APR 10 1997

97-12

REQUEST FOR TECHNICAL ASSISTANCE

DATE: APRIL 4, 1997

TO: DON COOL, Director, Division of Industrial and Medical Nuclear Safety, NMSS

FROM: for CASSANDRA FRAZIER (Kevin A Hart), Acting Chief, Nuclear Materials Safety Branch Region III

LICENSEE: CLEVELAND CLINIC FOUNDATION LICENSE NO. 34-00466-01

X Control No. 302384 (enclosed)

_____ Letter dated _____ (enclosed)

_____ Suggested change in licensing procedure (enclosed)

_____ Other (see remarks)

Problem/Issue: THE LICENSEE HAS SUBMITTED A REQUEST FOR AUTHORIZATION TO USE PHOSPHOROUS-32 FOR INTRAVASCULAR USE AS A CARDIAC STENT. SPECIFICALLY, THEY ARE REQUESTING THE POSSESSION AND USE OF THE FISCHELL ISOSTENT WITH DELIVERY SYSTEM. THE DEVICE IS MANUFACTURED BY ISOSTENT,INC. AND HAS BEEN EVALUATED AND AN "INVESTIGATIONAL DEVICE EXEMPTION " (IDE) HAS BEEN APPROVED BY THE FDA (IDE # 960087). THE LICENSEE'S REQUEST AND PROCEDURES ARE ATTACHED FOR YOUR REVIEW.

Action Required: PLEASE EVALUATE AND PROVIDE COMMENTS.

Alternatives Considered: THE REGION USED THE CRITERIA OUTLINED IN A TAR COMPLETED FOR BORGESS MEDICAL CENTER DATED SEPTEMBER 27, 1996 FOR OUR REVIEW. THE LICENSEE HAS PROPOSED ALTERNATIVE AUTHORIZED USER CRITERIA (35.930 OR 35.940.) WHICH WE FIND ACCEPTABLE.

Recommended Alternative: THE TAR RESPONSE FOR BORGESS MEDICAL CENTER INSTRUCTED THE REGION TO ADD A LENGTHY PARAGRAPH TO THE LICENSE. WE WOULD LIKE TO PROPOSE AN ALTERNATIVE, ADD THE P-32 STENTS AS A SEPARATE LINE ITEM UNDER ITEMS 6, 7, 8, AND 9. OF THE LICENSE (WE COULD SPECIFY FORM, ACTIVITY PER STENT, TOTAL ACTIVITY POSSESSED, AND SPECIFIC USE IN THIS PART OF THE LICENSE). THE PROCEDURES FOR USE WOULD BE INCLUDED IN THE "TIE-DOWN" CONDITION. THIS WOULD ELIMINATE THE NEED FOR THE LENGTHY PARAGRAPH ORIGINALLY PROPOSED AND REMAINS CONSISTENT WITH OUR CURRENT LICENSING PROCEDURES.

Remarks: WE HAVE INCLUDED THE LICENSEE'S ORIGINAL REQUEST, A COPY OF OUR CONVERSATION RECORD FOR ADDITIONAL INFORMATION AND THEIR RESPONSE. WE REQUEST THAT YOU EVALUATE THIS TAR FOR GENERIC USE.

Regional Reviewer: PATTY PELKE, (PJP2)
Reviewer Code: R6
Reviewer Phone No. (630) 829-9868

cc: R.J. Caniano

March 24, 1997
License No.: 34-00466-01
Control Number 02384

Item 2 Training

The training that will be provided to personnel involved in the placement of the Isostent is outlined in Attachment 2.

Item 3 Special Equipment

The IsoStent will be supplied with a clear plastic radiation shield attached with a Touhy-Borst over the distal end of the stent delivery catheter and covers the stent so as to minimize radiation exposure to the patient and health care workers. The distal end of the radiation shield is designed to fit into the Touhy-Borst of guiding catheter "Y" adapter. No other special equipment will be required.

When necessary, additional shielding will be provided.

Item 4 Personnel Monitoring

According to the manufacturer, the shielding supplied with the Isostent will reduce the radiation exposure from the P-32 to a value approximately equal to background radiation. The cardiologists who will place the Isostent in the patient will be provided with radiation monitoring finger badges. The cardiologists who perform the procedure are required to wear whole body monitoring badges and ring badges. The finger badges and whole body monitoring badges are not required for other personnel participating in the procedure. The whole body radiation monitoring badges are required for personnel in the room when the angiographic unit is used during the procedure.

