AUG 14 1996
REGION III

PM; 8-13-96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 12 1996

Ms. A. Jill Schweiger
Vice President, Regulatory and Clinical Affairs
IsoStent, Incorporated
957 P Industrial Road
San Carlos, California 94070

Re: IDE Number G960087/S1
Palmaz-Schatz™ Balloon-Expandable IsoStent™ with Delivery System
Dated: July 3, 1996
Received: July 5, 1996

Dear Ms. Schweiger:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application. You have corrected the deficiencies cited in our May 28, 1996, conditional approval letter. Therefore, your supplement is approved and you may continue your investigation at the institutions enrolled in accordance with the investigational site waiver granted below. Your investigation is limited to three institutions and thirty subjects.

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of institutional review board (IRB) approval for the addition of investigational sites (21 CFR 812.35(b)) provided:

1. The total number of investigational sites does not exceed three.

2. You maintain current records on:

   a. the names and addresses of all investigational sites;

   b. the names and addresses of all investigators identifying those that are currently participating;

   c. the names, addresses and chairpersons of all IRBs;

   d. the dates of IRB approvals; and

e. the dates of first shipments or first use of investigational devices for all participating institutions.

3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.

5. You submit to FDA, within 2 days of receipt of a request by FDA, a current list containing the information specified in 2(a-e) above.

6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent, that is, require any change which may increase the risks to subjects or affect the scientific soundness of the study. (Please note: If a significant change is requested, this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site.) Minor changes requested by the IRB may be made without prior FDA approval.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has approved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement. Please note, however, that you must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation past the limit specified above. Additionally, if you do not agree to these conditions, you must comply with the full requirements for the submission to FDA of a supplemental IDE application for new investigational sites not already specifically approved for participation in your study (21 CFR 812.35.(b)).

If you have questions, please contact H. Semih Oktay, Ph.D. at (301) 443-8243.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

IsoStent, Inc.

August 9, 1996

Ms. Evelyn Matson
Medical Licensing-Region 3
Nuclear Regulatory Commission
801 Warrenville Rd.
Lisle, IL 60532

Re: Borgess Hospital
Nuclear License Amendment Application or Exemption
License 21-12275-02

Dear Ms. Matson:

On Friday August 9, 1996, IsoStent, Inc. received our IDE approval letter regarding our July 3, 1996 IDE Supplement for the Palmaz-Schatz Balloon-Expandable IsoStent. I have attached a copy of this letter for your reference.

The FDA has given us approval to conduct our investigation at 3 clinical sites. We would like for Borgess Hospital to be one of these sites. It will be important for Borgess to receive their license amendment or exemption from the NRC, in order for them to be able to participate.

We are planning to begin the study during the first week of September. The production of the radioactive stents has been scheduled for the last 2 weeks of August in order to have the product available for shipment. Since phosphorous 32 has a short half-life of 14.3 days, our stents are only usable for 2 weeks. Thus, any delay at a site could result in thousands of dollars of scrapped product.

We certainly appreciate the NRC's efforts in a timely review of Borgess Hospital's request. If you have any additional questions, please feel free to contact me at 415-593-2555 ext. 11.

Very truly yours,

Jill Schweiger
Vice President,
Regulatory & Clinical Affairs

Att. 1

957 F Industrial Road • San Carlos, California 94070
Tel (415) 593-2555 • Fax (415) 593-4479

IsoStent, Inc.

August 7, 1996

Ms. Evelyn Matson
Medical Licensing-Region 3
Nuclear Regulatory Commission
801 Warrenville Rd
Lisle, IL 60532

Re: Borgess Hospital
Nuclear License Amendment Application
License 21-12275-02

Dear Ms. Matson:

Thank you for speaking with me regarding the NRC review status of the Borgess Hospital nuclear license amendment application. Per our conversation, you had several issues that I will try to address with some additional information.

1. The IDE supplement indicates that the study will be performed at institutions that have a broad scope license. The NRC needs confirmation of whether the broad scope license is an FDA requirement for the study.

   Originally, we had planned to perform the clinical study at Vanderbilt University, Washington Hospital Center and Beth Israel Hospital, all of which are broad scope licensed facilities. In the meantime, the Vanderbilt clinical investigator accepted a new research position with Borgess Hospital and resigned from Vanderbilt. Thus, we had to submit an amendment to our IDE to add Borgess hospital as our 3rd clinical site for the study. At the time of this amendment, we did not know that Borgess did not have a broad scope license.

