Washington University in St. Louis

Environmental Health & Safety **Radiation Safety Office**

July 20, 2017

U.S. Nuclear Regulatory Commission
Region III
Division of Nuclear Materials Safety
2443 Warrenville Road, STE 210
Lisle, Illinois 60532-4352

Attn: John B. Giessner, Director

RE: License No. 24-00167-11
Docket No. 030-02271

Subject: Response to the Apparent Violation in Inspection Report No. 03002271/2017001 (DNMS); EA-17-082

In accordance with the NRC request (dated June 21, 2017), Washington University in St. Louis submits this written response to the apparent violation identified in Inspection Report No. 03002271/ 2017001(DNMS). The NRC described the apparent violation as follows:

> "The apparent violation concerned the licensee's failure to notify the NRC Operations Center, by telephone, no later than April 17, 2016, the next calendar day after the licensee had necessary information to discover the medical event, as required by Title 10 of the *Code of Federal Regulations* (CFR) Part 35.3045(c)."

Washington University appreciates this opportunity to respond to the Inspection Report and apparent violation. Although we maintain there was no reportable medical event, we do not believe it is productive to further dispute NRC's different determination. Instead, we offer in this response mitigating information in favor of a reduced severity-level for the violation. Here are key points of the information described herein:

- Washington University performed the medical procedures without error.
- The patient suffered no ill effects.
- The wrong-site delivery was identified only because of our use of a cutting-edge imaging machine to develop a post-treatment imaging protocol designed to improve patient outcomes.
- There is no evidence of any cause for the wrong-site delivery other than patient intervention.

Washington University in St. Louis, Campus Box 8053, 660 S. Euclid Avenue, St. Louis, MO 63110-1093
(314) 362-3476, Fax: (314) 362-4776, radsafety@wustl.edu, http://radsafety.wustl.edu

- Washington University exercised due diligence and good faith in interpreting NRC's medical event reporting requirements.
- Washington University voluntarily disclosed this incident upon a general inquiry from Region III.
- Washington University took prompt and appropriately comprehensive corrective action once notified by Region III of NRC's medical event determination.
- Washington University commits to making medical event notifications to NRC of future similar incidents if we have not observed a patient action which led to movement of the catheter tip.

Reason for the Apparent Violation

As described in Washington University in St. Louis' written report (ML17052A302 and ML17076A278) in response to our January 31, 2017 notification of a 10 CFR 35.3045 medical event, we originally concluded the cause of the deposition of the TheraSpheres in the right liver lobe rather than in the left liver lobe, was movement of the catheter tip due to patient intervention. In 10 CFR 35.3045(a) and in "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance" (Revision 9), patient intervention is excluded as a medical event.

We do not agree with the NRC conclusion that we had the "necessary information to discover the medical event" on April 16, 2016. The reporting criteria in 10 CFR 35.3045(c) state:

> "The licensee shall notify by telephone the NRC Operations Center no later than the next calendar day after discovery of the medical event."

The date (April 16, 2016) that the deposition of Y-90 microspheres in the right rather than the left liver lobe was identified was a Saturday. As RSO, I discussed the incident with the chief medical physicist and we both agreed that more investigation was needed to discover what had occurred. We decided to meet on Monday (April 18, 2016) to investigate further the cause of the Y-90 incident to determine whether this was a medical event. Based on our review of the incident, the completion of the treatment in accordance with the manufacturer's procedures, the "ACMUI Final Report on Yttrium-90 (Y-90) Microsphere Brachytherapy Medical Event Criteria" (ML14300A138), and the medical event reporting criteria, we made a good-faith determination on April 18, 2016 that the incident was not a medical event as, in our judgment, patient intervention was the likely cause of the catheter tip moving during the microsphere administration.

The Washington University Department of Radiation Oncology reported the incident to

the Barnes-Jewish Hospital Patient Safety & Quality Department and participated in a thorough patient safety review of the incident. The patient safety review did not identify an alternative cause of the Y-90 incident beyond patient intervention. The patient safety review included a focused evaluation of the treatment procedure and treatment team interactions during the Y-90 incident to also identify and implement process improvements, described in more detail in the NRC inspection report. The results of all the reviews of the Y-90 incident were discussed at the November 8, 2016 and January 10, 2017 Washington University Radiation Safety Committee meetings. Furthermore, the NRC's medical consultant (ML17118A206) agreed that the patient suffered no ill effects due to this procedure.