Item 5 Rules for Safe Use

The rules for safe handling are outline by the manufacturer's package insert (Attachement-1). The manufacturer's instruction shall be followed. In addition:

a) Each Isostent shall be secured from any unauthorized removal or use.
b) In the event that an Isostent dislodges from the shield, remote handling tools shall be used to handled the Isostent.
c) The Isostent shall never be cut, bent or any other deformation that may damage the integrity of the Isostent.
d) Each Isostent source shall be accounted for at all times.
e) Radiation Safety shall be notified of any abnormal event to ensure that the appropriate corrective actions are implemented and, proper procedures are followed to record and report the event.

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Item 6 Emergency Procedure
See Attachment-3.

Item 7 Inventory Procedures

See Attachment-4

Item 8 Modified Quality Management Program
See Attachment 5

Item 9 Other Procedures
The existing ordering, package receipt, and waste disposal procedures will be followed when applicable to Isostent for Restenosis Intervention Study (IRIS).

As we discussed on March 13, 1997, the P-32 isostent dosage is exempt from measuring with a dose calibrator (10CFR35.53), because the Isostent contains less than 2 μCi of the beta emitter P-32, and is provided as an "unit dosage" from the manufacturer.

Your assistance in facilitating a timely review of the request is most appreciated. Please do not hesitate to contact me for additional information with regard to these requests. I can be contacted at (216)-444-6645 or by e-mail on the internet at ZHUX@CESMTP.CCF.ORG.

Sincerely,

Xiaowei Zhu, M.S. DABMP
Radiation Safety Officer

NRC License No. 34-00446-01
Control 05564
Attachment - 1

ISOSTENTS FOR RESTENOSIS INTERVENTION STUDY (IRIS)

FISCHELL™ ISOSTENT™ with delivery system

PRODUCT CODES: PSI 1530
PSI 1535

Directions for Use:

INCLUSION CRITERIA FOR ENROLLING PATIENTS

Patients with symptomatic coronary artery disease who are eligible for balloon angioplasty may be enrolled in the IsoStents for Restenosis Intervention Study (IRIS) if they meet all of the inclusion criteria of the IRIS protocol.

Once the physician has determined that revascularization is indicated for the patient, the alternative treatments if the patient is not entered into the study include PTCA (balloon angioplasty), elective P-S stenting (non-radioactive), directional atherectomy, or bypass surgery of the stenosed vessel(s).

EXCLUSION CRITERIA

Patients must be excluded from the IsoStents for Restenosis Intervention Study (IRIS) if they meet any of the IRIS protocol exclusion criteria.

WARNINGS

Use of this device carries the associated risks of subacute thrombosis, an excess of vascular complications and/or bleeding events, and an increased length of hospital stay when compared with balloon angioplasty. Judicious selection of patients to receive this device rather than balloon angioplasty is strongly advised.

Infection secondary to contamination of the stent may lead to thrombosis, pseudoaneurysm, or rupture. The metal stent may cause a spasm, distal embolization, thrombus, or could migrate from the site of implant down the arterial lumen. Excessive stretching of the artery may cause rupture and life threatening bleeding. However, no instance of coronary arterial rupture or stent migration from the site of implant was reported in recent studies of the non radioactive Palmaz-Schatz stent.

Anticipated Adverse Events

Table 1 lists the anticipated adverse reactions/complications for FISCHELL ISOSTENTS (P-S ISOSTENTS) which must be entered on the IRIS Complication Report Form.

Table 1. Anticipated Adverse Events

(1) Death	(10) Prolonged Angina
(2) CABG	(11) Hypotension
(3) Myocardial Infarction	(12) Cerebrovascular Accidents
(4) Stent Thrombosis	(13) Vascular Complications
(5) Groin Complications	(14) Stent Delivery Failures
(6) Intimal Dissection	(15) Stent Migration/Embolization
(7) Spasm	(16) VT/VF
(8) Distal Emboli	(17) Brachycardia Requiring Pacemaker
(9) Side Branch Closure	

Unanticipated Adverse Events

Any adverse device effect not listed in Table 1 must be reported to IsoStent within 24 hours of the event.

PRECAUTIONS

The implantation of the FISCHELL ISOSTENT should be performed only by physicians who are experienced in standard Palmaz-Schatz stent implantation.

A cardiac surgery team should be on stand-by while stent implantation is being performed.

Technique of Stent Placement

The FISCHELL ISOSTENT is provided sterile for one procedure only. Do not resterilize.

These stents may contain radioisotopes with a limited shelf life so the devices must be used between the DO NOT USE BEFORE DATE and the DO NOT USE AFTER DATE noted on the package.