   In response to our original IDE submission, the FDA asked us to outline the radiation safety training that would be provided to the clinical investigators. Since each institution has a Radiation Safety Officer (RSO) that is responsible for providing radiation safety training to hospital personnel, we decided to provide each RSO a guideline to use for training specific to the P-32 stent handling. This training guideline was outlined in Appendix 5.1 of our IDE submission and was forwarded to the NRC in support of the license amendment. As you noted, in this guideline, we stated that the study was being conducted at broad scope licensed facilities. This was of course an oversight on our part, because we thought that Borgess was also a broad scope facility.

957 P Industrial Road • San Carlos, California 94070
Tel (415) 593-2555 • Fax (415) 593-4479

To date, the FDA has not imposed any additional regulatory requirements related to the handling of radioactive stents. They have alerted IsoStent to follow any nuclear regulatory requirements related to the handling of P-32 stents and to contact the NRC for these requirements. Therefore, it is not an FDA requirement for the clinical sites to be broad scope licensed facilities.

2. Has Borgess been approved by the FDA to be one of the clinical sites for this study?

We submitted an amendment to our original IDE application to add Borgess Hospital to our clinical study on July 3, 1996. I spoke to the FDA reviewer on Wednesday July 31, 1996 and he indicated that our supplement had been recommended for approval and the letter should be mailed to us by the end of the week. The IRB for Borgess Hospital is in the process of reviewing the protocol and should be notifying us shortly of their review.

Per FDA requirements, IsoStent cannot begin the study without having FDA and IRB approval of the site.

3. What are the maximum and minimum number of patients that Borgess can enroll in the study?

Borgess will be allowed to enroll from 5 to 15 patients in this study.

Please let me know if you have any additional questions or require additional information. I can be reached at 415-593-2555 ext. 11 or via FAX at 415-593-4479.

Sincerely,

Jill Schweiger

Jill Schweiger
Vice President,
Regulatory & Clinical Affairs

957 P Industrial Road • San Carlos, California 94070
Tel (415) 593-2555 • Fax (415) 593-4479

IsoStent, Inc.

August 9, 1996

Ms. Evelyn Matson
Medical Licensing-Region 3
Nuclear Regulatory Commission
801 Warrenville Rd.
Lisle, IL 60532

Re: Borgess Hospital
Nuclear License Amendment Application or Exemption
License 21-12275-02

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We certainly appreciate the NRC's efforts in a timely review of Borgess Hospital's request. If you have any additional questions, please feel free to contact me at 415-593-2555 ext. 11.

Very truly yours,

Jill Schweiger

Jill Schweiger
Vice President,
Regulatory & Clinical Affairs

Att. 1

PM 8/8/96

957 P Industrial Road • San Carlos, California 94070
Tel (415) 593-2555 • Fax (415) 593-4479

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 12 1996

Ms. A. Jill Schweiger
Vice President, Regulatory and Clinical Affairs
IsoStent, Incorporated
957 P Industrial Road
San Carlos, California 94070

Re: IDE Number G960087/S1
Palmaz-Schatz™ Balloon-Expandable IsoStent™ with Delivery System
Dated: July 3, 1996
Received: July 5, 1996

Dear Ms. Schweiger:

The Food and Drug Administration (FDA) has reviewed the supplement to your investigational device exemptions (IDE) application. You have corrected the deficiencies cited in our May 28, 1996, conditional approval letter Therefore, your supplement is approved and you may continue your investigation at the institutions enrolled in accordance with the investigational site waiver granted below. Your investigation is limited to three institutions and thirty subjects.

FDA will waive those requirements regarding submission and prior FDA approval of a supplemental application and receipt of certification of institutional review board (IRB) approval for the addition of investigational sites (21 CFR 812.35(b)) provided:

1. The total number of investigational sites does not exceed three.

2. You maintain current records on:

   a. the names and addresses of all investigational sites;

   b. the names and addresses of all investigators identifying those that are currently participating;

   c. the names, addresses and chairpersons of all IRBs;

   d. the dates of IRB approvals; and

e. the dates of first shipment or first use of investigational devices for all participating institutions.

