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February 12, 2001

VIA HAND DELIVERY

Mr. John W. Hickey
Chief, Material Safety & Inspection Branch
Division of Industrial & Medical Nuclear Safety
Office of Nuclear Materials Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, D.C.

Dear Mr. Hickey:

On behalf of Novoste Corporation ("Novoste"), I want to thank you and the other Nuclear Regulatory Commission ("NRC") personnel for your participation in the conference call with me and Novoste representatives on January 31, 2001. Novoste is committed to the protection of the health and safety of the public in the use of its Beta-Cath System, and wants to do all that is necessary to support sound guidance to the NRC regions on the licensing of this device.

Our discussions on the 31st were very helpful to us in understanding some of the bases for the draft NRC Staff guidance that was made available publicly a short time prior to the call, and we hope that some of our preliminary observations on this draft guidance were also very helpful to you. We understand that you will take into account the written comments which follow in issuing final guidance.[1] It is very important to us that we develop and maintain a good working relationship with NRC on this matter, and we would be pleased to meet with you if this would be useful in producing sound guidance. Moreover, if you have any questions about the comments which follow, please do not hesitate to give me a call. However, as we explained

[1] These comments are directed at the version of the draft guidance on the licensing of the Beta-Cath System that was available prior to the telephone conference on January 31, 2001.

during the call, we do not want to delay the normal processing of applications by 10 C.F.R. Part 35 licensees for permission to use the Beta-Cath System.[2]

Background

About 700,000 Americans undergo balloon angioplasty each year to reopen obstructed coronary arteries. Most of these, about eighty percent, will also be given a stent, a tiny metal scaffold that props open the vessels. But in about twenty percent of those cases, the stents become plugged up because of the build-up of scar tissue. This results in a new condition called in-stent restenosis which affects more than 100,000 patients in the United States alone.

Novoste's Beta-Cath system is a major advance in the prevention of this condition, which would otherwise require very invasive and expensive by-pass surgery. Novoste has invested about $175 million in developing and assuring the safety and efficacy of the device, and the Beta-Cath System has been the subject of extensive research and clinical trials, approved by the Food and Drug Administration ("FDA") for routine use, reviewed and approved by Agreement State (Georgia) officials, and placed in the NRC's Sealed Source and Device Registry ("SSDR") maintained pursuant to 10 C.F.R.§ 32.210 (See Attachment A for a copy of the SSDR certificate). In addition, since the Beta-Cath System uses beta as opposed to photon emitting isotopes, it represents a major advance in assuring that radiation exposures to medical personnel are ALARA, as required by 10 C.F.R. § 35.20.[3] Indeed, since the use of the Beta-Cath System tends to reduce exposures to medical personnel, the imposition of unnecessary regulatory requirements on its use would be inconsistent with the ALARA concept.[4]

While many features of the NRC Staff draft guidance are entirely appropriate, certain other features are not and could severely restrict the use of this medical treatment. As a result, in many circumstances qualified physician-users would be prevented from exercising their best medical judgment to use the Beta Cath System for treating patients with coronary restenosis. We

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[2] The comments which follow were developed in accord with the version of 10 C.F.R. Part 35 currently in effect for applicants and licensees. We recognize that the NRC has approved a new version of this Part that may be published in the Federal Register and come into effect sometime in the future. See SECY-00-0118, May 31, 2000. We believe that our comments are consistent with this new Part as well.

[3] The Beta-Cath System is the subject of extensive, favorable comment in the literature. See, e.g., the January 25, 2001 issue of the New England Journal of Medicine, at http:/www.negm.org.

[4] NRC Staff licensing guidance for a photon emitting device also intended for prevention of coronary restenosis makes note of the requirements for shielding and special measures needed to assure that dose limits for restricted and unrestricted areas are not exceeded.

respectfully request that these features be reconsidered. As explained below, we believe that the features of the draft guidance which concern us have no adequate safety basis, are contrary to NRC regulations, and are inconsistent with NRC's published policy in the licensing and regulation of radiation medicine.