Guiding catheters used must have lumen sizes which are suitable to accommodate the introduction of the 5F stent delivery system. This requires a guide catheter size of at least 8F (internal diameter > 0.084"). When catheters are in the body, manipulation should only be performed under fluoroscopy with radiographic equipment that provides high-quality images.

Excessive manipulation may cause dislodgment of the stent from the carrier balloon.

DO NOT PRE-INFLATE THE BALLOON CATHETER. This could cause premature expansion and dislodgment of the stent from the balloon. If any resistance is encountered while advancing the sheath or stent/balloon assembly to the site of the previously dilated lesion, the assembly may be drawn through the guide catheter and introducer sheath and the procedure aborted.

The sheath should not be withdrawn until the operator is ready to expand the stent. In the event of inadvertent advancement of the sheath, the entire system should be removed from the patient and another system should be utilized for treatment. "Snagging" of the stent on atherosclerotic plaque in the arterial lumen may occur if the stent is advanced without the protective sheath, leading to an inability to place the stent at the intended treatment site.

DO NOT APPLY NEGATIVE PRESSURE TO THE CATHETER PRIOR TO PLACEMENT OF THE STENT ACROSS THE LESION AND RETRACTION OF THE SHEATH. This may cause premature dislodgment of the stent from the carrier balloon.

Do not exceed recommended balloon inflation pressure. Use of an inflation device with a manometer is recommended during the stent delivery procedure. Stents should be sized to assure full contact with the vessel wall. Stent wall contact should be verified through routine angiography and intravascular ultrasound. When deemed appropriate further dilatation of the stent may be performed using a larger diameter balloon catheter and/or a balloon catheter capable of higher pressure inflation.

Although the stent delivery balloon catheter is strong enough to expand the stent without rupture, circumferential tear of the carrier balloon distal to the stent and prior to complete expansion of the

stent could cause the balloon to become tethered to the stent, requiring surgical removal. In case of rupture of the balloon, it should be withdrawn and, if necessary, a new balloon catheter exchanged over the guidewire to complete expansion of the stent.

Although this trial is intended to enroll only patients treatable with a single stent, in the event that two or more stents are used in a single vessel, the distal lesion should be stented first, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent to place the distal stent and reduces the chances for dislodging the proximal stent.

When removing a recently implanted stent, care should be taken to assure the guidewire is placed within the lumen and not between the stent and the vessel. Otherwise, inadvertent dislodgment of the stent may occur leading to inappropriate positioning of the stent.

Magnetic Resonance Imaging (MRI)

A magnetic resonance imaging scan should not be performed until the implanted stent has been completely endothelialized (eight weeks), in order to minimize the risk of migration of the stent under a strong magnetic field. The stent may cause susceptibility artifacts in MRI scans due to distortion of the magnetic field.

DEVICE DESCRIPTION

General Features

The device is enclosed in a sterile package. It consists of a balloon-expandable intracoronary stent premounted onto the balloon of a delivery catheter. The stent/balloon assembly is covered with an integral sheath. The stent is provided on balloon catheters with 3 mm (PSI-1530) and 3.5 mm (PSI-1535) diameter balloons. In the IRIS trial, the stents will contain the radioisotope Phosphorous 32 embedded beneath the surface of the metal. Phosphorous 32 is a pure beta emitting radioisotope with half-life of 14.3 days and maximum beta energy of 1.7 Mev.

The sheath is intended to protect the stent/balloon assembly and the coronary vessel as the stent is being advanced to the lesion site.

A "lock-out" component is attached to the back end of the catheter/sheath assembly. This component maintains the sheath in the correct position in relation to the catheter during insertion and advancement of the device through the vasculature. It also prevents premature retraction of the sheath.

A clear plastic radiation shield is attached with a Touhy-Borst over the distal end of the stent delivery catheter and covers the stent so as to minimize radiation exposure to the patient and health care workers. The distal end of the radiation shield is designed to fit into the Touhy-Borst of the guiding catheter "Y" adapter.

The FISCHELL ISOSTENT with delivery system does not provide for distal dye injection or pressure measurement with the guidewire in position because the polymer coating of the inner lumen is not intended to withstand internal pressures greater than 250 psi. If distal injections are required, only manual injections with a 5 cc or larger syringe should be attempted, and only when the guidewire is withdrawn.

The nominal length of the stent is 15 mm. The stent consists of two 7 mm long segments connected by a 1 mm bridge or articulation. This bridge facilitates negotiation of the stent through the coronary anatomy to distal lesions. The stent has been polished to remove irregularities from the surfaces and edges. The usable length of the delivery system is 127 cm. The outside diameter of the system is 5F.