3. Within 5 days of reaching the investigational site limit, you submit to FDA a current list containing the information specified in 2(a-e) above.

4. The current investigator list to be submitted to FDA at 6-month intervals (21 CFR 812.150(b)(4)) will contain the information specified in 2(a-e) above.

5. You submit to FDA, within 2 days of receipt of a request by FDA, a current list containing the information specified in 2(a-e) above.

6. The reviewing IRB does not require any significant changes in the investigational plan or in the informed consent, that is, require any change which may increase the risks to subjects or affect the scientific soundness of the study. (Please note: If a significant change is requested, this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site.) Minor changes requested by the IRB may be made without prior FDA approval.

If you agree to these conditions, you may begin an investigation at a new investigational site after the IRB has approved the investigation. No documentation should be submitted for any institution within the approved limit until the investigational site limit is reached or the 6-month current investigator list is due. FDA assumes that you have agreed to the conditions of this waiver unless you specifically notify us in writing of your disagreement. Please note, however, that you must submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation past the limit specified above. Additionally, if you do not agree to these conditions, you must comply with the full requirements for the submission to FDA of a supplemental IDE application for new investigational sites not already specifically approved for participation in your study (21 CFR 812.35.(b)).

If you have questions, please contact H. Semih Oktay, Ph.D. at (301) 443-8243.

Sincerely yours,

Thomas J. Callahan, Ph.D.
Director
Division of Cardiovascular, Respiratory,
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

96-54

MEMORANDUM TO: John R. Madera, Chief
Materials Licensing Branch
Division of Nuclear Materials Safety, RIII

FROM: Donald A. Cool, Director
Division of Industrial and
Medical Nuclear Safety, NMSS

SUBJECT: TECHNICAL ASSISTANCE REQUEST DATED JULY 23, 1996, (CONTROL NUMBER 301576) REGARDING BORGESS MEDICAL CENTER

I am responding to your technical assistance request (TAR) (attached) dated July 23, 1996, regarding the request by Borgess Medical Center for authorization to use phosphorus-32 (P-32) for intravascular use as a cardiac stent. We have reviewed the TAR and have determined that the ion-implanted stent is not a sealed brachytherapy source as defined in 10 CFR 35.2 and authorized under 10 CFR 35.400, *Use of sources for brachytherapy*, nor does it fit into the uses of unsealed byproduct material for therapy as authorized under 10 CFR 35.300, *Use of unsealed byproduct material for therapeutic administration*. Therefore, neither an exemption from the provisions of 10 CFR 35.400 nor an authorization for use under 10 CFR 35.300 is appropriate.

NRC does not intend to prevent the research allowed under the Investigational Device Exemption (IDE) granted by the U.S. Food and Drug Administration, in the absence of applicable medical use regulations. Therefore, after review of the information submitted, I suggest that the region grant the licensee's request for authorization to use the P-32 stents under the IDE by using the following license condition:

> "As requested in the licensee's letter dated July 5, 1996, the licensee is authorized to order, receive, and implant phosphorus-32 (P-32) ion-implanted Palmaz-Schatz Balloon-Expandable IsoStent for use under the Investigational Device Exemption (IDE) of the device, authorized by the U.S. Food and Drug Administration (FDA) in the FDA letter to IsoStent, dated May 28, 1996, and subsequent phases of the IDE process associated with the device which are approved by the FDA. The devices are to be used by, or under the supervision of only those physicians who: 1) are identified in the licensee's letter requesting this authorization; 2) are subsequently authorized by the licensee pursuant to 10 CFR 35.13; or 3) are subsequently authorized, by license amendment, pursuant to 10 CFR 35.930(b) for use of 10 CFR 35.300 materials."

Contact: James Smith, NMSS
(301) 415-7904

In addition, it is our understanding that the FDA considers use of this device for treatment to prevent restenosis as a "significant risk" procedure; therefore, the granting of the IDE for these trials represents a detailed review of the radioactive stent, the associated implantation procedures, and research protocol. Since the research is conducted under an FDA IDE, and the FDA has adopted the Federal Policy for the Protection of Human Subjects, no additional information is needed from the licensee regarding compliance with Section 35.6, *Provisions for research involving human subjects*. This approach to human research will satisfy the informed consent and approval provisions of Section 35.6.