The Beta-Cath System

As described in the SSDR certificate (No. GA-1115-D-101-S, as revised November 20, 2000), the Beta Cath System is a "manually-controlled intra vascular brachytherapy device" that has been developed to reduce the incidence of coronary restenosis (SSDR certificate at 2). There are three models, and each includes four principal components: the source train; the delivery catheter; the transfer device; and system accessories. The device uses sealed sources, each consisting of a Sr-90 ceramic matrix contained within a very small stainless steel tube with laser-welded steel lids at each end. The source train, which consists multiple, individual sealed sources (in quantities of 12, 16 or 24) with a non-radioactive radiopaque marker seed at each end, provides a radiation dose along a fixed treatment length. The source train is designed to easily navigate within a delivery catheter and, when not in use, is stored within the transfer device (SSDR certificate at 2). The SSDR states specifically that "[f]or all models, no single source [is] to exceed 5.0 millicuries (185 MBq)(SSDR certificate at 1). The SSDR meets all of the requirements of 10 C.F.R. § 32.210 and NRC guidance in NUREG-1556, Vol 3.

Comments

1. The Limitation to 3.5 mCi Sources.

NRC's regulations in 10 C.F.R. §' 32.74, 32.210, 35.49, and 35.59 establish the regulatory framework for the NRC licensing of medical devices such as the Beta-Cath System. These regulations establish an NRC pre-marketing approval system for sealed sources and devices containing by-product material, commonly called the SSDR system. See, e.g., "Palladium-103 for Interstitial Treatment of Cancer," 54 Fed. Reg. 41819, October 12, 1989.[5] In legal effect, these regulations operate much like an NRC Staff approval of a nuclear facility design under 10 C.F.R. Part 50, Appendix O, except that an SSDR certificate has an even greater legal status than an Appendix O design approval because the NRC incorporates the radiation safety and handling conditions, as described by the manufacturer and included in the approved SSDR certificate, into its regulations in 10 C.F.R. Part 35. 10 C.F.R. § 35.59. The SSDR review process is comprehensive, and addresses design, manufacture, testing, quality

[5] The new 10 C.F.R. Part 35 would include a definition of the SSDR as follows. "Sealed Source and Device Registry means the national registry that contains all the registration certificates, generated by both NRC and the Agreement States , that summarize the radiation safety information for the sealed sources and devices and describe the licensing and use conditions approved for the product."

assurance, labeling, leak testing, servicing, installation, servicing, maintenance, approved uses, and operating and safety instructions. 10 C.F.R. § 32.210.

NRC's approval of a device under § 32.210 and issuance of SSDR registration certificate, and NRC's inclusion of an equivalent Agreement State SSDR certificate in the NRC SSDR, reflect an NRC finding that "the radiation safety properties of the device or sealed source are adequate to protect health and minimize danger to life and property." 10 C.F.R. § 32.210 (d).[6] In short, apart from possible additional restrictions related to the special circumstances of the proposed user and other specific additional requirements of the NRC regulations, an SSDR certificate constitutes an NRC pre-licensing approval for use of the sealed source or device. It would be wholly contrary to the regulations, and indeed wholly contrary to the whole concept of the NRC's SSDR, were NRC to include a sealed source in its SSDR, and then repudiate that regulatory action by imposing requirements on 10 C.F.R. Part 35 applicants and licensees that are inconsistent with the SSDR certificate. We suggest that NRC repudiation of the sufficiency of a certificate would destabilize the entire system of licensing and regulation of sealed sources and devices, and make SSDRs worthless.

Unfortunately that is what the draft guidance for the Beta-Cath System appears to do. The most egregious aspect of the proposed guidance would restrict Part 35 licensees to sources not exceeding 3.5 mCi. This would make it impossible for many licensees to accept the Beta-Cath System, since many include higher activity sources, and is contrary to the express conditions of the SSDR certificate, which as indicated above specifically provides that "no single source [can] exceed 5.0 millicuries (185 MBq.) (SSDR certificate at 1). Moreover, the FDA approval is consistent with the SSDR certificate and does not include any 3.5 mCi limit.