Table 2. Expanded Stent Dimensions

Stent Inner Diameter	Stent Length
3.0 mm	15.1 mm
3.5 mm	14.7 mm

Stent Physiology: After expansion of the stent by complete inflation of the carrier balloon, the atherosclerotic plaque is compressed against the stretched media and adventitial layers of the artery. The metal mesh is incorporated in the arterial wall as neointimal cells and endothelium bridge over the struts to completely cover the inner surface of the stent. Experimental animal studies have shown that non radioactive metal mesh stents are completely endothelialized in one week in rabbits, and in three weeks in dogs in native coronary arteries. Specimens obtained at autopsy two-months post-implant reveals that a similar endothelialization occurs following stent implantation in humans.

In animal experiments at radiation dose levels equivalent to that of the FISCHELL ISOSTENT, stents were completely endothelialized in 4 weeks.

CLINICAL PROCEDURE

Method: The placement of the stent in a native coronary artery should be done following standard percutaneous transluminal coronary angioplasty procedures.

Recommended Drug Regimen

This information is provided as a guide and is not intended to dictate medical practice. (For further information see discussion in WARNINGS). Prothrombin times and Partial Thromboplastin Time (PT and PTT) levels and platelet counts should be obtained at hospital admission in order to establish patient baseline levels.

Prior To Stent Implantation:
- Aspirin (non-enteric coated, non-buffered) • 325mg po qd • 48 hours prior to procedure
- Ticlopidine •250 mg po bid • 0-48 hours prior to procedure (administer starting 48 hours prior to procedure whenever possible)

During Stent Implantation:
- Heparin • 10,000-15,000 units IV bolus depending on patient weight, then as needed to maintain ACT above 300 seconds

Immediately After Stent Implantation:
- Heparin • Discontinue

Remaining In-Hospital Phase:
- Aspirin (non-enteric coated, non-buffered) • Continue 325mg po qd.
- Ticlopidine 250 mg po bid
- Heparin • Following sheath removal (preferably 4-6 hours following completion of stent implantation) and access site hemostasis, give heparin 5,000 units subcutaneously q 12h for 3-4 doses.

Long-Term Post-Stent:
Aspirin (non-enteric coated, non-buffered) • 325mg po qd • indefinitely.
- Ticlopidine • 250 mg po bid• for 4 weeks

Preparation of the Stent Delivery System

Carefully inspect the stent delivery system package for damage to the sterile barrier. Remove the device from the package and rinse it in sterile saline. Do not remove the clear plastic radiation shield that is positioned over the stent at the distal end of the catheter.

DO NOT PRE-INFLATE THIS BALLOON CATHETER. This could cause premature expansion and dislodgment of the stent from the balloon.

DO NOT APPLY NEGATIVE PRESSURE TO THE CATHETER PRIOR TO PLACEMENT OF THE STENT ACROSS THE LESION AND RETRACTION OF THE SHEATH. This may cause premature dislodgment of the stent from the corner balloon.

Route of Introduction of the Stent Delivery System

Utilizing standard procedures for balloon angioplasty, an introducer sheath (a minimum of 8F is required) with a side arm adapter is placed in the femoral or brachial artery and flushed with saline. Under fluoroscopic control, the occluded area is gently probed with a 0.014" coronary guidewire. Once the lesion is traversed a standard balloon angioplasty procedure is performed to predilate the lesion prior to stent implantation. Care should be taken not to over-dilate the lesion, in order to minimize the potential for balloon angioplasty related complications. The lesion may be intentionally under dilated. Following a wire exchange (if necessary), the balloon angioplasty catheter is withdrawn, leaving the guidewire positioned across the lesion.

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 sheathed 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.

Under fluoroscopic observation, the sheath is pulled back exposing the stent at the lesion site. The radiopaque markers of the balloon catheter should bracket the previously dilated lesion to assure proper positioning of the stent. Attach inflation device and inflate the balloon to at least 5 atmospheres of pressure but do not exceed the labeled maximum inflation recommendation (see table below).