Attachment: RIII TAR dtd 7/23/96

SEP 3 0 1996

Gary Beaulac
Vice President, Ambulatory Services
Borgess Medical Center
1521 Gull Road
Kalamazoo, MI 49001

Dear Mr. Beaulac:

Enclosed is Amendment No. 73 to your NRC Material License No. 21-12275-02 in accordance with your request.

Please review the enclosed document carefully and be sure that you understand all conditions. If there are any errors or questions, please notify the U.S. Nuclear Regulatory Commission, Region III office at (630) 829-9887 so that we can provide appropriate corrections and answers.

We have determined that the ion-implanted stent is not a sealed brachytherapy source as defined in 10 CFR 35.2 and authorized under 35.400, Use of Sources for Brachytherapy, nor does it fall under the use of unsealed byproduct material for therapy as authorized in 10 CFR 35.300, Use of Unsealed Byproduct Material for Therapeutic Administration. Neither an exemption from the provision of 10 CFR 35.400 nor an authorization for use under 10 CFR 35.300 is appropriate; therefore, we have authorized the use of the device in Subitem F to Items 6., 7., 8. and 9. of your license.

In addition, we have granted the use of the device to the physicians as requested in your July 5, 1996 letter.

Please be advised that your license expires at the end of the day, in the month, and year stated in the license. Unless your license has been terminated, you must conduct your program involving byproduct materials in accordance with the conditions of your NRC license, representations made in your license application, and NRC regulations. In particular, note that you must:

1. Operate in accordance with NRC regulations 10 CFR Part 19, "Notices, Instructions and Reports to Workers; Inspections," 10 CFR Part 20, "Standards for Protection Against Radiation," and other applicable regulations.

2. Notify NRC, in writing, within 30 days:

   a. When an authorized user or Radiation Safety Officer permanently discontinues performance of duties under the license or has a name change; or

301576

b. When the licensee's mailing address changes (no fee is required if the location of byproduct material remains the same).

3. In accordance with 10 CFR 30.36(b) and/or license condition, notify NRC, promptly, in writing, and request termination of the license when you decide to terminate all activities involving materials authorized under the license.

4. Request and obtain a license amendment before you:

   a. Receive or use byproduct material for a clinical procedure permitted under Part 35 but not permitted by your license issued pursuant to this Part;

   b. Permit anyone, except individuals described in 10 CFR 35.13(b), to work as an authorized user under the license;

   c. Change Radiation Safety Officers;

   d. Order byproduct material in excess of the amount, or radionuclide, or form different than authorized on the license;

   e. Add or change the areas of use or address or addresses of use identified in the license application or on the license; or

   f. Change ownership of your organization.

5. Submit a complete renewal application with proper fee or termination request at least 30 days before the expiration date of your license. You will receive a reminder notice approximately 90 days before the expiration date. Possession of byproduct material after your license expires is a violation of NRC regulations. A license will not normally be renewed, except on a case-by-case basis, in instances where licensed material has never been possessed or used.

In addition, please note that NRC Form 313 requires the applicant, by his/her signature, to verify that the applicant understands that all statements contained in the application are true and correct to the best of the applicant's knowledge. The signatory for the application should be the licensee or certifying official rather than a consultant.

You will be periodically inspected by NRC. Failure to conduct your program in accordance with NRC regulations, license conditions, and representations made in your license application and supplemental correspondence with NRC will result in enforcement action against you. This could include issuance of a notice of violation, or imposition of a civil penalty, or an order suspending, modifying or revoking your license as specified in the General Policy and Procedures for NRC Enforcement Actions. Since serious consequences

to employees and the public can result from failure to comply with NRC requirements, prompt and vigorous enforcement action will be taken when dealing with licensees who do not achieve the necessary meticulous attention to detail and the high standard of compliance which NRC expects of its licensees.

Sincerely,

Original Signed By
Kevin G. Null
Nuclear Materials Licensing Branch

License No.: 21-12275-02
Docket No.: 030-02115

Enclosure: Amendment No. 73

DOCUMENT NAME: M:\03002115.CL6

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NAME	KGNULL:jaw	KGN	EMATSON		JRMADERA					
DATE	09/30/96		09/ /96		09/ /96					

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