We think that the source of this proposed limit may be some confusion associated with the NIST traceable calibration technique used in the clinical trials. Although neither the radiation dose nor the radiation sources (BEBIG Model SrO.S03) have ever changed, the NIST traceable calibrated source train dose rate was associated originally with a NIST traceable calibrated nominal activity of 3.5 mCi per source, based on a radio-chemical analysis of a single typical seed. Later, NIST provided a new calibration factor that enabled Novoste to relate the

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[6] We do not argue here that NRC is legally bound by every safety determination of an Agreement State. However, Agreement State SSDR determinations have a special status, since NRC incorporates them into its regulations and NRC's safety requirements on sealed sources and devices intended for distribution are matters of strict compatibility for Agreement States (State requirements must be essentially identical). In our case, Georgia's Agreement State program has been found by NRC to be adequate and compatible. Moreover, NRC reviews Agreement State SSDR certificates and reserves the right to reject them. However, in such a case, NRC must inform the State of its concerns. To our knowledge, NRC has not commented adversely on any aspect of the Georgia SSDR certificate for the Beta-Cath System.

typical seed. Later, NIST provided a new calibration factor that enabled Novoste to relate the total Sr-90 activity in a source train to a NIST traceable dose rate at 2mm in water, the reference distance and medium. This enabled Novoste to provide both a NIST traceable dose rate and a NIST traceable activity unique to a specific source train. In fact, the actual sources varied somewhat (less than 5.0 mCi), once the new calibration factor was implemented. This additional activity calibration is explained in the SSDR certificate at pages 9-10.

In any event, with no change in the measured dose rate, there is no basis for NRC's draft 3.5 mCi limit. After all, radiation health effects are related directly to doses, not activity, and the dose rate is traceable beyond the 3.5 mCi value. The use of sources with activities up to 5.0 mCi is fully consistent with the FDA approval, and we would also note that NRC has assumed no regulatory obligation to enforce FDA requirements in any event. If NRC wants to enforce a 3.5 mCi limit, it needs to justify such a limit based on its own safety determination. We are aware of no NRC safety evaluation that supports a 3.5 mCi limit.

2. The Authorized Use Condition.

The draft guidance would specify that the Beta-Cath System be used "for the treatment of coronary arteries for in-stent restenosis lesions less than 20 millimeters in length . . . ." This is inconsistent with the FDA approval, which provides that the Beta-Cath System "is indicated to deliver beta radiation to the site of successful Percutaneous Coronary Intervention (PCI) for the treatment on in-stent restenosis in native coronary arteries with discrete lesions (treatable with a 20 mm balloon) in a reference vessel diameter ranging from 2.7 mm to 4.0 mm." The NRC limitation, expressed in terms of lesion size as opposed to balloon size, will have unknown effects on treatment options, and has no safety basis. We understand that NRC Staff agrees that its guidance should conform to the FDA approval.

This kind of restrictive condition is also contrary to the SSDR certificate, which has no similar language in its "Limitations and/or Other Considerations of Use." (See SSDR certificate at pages 11-12).

Finally, and perhaps most importantly, this kind of restrictive condition on use of the device by individual licensees is contrary to NRC policy on the licensing and regulation of radiation medicine, even if the NRC language is conformed to the language of the FDA approval. Long ago, NRC sought to apply FDA limitations directed at distribution and advertising of devices containing Atomic Energy Act materials to the actual practice of medicine by physicians who used those materials, but NRC policy has changed substantially since then.

In 1990 NRC completed rule making that specifically authorized its licensees and authorized users "to depart from the FDA approved instructions to obtain diagnostic or therapeutic medical results not otherwise obtainable or to reduce medical risks to particular

patients because of their medical condition." 55 Fed. Reg. 34513, August 23, 1990. This was based on the essential NRC regulatory premises that "physicians have the primary responsibility for the protection of their patients," and that "basic decisions concerning the diagnosis and treatment of disease are a part of the physician-patient relationship and are traditionally considered to be part of the practice of medicine." Id. More recently, in its "Medical Use Of Byproduct Material; Policy Statement, Revision," 65 Fed. Reg. 47654, August 3, 2000 (2000 Policy Statement), NRC stated specifically that its policy "is not to intrude into medical judgments affecting patients, except as necessary to provide for the radiation safety of workers and the general public," and that "the focus of NRC regulation to protect the patients health and safety is primarily to ensure that the authorized user physician's directions are followed."