Table 3. Maximum Recommended Inflation Pressure

Product Code	Balloon Diameter	Maximum Recommended Inflation Pressure	Stent Length at Nominal Diameter
PSI-1530	3.0 mm	8 atm	15.1 mm
PSI-1535	3.5 mm	7 atm	14.7mm

Visual observation should be used to determine proper expansion. Fluoroscopic visualization during stent expansion should be used in order to properly judge the optimum expanded stent diameter as compared to the proximal and distal native coronary artery diameter(s). Optimal expansion requires that the stent be in full contact with the arterial wall. If the stent is not optimally expanded by the stent delivery balloon, a larger balloon (up to 4 mm) and higher pressures (using an appropriate balloon dilatation catheter) may be used to further expand the stent to its optimal size. The final stent internal diameter should match or slightly exceed the size of the referenced vessel diameter. All efforts should be taken to assure that the stent is not under dilated. For the protocol for the IRIS trial all stents should be assessed with intravascular ultrasound (IVUS) after high pressure balloon inflation. Further stent expansion would be indicated in those cases in which the stent is 1) not fully apposed to the vessel wall, and/or 2) stent symmetry is deemed suboptimal, and/or 3) the stent cross-sectional area is not appropriately large compared to adjacent reference segment(s).

Completion of Procedure

Following angiographic and IVUS confirmation of complete and adequate stent expansion, remove the coronary guidewire, balloon catheter and guiding catheter through the sheath introducer. The following sheath removal technique may minimize the risk of access site complications. In the event of access site complications ultrasound guided compression of small pseudoaneurysms may reduce the need for further therapy.

Discontinue heparin following the end of the procedure. When the ACT is less than 150-160 seconds, remove the sheaths (typically 4-6 hours post-procedure).

Apply groin pressure for 15 to 30 minutes as necessary, followed by a C-clamp or femostop for 1-2 hours. A pressure bandage may be applied and the patient should remain flat in bed for a minimum of 6-8 hours.

Following sheath removal and access site hemostasis, begin heparin 5,000 units subcutaneously q12h x 3-4 doses.

Aspirin and ticlopidine should be continued, as above for the time periods described. Patients taking ticlopidine should have a complete blood count drawn at 2 and 4 weeks after starting that medication to monitor for any signs of neutropenia. This medication should be discontinued immediately if the white blood cell count falls to <3,000 and/or < 50% of baseline values.

THE FISCHELL ISOSTENT WITH DELIVERY SYSTEM IS PROVIDED STERILE. DO NOT RESTERILIZE.

Protected under one or more of the following U.S. Patents: B1-4,733,665; 4,739,762; 4,776,337; 5,102,417; 5,195,984; 5,059,166 others pending.

PALMAZ-SCHATZ is a trademark of Johnson & Johnson Interventional Systems Co.
ISOSTENT is a trademark of IsoStent, Inc.

REFERENCES

1. Fischman, D.L., Savage, M.R. Leon, M.B., Schatz, R.A., Ellis, S., Clemen, M.W., Hirshfeld, J.W., Teirstein, P., Reilly, S., Walker, C.M., Goldberg, S., "Fate of Lesion Related Side Branches after Coronary Stenting," JACC 1993; 22: 1641-8.
2. Palmaz, J. C., Windeler, A. S., Garcia, E, et al, "Expandable Intraluminal Grafting in Atherosclerotic Rabbit Aortas," Radiology 1988; 160:723-726.
3. Palmaz, J. C., Sibbitt, R.R., Tio, F.O., et al, "Expandable Intraluminal Vascular Graft: A Feasibility Study," Surgery 1986, 99:199-205.

Attachment -2 -Training

NRC License No. 34-00466-01
Control 02384 (CCF ^ '24/97)

Training Guidelines for Radiation Safety

All individuals who will be involved in the placement of Fischell Isostent study shall attend the training to address issues as outline in this guideline. The training will be provided by Radiation Safety, and Cardiology staff.

1. Radiation Principals

a) The units of radioactivity, occupational radiation exposure limits. Some aspects of natural radioactivity and background radiation.

b) The specific attributes of phosphorous-32. Dose to tissue from the Isostent.

2. Device Training

a) Size and appearance of the Isostent and shield.
Each stent will be crimped onto a balloon angioplasty catheter, covered with a sheath and a sheath and a 1 inch diameter clear plastic radiation shield will be locked over the distal section of the catheter containing the Isostent.

b) Inventory and preventing of unauthorized removal
Review inventory requirements specifically applicable to the storage, use and return of the Isostent. Each Isostent shall be stored and used in the areas secured or attended from unauthorized removal.

3. Device Safe Handling and Use of Shielding

The Directions for Use which describe the handling methods for the Isostent delivery system will be included in each stent package. The training review 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 sheathed 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.

Also,

- 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 the stent at any time before the delivery catheter is advanced into the body. If the radiation shield accidentally come 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 the radiation shield at any time.

- If the stent delivery system has been advanced into the body, but for some reason the Isostent 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 Radiation Safety 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 Radiation Safety should be contacted to provide an appropriate disposal container.

