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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.





301576

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
21-12270-02 amendment request
1996

P-32 Stent Program Only
RADIOACTIVE MATERIAL AND USE

| *Item 5* *Byproduct Material* | *Item 6* *Amount* | *Purpose* |
|---|---|---|
| Please add to our existing authorized materials: | | |
| 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.

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.

*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. 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

| 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: _____

# 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 | _____ |

# 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 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.

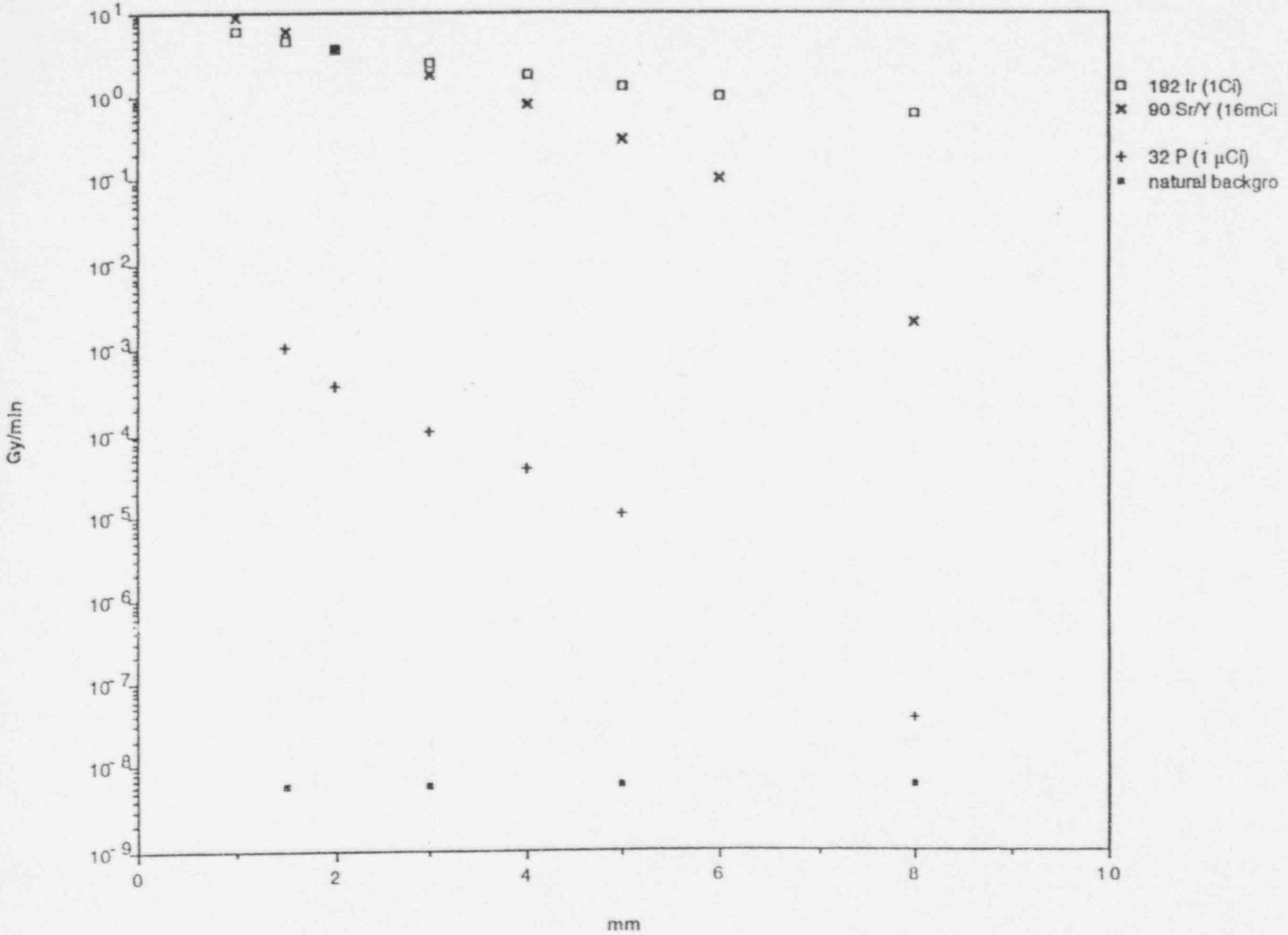
4. If a stent is ever lost, its activity level becomes undetectable as compared to background at approximately five months after it is manufactured. It therefore poses no possibility of a long term hazard as could be the case for long-lived isotopes.

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 the 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 | 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 | 22.1 | 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

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 F 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 s ...ed 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 graft. Please clarify 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 educati...

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