Accordingly, consistent with the 1990 rule making, the regulations in 10 C.F.R. § 35.400 on the use of sources for brachytherapy include only very general limitations on indications (e.g., "for interstitial treatment of cancer"). Moreover, the revised 10 C.F.R. Part 35 Notice of Rule Making, that NRC has approved but is not yet published, would not only eliminate even these very general restrictions, but would also reiterate that "NRC regulations are predicated on the assumption that properly trained and adequately informed physicians will make decisions that are in the best interests of their patients," and state that "the NRC does not intend to develop requirements that are redundant with those of the FDA." The Notice of Rule Making also provides that a deviation from the terms of an FDA approval by an individual NRC licensee does not necessarily require a license amendment, so long as the conditions of the SSDR registration are satisfied and the device was properly distributed under 10 C.F.R. § 32.74. See draft Notice of Rule Making at page 183.

The draft guidance contains no reason why the NRC must interfere in the exercise of medical judgment by physicians using the Beta-Cath System because of the health and safety of workers or the general public. Given this, it is contrary to NRC policy as explained above to restrict uses of the System to the particular indications in the FDA approval. To impose such a restriction would produce the very result sought to be avoided by the 1990 rule making and the 2000 Policy Statement. It would prevent authorized user physicians from exercising their best medical judgment in circumstances where a departure from the exact terms of the FDA approval are required for therapeutic results that are not otherwise obtainable or to reduce patient risk.

Therefore, we request that the draft use restriction be changed to read simply "to reduce the incidence of restenosis in native coronary arteries." This would conform the draft guidance to NRC policy. Nothing in NRC's relationship with the FDA requires any further restriction, since

10 C.F.R. § 35.7 makes it clear that NRC can do nothing to relieve anyone from complying with any and all FDA requirements.[7]

3. Verifying Source Strength.

The draft guidance would require an "independent verification of the source strength by the licensee." This is contrary to the SSDR certificate, which includes no such limitation, and is not required by NRC regulations in 10 C.F.R. § 35.59. Moreover, as explained below, even if there were an NRC regulation that required a verification of source strength as a generic matter, such a requirement is not necessary for safety in the use of this particular device. Therefore, an exemption from a verification requirement under 10 C.F.R. § 35.19 would be warranted.

The Beta-Cath System is a closed system where the sources are not interchangeable. The source train is calibrated by Novoste for activity and dose rate traceable to NIST and a certificate is provided unique to that source train and transfer device. Because of the half life of the material. the user is not required to adjust the Novoste provided NIST traceable dose rate during the approved six month use period included in the SSDR certificate. The source train is never handled or even removed from the transfer device by the user. Moreover, after the approved six months use period the device is to be returned to the manufacturer for maintenance. See SSDR certificate at page 11. The NIST traceable calibration is adequate for this approved use period and radioisotope.

Novoste believes that independent source strength verification is good practice, and can recommend instrumentation specifically designed to measure these source trains. But the cost is significant and may be a significant burden for some facilities such as small community hospitals. While we have no objection to NRC requiring that licensees consider the use of such instrumentation to measure source strength, as explained above we feel that there is no safety basis to mandate its use.

4. Use of the Arrow Introducer Sheath.

The draft guidance would require the user to use the Beta-Cath System with a particular name-brand product, an Arrow introducer sheath, to prevent source transport blockage during treatment. This is apparently based on NRC Staff's own review of some clinical trial or use data, and the conclusion that use of the Arrow sheath will prevent mis-administrations. While, as in the case of use of instrumentation for independent source strength verification, Novoste encourages users to evaluate the use of this accessory device, and has no difficulty with an NRC

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[7] We also note that NRC Staff guidance for another product also intended to prevent coronary restenosis does not include any restrictive use condition like the one recommended in the draft guidance for the Beta-Cath System.

requirement that use of this accessory be considered by licensees, Novoste believes that a regulatory requirement for use is not justified.

First, requiring use is contrary to the SSDR certificate, which reflects careful consideration of the problem of crimping of the delivery catheter, but clearly treats this accessory device as optional. See SSDR certificate at pages 6, 11. At the least, NRC would need to justify requiring the use of this accessory by an analysis of the mis-administration events to determine whether use of the Arrow introducer sheath would have, in fact, prevented them. We have not seen or had the opportunity to comment on any such evaluation.

Moreover, the FDA imposes no comparable requirement. We understood from the conference call on January 31 that NRC Staff believed that FDA's decision not to require this accessory was based on FDA mis-administration risk prevention goals that were, in NRC's view, not sufficiently protective of public health and safety. While we recognize that NRC policy provides for an NRC role in preventing mis-administrations, we question whether NRC should exercise this role in the circumstance here, where to do so would reflect distrust of a sister federal agency's expertise and regulatory judgment.