- All personnel should avoid any direct handling of the bare stent with their fingers if possible. If not possible, the wearing of surgical gloves will reduce the direct contact dose rate for a 1 uCi P32 stent to less than 100 mrem per minute.

4. Patient Control

5. Principles of Quality Management Program

6. Emergency Response

7. Applicable Institutional Policies

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Attachment -3 Emergency Procedures

A. In the event of losing the Isostent during the procedure

a) Notify persons in the area that loss of Isostent has occurred.
b) Do not allow any one to leave the immediate area.
c) Notify Radiation Safety immediately.
d) Radiation Safety will survey everyone who was in the room, with a sensitive survey meter before anyone leaves the area
e) The area will remain closed until the Isostent is found or the entire area is surveyed with a sensitive survey meter by Radiation Safety.
f) Immediately notify the Radiation Safety Officer to facilitate proper investigation, records and reports.

B. In the event of medical emergency

A cardiac surgery team MUST be on stand-by while the Isostent implantation is being performed.

a) In the event of a medical emergency, the Isostent should be retrieved whenever medically possible from the patient.

b) The Radiation Safety Officer and the authorized user physician shall be informed immediately to facilitate proper investigation, record keeping and report filing.

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Attachment 4 Inventory Procedure

The Isostent will be delivered to Radiation Safety and stored in Radiation Safety. Radiation Safety shall initiate an inventory record to document the serial number, date received, radioactivity of each Isostent (on calibration date) received, and total number of un-expired Isostents in storage at the date of receipt.

Prior to the procedure, Radiation Safety will deliver the Isostents to the designated room, at the anticipated procedure time. Radiation Safety staff shall record the removal of the Isostent from Radiation Safety to the procedure room. The number of Isostents, delivered to the procedure room, the identification of each Isostent and radioactivity of each Isostent shall be recorded by the Radiation Safety staff and verified by a second trained individual from the Isostent study.

Before the Isostent is implanted, the Cardiologist shall verify Isostents delivered, and select the proper size of the Isostent.

After the Isostent is implanted, the cardiologist or the authorized user physician shall record the actual Isostent implanted in the patient treatment record. Radiation Safety shall update the Isostent inventory record and return the unused Isostents to Radiation Safety.

Radiation Safety will periodically check the Isostent inventory. All expired Isostents will be removed for storage-for-decay. The Isostent inventory will be updated after each removal of the expired Isostents.

March 24, 1997
License No.: 34-00466-01
Control Number 02384

Attachment 5 - Quality Management Program

The Cleveland Clinic Foundation

Quality Management P ogram - P-32 Fischell Isostent

1. A Written Directive will be prepared before administration

The Authorized user physician shall indicate the radionuclide, number of Isostents, and a range of the Isostent strength (in radioactivity) for the specific patient on Isostent for Restenosis Intervention Study Record (IRIS Record).

Written revision to the written directive may be made prior to administration of the treatment. The authorized user physician must sign and date the revision of the written directive. Oral revisions are acceptable, if a delaying to provide for a written revision will jeopardize the patient's health due to emergent nature of the patient's medical condition. Changes resulting from an oral revision shall be noted in the patient's record immediately and revised written directive shall be signed by the authorized user physician and dated within 48 working hours.

2. The patient's identity will be verified by more than one method prior to administration.

The patient's identity will be confirmed by the authorized user physician, or a cardiologist for the study, or a trained nurse, or a trained research coordinator for the study. Confirmation will be by two of following: patient stating name; confirming with patient record the birth date, or address, or social security number, or signature; check the patient name on the patient's ID bracelet, hospital ID card, or patient's medical insurance card; comparison with a photograph of patient's face. The two methods used will be documented on the checklist and initialed by the individual performing the verification in the (IRIS Record).

3. Before the administration of the Isostent the removed shall be verified

Prior to administration, the radionuclide, number of the Isostents and strengths of the Isostents delivered to the procedure room will be verified by a second trained individual (authorized user physician, or a cardiologist for the study, or a trained nurse, or a trained research coordinator for the study). The verification will be recorded on the IRIS record.

4. All individuals will be instructed to seek guidance from the authorized user physician for clarification if they do not understand a written directive.

All personnel involve in implantation of the Isostent are instructed to seek guidance from the authorized user physician signing the written directive if there are any questions or incomplete

information. If the authorized user physician is not immediately available, the treatment should not be initiated until clarification is received.

5. Verify the Isostent to be implanted before administration

Before the Isostent is implanted, the Cardiologist who performs the implantation shall verified that the radionuclide, number and strength of the Isostent are in accordance to the written directive. The Cardiologist shall sign the IRIS record for the verification.

6. Verification of Isostent adequate expansion

The adequate expansion of the Isostent will be confirmed by diagnostic procedures (e.g. angiography) as determined by the Cardiologist or authorized user physician.

7. Record of adminstration:
Promptly after the implantation, a record of actual loading information (radionuclide, site of implant, and activity of the Isostent, and that the Isostent a permanent implantation) of the Isostent shall be entered in the patient's chart by the authorized user physician or the cardiologist who performed implantation. The authorized user physician shall review and enter the actual loading information to the IRSI record, date and sign the record

8. Each administration shall be reviewed to ensure treatment was in accordance with the written directive.

Following completion of treatment, the administration dose will be compared with that prescribed. The authorized user physician shall sign and date the IRIS indicating that the administration is in accordance with the prescriptions. Any unintended deviation will be noted in the IRIS Record. Immediately report to the Radiation Safety Officer (RSO) any deviations greater than +/- 10% to permit proper investigation, reporting, documentation and follow up.

The Isostent study shall be reviewed by the RSO as per "The Cleveland Clinic Quality Management Program; All Aspect of Quality Management " as applicable.

CONVERSATION RECORD

TIME 10:45 am DATE 3/13/97

O VISIT O CONFERENCE X TELEPHONE

O INCOMING
X OUTGOING

NAME OF PERSON(S) CONTACTED OR IN CONTACT: WINNIE ZHU
ORGANIZATION (OFFICE, DEPT.ETC.): CLEVELAND CLINIC
TELEPHONE NO.: 216-444-5199

SUBJECT

AMENDMENT REQUEST DATED 2/25/97 (LN 34-00466-01, CN 02384)

SUMMARY

I CONTACTED MS. ZHU TO DISCUSS THE INFORMATION PROVIDED IN THE 2/29/97 LTR. I INDICATED THAT WE WOULD NEED NO FURTHER INFORMATION REGARDING ITEMS 1. AND 5. OF THEIR LETTER. HOWEVER, WE WILL NEED THE FOLLOWING ADDITIONAL INFORMATION IN ORDER TO EVALUATE THE REQUESTS IN ITEMS 2. AND 4. OF THE LETTER:

PLEASE PROVIDE THE FOLLOWING INFORMATION REGARDING THE FICHELL P-32 STENTS:

1. SPECIFY THE PHYSICAL FORM OF THE P-32 (ION IMPLANTED, PLATED, LIQUID, ETC) THAT'S USED IN THE STENT, THE ACTIVITY PER STENT, AND THE TOTAL ACTIVITY THAT YOU WILL POSSESS. ALSO SPECIFY THE NAME OF THE STENT MANUFACTURER;

2. TRAINING THAT WILL BE PROVIDED TO PERSONNEL INVOLVED IN THE PLACEMENT OF THE STENT;

3. ANY SPECIAL EQUIPMENT THAT WILL BE REQUIRED FOR THE STENT PROGRAM (EG, SPECIALIZED SHIELDING OR HANDLING EQUIPMENT);

4. PERSONNEL MONITORING;

5. RULES FOR THE SAFE USE OF THE STENTS. IT MAY BE HELPFUL IF YOU PROVIDE A COPY OF THE PROTOCOL YOU WILL USE FOR THIS PROCEDURE;

6. EMERGENCY PROCEDURES;

7. INVENTORY PROCEDURES; AND

8. MODIFICATION OF YOUR QMP PROGRAM TO ADDRESS THIS PROCEDURE.

9. ALSO CONFIRM THAT THE PROCEDURES YOU ALREADY HAVE ON FILE FOR ORDERING, PACKAGE RECEIPT, AND WASTE DISPOSAL WILL BE FOLLOWED FOR THIS APPLICATION.

IN ORDER TO CONTINUE OUR REVIEW OF YOUR REQUEST TO USE THE HDR UNIT FOR ENDOVASCULAR THERAPY, IT WILL BE NECESSARY FOR YOU TO PROVIDE THE FOLLOWING INFORMATION:

1. PLEASE DEFINE/CLARIFY THE TERM "ENDOVASCULAR THERAPY";

2. SUBMIT A COMPLETE DESCRIPTION OF THE PROTOCOL YOU WILL FOLLOW FOR THIS THERAPY AND CLARIFY THAT THIS USE WILL BE FOR RESEARCH PURPOSES;