Finally, we object to NRC requiring use of a particular name brand, since to do so would give the vendor of this device an competitive advantage over current and, more importantly, future vendors of equivalent devices.

5. Use of a Dual Syringe System.

The draft guidance would require the use of a dual syringe system to avoid mis-administrations associated with premature depletion of the source transport fluid. Again, Novoste encourages licensees to evaluate the use of this accessory, and would have no difficulty with an NRC requirement that licensees consider doing so, but objects to an NRC requirement that the accessory be used. Our reasons are essentially the same as our reasons for opposing the requirement for use of the introducer sheath. Such a requirement is contrary to the SSDR certificate, which reflects careful consideration of the fluid depletion issue but imposes no dual syringe use requirement (see SSDR certificate at pages 6, 11), is not required by the FDA, and has not been justified by any available NRC evaluation which shows that mis-administrations would have been prevented by use of dual syringes.

6. Characterization of the Device as a "Remote" Afterloader.

Several features of the draft guidance reflect NRC Staff's determination that the Beta-Cath System is a remote, as opposed to a manual device. For example, the requirement to use a written directive with the information under paragraph (6) of the directive content specification in 10 C.F.R. § 35.2 would appear to reflect such an NRC judgment. This may be especially

significant in the future, because the new Part 35 will have a revised section 35.400 which, by its terms, will apply only to the use of sealed sources for "manual" brachytherapy.

NUREG/CR-6642 includes a working definition of manual brachytherapy as "manually placing radioactive sources in applicators or catheters that have previously been placed in a patient's body...." NUREG/CR-6642, Vol. 2 at 3.8.1. The new Part 35 would include a comparable definition. The SSDR certificate is clear that the Beta-Cath System is a "hand-held, manually controlled, ergonomically designed unit," SSDR at page 3. Therefore, the Beta-Cath System meets the NRC definition of a manual system. While NRC requirements tailored to a device intended to emit beta radiation are appropriate, requirements that depend on classification of the Beta-Cath System as a "remote" device are not appropriate.

7. Training and Education Requirements.

The draft guidance would require that user training and education requirements "shall be that set forth in 10 C.F.R. § 35.940 for use of 35.400 materials." This requirement cannot be based on NRC regulations, since 10 C.F.R. § 35.940 by its terms applies only to uses and sources listed in 10 C.F.R. § 35.400, and the use of Sr-90/Y-90 for prevention of restenosis is not among the sources and uses listed therein.

Thus the application of these training and user requirements must be justified independently of the regulations. Novoste, of course, would support reasonable and necessary training requirements, but suggests that the requirements in 10 C.F.R. § 35.941 are more logically relevant that the requirements of 10 C.F.R. § 35.940, since the former section, "Training for ophthalmic use of strontium-90," applies to the same isotope with similar activities using a manual device. We also note that the SSDR certificate addresses the subject of training and use of the Novoste Beta-Cath System, and the imposition of the training and education requirements of 10 C.F.R. § 35.940 is inconsistent with the certificate. At the least, NRC Staff should explain why the provisions of the certificate, and analogous requirements in 10 C.F.R. § 35.941, are not sufficient.

8. The Reference to Source trains and Shipping Containers.

In the license authorization language included in the draft guidance reference is made to additional source trains in shipping containers for source train replacement. This will be confusing to NRC inspectors, who may find four devices (with four source trains). To

be consistent with the SSDR certificate we suggest that this language be revised to refer to "two source trains (in devices) for replacement."

Sincerely,

Martin G. Malsch

cc: Dr. Carl J. Paperiello
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April 27, 2001

via Hand Delivery
Mr. John W. Hickey
Chief, Material Safety & Inspection Branch
Division of Industrial & Medical Nuclear Safety
Office of Nuclear Materials Safety and Safeguards
U.S. Nuclear Regulatory Commission
Washington, DC

Dear Mr. Hickey:

The purpose of this letter is to supplement our February 12, 2001 letter to you regarding NRC licensing of Novoste's Beta-Cath System by providing information you requested yesterday about maximum activity levels.