3. CONFIRM THAT THE RESEARCH MEETS THE REQUIREMENTS OF 10 CFR PART 35, SECTION 35.6. IF THE RESEARCH FALLS OUTSIDE OF THESE REQUIREMENTS (E.G., NOT SPONSORED, REGULATED FUNDED, ETC. BY A FEDERAL AGENCY THAT HAS ADOPTED THE "FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS"), PLEASE CONFIRM THAT YOU WILL OBTAIN "INFORMED CONSENT" FROM THE RESEARCH SUBJECTS AND THAT YOUR IRB WILL REVIEW AND APPROVE THE RESEARCH PROCEDURES;

3. THE HDR DEVICE IS NOT CURRENTLY REGISTERED FOR USE "ENDOVASCULARLY". THE DEVICE REGISTRATION WILL NEED TO BE AMENDED TO INCLUDE THIS USE. PLEASE PROVIDE A DESCRIPTION OF ANY UNIQUE EQUIPMENT OR APPLICATORS THAT WILL BE USED FOR ENDOVASCULAR THERAPY. IF THIS USE WILL NOT REQUIRE ANY NEW OR UNIQUE EQUIPMENT, PLEASE INDICATE THIS IN YOUR RESPONSE.

4. CONFIRM THAT YOU WILL FOLLOW THE PROCEDURES CURRENTLY ON FILE FOR THE USE OF THE DEVICE (OPERATION, SAFETY CHECKS, CALIBRATION, ETC.);

5. DESCRIBE ANY ADDITIONAL TRAINING THAT WILL BE PROVIDED TO THE STAFF (NURSES, TECHNOLOGISTS, ETC.) THAT WILL BE INVOLVED IN THIS PROCEDURE AND CONFIRM THAT THE PHYSICIAN USERS WILL MEET THE QUALIFICATIONS OF 35.940. ALSO IDENTIFY ANY ADDITIONAL STAFF THAT MAY BE INVOLVED IN THIS PROCEDURE.

ON ORDER TO CONTINUE OUR REVIEW OF YOUR REQUEST FOR "IN-VIVO" USE OF THE RHENIUM WIRE (SUBITEM JJ. OF YOUR LICENSE), PLEASE PROVIDE THE FOLLOWING:

1. CONFIRM THAT THESE ARE "IN-VIVO" ANIMAL STUDIES, NOT HUMAN RESEARCH STUDIES. ALSO CLARIFY THAT THESE ARE TEMPORARY NOT PERMANENT IMPLANTS;

2. SUBMIT A DESCRIPTION OF THE STUDY AND INCLUDE MAXIMUM ACTIVITY PER ANIMAL AND THE TYPES OF ANIMALS THAT WILL BE INVOLVED IN THIS RESEARCH, (E.G., RABBITS, DOGS, COWS, ETC.);

3. DESCRIBE YOUR PROCEDURES FOR HANDLING THE WIRE. CLARIFY WHETHER THIS IS PRECUT WIRE OR IF YOU WILL BE CUTTING THE WIRES. INCLUDE THE MAXIMUM ACTIVITY PER WIRE AND THE ACTIVITY THAT WILL BE USED ROUTINELY. IF YOU WILL BE CUTTING THE WIRE, INCLUDE YOUR PROCEDURES AND ANY SPECIALIZED EQUIPMENT THAT WILL BE NECESSARY;

4. DESCRIBE THE RADIATION SAFETY PROCEDURES YOU HAVE ESTABLISHED FOR THIS USE. INCLUDE THE SURVEYS, CONTAMINATION CONTROL, PERSONNEL MONITORING, HANDLING EQUIPMENT, INVENTORY PROCEDURES, SHIELDING, AND ANY ADDITIONAL INFORMATION WE MAY NEED TO EVALUATE YOUR REQUEST; AND

5. A DESCRIPTION OF THE FACILITY WHERE THESE STUDIES WILL BE DONE AND A DESCRIPTION OF THE FACILITIES USED TO HOUSE THE ANIMALS. ALSO INCLUDE THE INSTRUCTIONS YOU PROVIDE TO ANIMAL CARETAKERS.

ACTION REQUIRED

PLEASE RESPOND IN DUPLICATE, WITHIN 30 DAYS, AND REFER TO CONTROL NO. 02384. REQUEST FOR P-32 STENTS AND HDR FOR ENDOVASCULAR USE WILL BE FORWARDED TO OUR HQ STAFF AS A "TECHNICAL ASSISTANCE REQUEST", WHICH WILL REQUIRE ADDITIONAL REVIEW TIME.

NAME OF PERSON DOCUMENTING CONVERSATION
PATRICIA J. PELKE

SIGNATURE
Patricia J. Pelke

DATE
3/14/97

ACTION TAKEN