In our February 12 letter we objected to a license condition that would limit single sources in a train to 3.5 millicuries, pointing out that the corresponding limit in the Georgia SSDR certificate was 5 millicuries, that a 3.5 millicurie limit would prevent many from using the device to treat patients, that the 3.5 millicurie figure related to a NIST analysis of a single seed that Novoste had used originally as a nominal activity level, that NIST had later provided numbers that enabled Novoste to calculate individual source train dose rates and activities, and that based on this the actual sources varied somewhat (less than 5 millicuries).

As you know, the Novoste Beta-Cath System has been approved by the FDA, based on clinical trial data submitted by Novoste. As would be expected, The Beta-Cath devices actually used in these trials produced dose rates that varied somewhat, ranging upward to 0.107 Grays/second for a particular train (which included a standard twelve sources or seeds). Using a NIST traceable factor that relates dose rate to activity, the activities of the source trains used in these trials ranged upward to a little over 46 millicuries. Since there were 12 sources in each train, this means that the mean source activity in the highest activity train used in the trials was a little over 3.8 millicuries. The range of the mean source activities for the trains used in these trials was 2.7-3.8 millicuries. For discussion purposes, we have rounded up the 3.8 number to 4.0 .

These activity numbers reflect actual dose rates (and corresponding calculated activities) for the trains used in the trials; the range of the mean was not intended to accommodate uncertainty around some single activity number (say 3.5 millicuries). There is, of course, some uncertainty in these measurements, as there is in all such measurements.

The 3.5 millicurie maximum activity per source specified in the August 4, 2000 Georgia SSDR certificate (superseded by the November 20, 2000 SSDR) was based simply on a NIST analysis of a single source. The 5.0 millicurie number referenced in the newer SSDR certificate (GA-1115-D-101-S) was intended to reflect the full range of the mean source activities for the trains used in the trials, with some allowance for measurement uncertainty. Since dose rates will only be measured for the full train (and in the trials were measured for the full trains), a license condition which specifies maximum source activity should either refer to the full train (twelve sources) or to the mean activity for the sources in a train.

Novoste's February 12 letter (and Novoste's written testimony before ACMUI) questioned whether NRC should or could enforce FDA requirements[1]. However, if NRC wants to adopt a license condition that imposes an activity limit based on the FDA approval, then Novoste suggests that the appropriate limit would be either 48 millicuries per 12 source train, or 4 millicuries mean activity for the 12 sources in a train.[2] We also believe that there should be some allowance for uncertainty when the licensee verifies the dose rate (and activity) after receiving the device. Also, consistent with NRC policy, we would expect that similar devices from other manufacturers would also be subject to maximum activity license conditions that are based on the dose rates and activities used in their clinical trial data submitted to FDA.

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[1]No NRC safety review is required under 10 C.F.R. § 35.57 for an individual Part 35 licensee to use a sealed source of up to 15 millicuries, that has been manufactured and distributed in accordance with NRC or Agreement State requirements, for check, calibration, and reference use. (The new Part 35 would increase this limit). Thus an NRC limit for a properly manufactured and distributed source of less than 15 millicuries would need to be based on safety concerns associated with some other use of the sealed source. Here that use would be for treatment of patients. However, under the August 3, 2000 Policy Statement, the focus of NRC regulation of patient safety is on assuring that properly trained and qualified user physician instructions are followed. It is not clear to us how a limit on source activity can be justified on this basis. If NRC were to impose a 5 millicurie limit based on the Georgia SSDR, Novoste's ability to distribute devices up to this limit would still be constrained by its need to comply with FDA requirements. See 10 C.F.R.§ 35.7.

[2] In our February 12 letter, we said we believed that the use of sources up to 5.0 millicuries was fully consistent with the FDA approval. Based on information Novoste recently received from FDA, Novoste believes that FDA does not currently approve of a shipments of a Beta-Cath device if the activity for the source train is measured to exceed 48 millicuries.

I hope this information satisfies NRC's needs. I want to express Novoste's appreciation for the consideration you and others at the NRC have given to our licensing concerns. As we said in our February 12 letter, Novoste wants to do all that is necessary to support sound licensing guidance on the use of the Beta-Cath system. Please do not hesitate to call me if you have any further questions.

Very truly yours,

Martin G. Malsch
Attorney for Novoste