On January 11, 2017, I received a routine telephone call from Mr. Robert Gattone, NRC Region III, inquiring about the status of our radiation safety program (ML17018A266). When asked about any medical administrations that deviated from written directives, I informed him of our review of the Y-90 incident. Mr. Gattone and I had several telephone calls and email exchanges in January 2017 further discussing the Y-90 incident. On January 30, 2017, Mr. Gattone telephoned Dr. W. John Smith, Washington University Associate Radiation Safety Officer, to let us know that in collaboration with NRC Headquarters and Region III staff and based on information that we had provided, the NRC considered the Y-90 incident to be a medical event. Based on his telephone notification to us, Mr. Gattone suggested we promptly notify the NRC Operations Center of the medical event in accordance with 10 CFR 35.3045(c) criteria to reduce the time of non-reporting. Based on this discovery that the NRC did not agree with our conclusion that the incident did not constitute a reportable medical event, we made prompt notification of the medical event on the next calendar day, January 31, 2017 (Event Report No. 52520), and submitted the written report in accordance with 10 CFR 35.3045(d).

We made the determination that patient intervention was the cause of the Y-90 incident because there was no evidence of any cause other than patient intervention. No procedure error was observed during the medical administration of the Y-90 TheraSpheres. We agreed with the ACMUI's description that a known risk of the Y-90 microsphere medical procedure "is in large part dependent on the practice of medicine, recognizing that:

- the placement of the infusion catheter tip at the time of Y-90 microsphere infusion is in alignment with the prior preparation;
- once injected into the vascular pathway to the treatment target at the catheter tip, flow of the microsphere brachytherapy sources and their sites of final implantation are entirely dependent on the patient's unique vascular anatomy and blood flow dynamics."

We did not understand until our January 30, 2017 discussion with Mr. Gattone that the NRC expects patient intervention to be an observed patient action. Such a standard is not described in NRC written regulations and guidance. Therefore, we believe the date we first obtained information necessary to discover this incident constituted a medical event was January 30, 2017,

not April 17, 2016, and we promptly notified NRC of the medical event.

Corrective Actions Taken and Results Achieved

Washington University in St. Louis made notification of the medical event to the NRC Operations Center on January 31, 2017, the next calendar day following our discovery that the NRC disagreed with our determination that the incident did not constitute a reportable medical event. The NRC also conducted a reactive inspection on February 1-2, 2017, which found no other apparent violation than the one being addressed in this written response.

Corrective Actions that Will be Taken to Avoid Further Violations

Washington University in St. Louis commits to reporting Y-90 microsphere medical administration incidents as described in the medical event reporting section of "Yttrium-90 Microsphere Brachytherapy Sources and Devices TheraSphere® and SIR-Spheres® Licensing Guidance", Revision 9 (ML15350A099), including those identified by post-treatment imaging, if we have not observed a patient action which led to movement of the catheter tip.

Date When Full Compliance was Achieved

We believe we achieved full compliance when we submitted the report of a medical event on January 31, 2017, one day after learning on January 30, 2017 that NRC disagreed with our original conclusion that the medical incident was caused by patient intervention and therefore not reportable.

Additional Comments Regarding NRC Inspection Report 03002271/2017001(DNMS)

Our original determination of patient intervention was based on the catheter tip having moved from its final location which was fluoroscopically verified to be in its intended position just prior to the administration of the microspheres. We were only uncertain about what patient movement caused the catheter tip to move. We did not understand prior to January 30, 2017, that the NRC expects a patient action is observed before considering patient intervention as an event cause.

Section 3.2 Observations and Findings discusses our use of a PET/MRI unit in the University's Center for Clinical Imaging Research to obtain post-administration images of Y-90 microsphere patients. We are concerned that the implication of this section suggests that we should be obtaining post-administration images for all microsphere patients. Washington

University Department of Radiation Oncology is world-renowned in its advancement of cancer care through education, research, and development of new technologies. Dr. Parikh has led research to develop quantitative techniques to measure Y-90 distribution in the body and look for clinical outcome correlations (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4858549/).

Post-administration imaging of Y-90 microsphere patients, such as PET/CT or PET/MRI imaging or Y-90 bremsstrahlung imaging, is not a standard of care. Based on preliminary results from the research project, Washington University is trying to obtain post-treatment PET/MRI as often as possible for these patients. We are concerned, however, that the NRC statements in Section 3.2 of the inspection report imply that post-administration imaging of Y-90 microsphere patients should be done in all cases to identify whether a medical event occurred. Washington University is not able to offer post-treatment PET/MRI to all of the patients receiving Y-90 radioembolization due to limited availability of the one PET/MRI unit we have. We also worry that NRC's implication of a post-administration imaging requirement may set too high of a standard and thus reduce the number of medical licensees who will be able to treat cancer patients with Y-90 microspheres.

To amplify this position, we offer the following information. The FDA-approved package insert for TheraSpheres® (https://www.btg-im.com/en-US/TheraSphere/Products/Indications) makes no mention of post-administration imaging. The FDA-approved package insert for Sir-Spheres® (https://www.sirtex.com/media/155126/ssl-us-13.pdf) *recommends, but does not mandate,* a SPECT scan of the upper abdomen immediately after implantation of SIR-Spheres microspheres to confirm placement of the microspheres in the liver. Professional society guidelines also mention, but do not mandate, post-administration imaging. The "American College of Radiology-Society of Interventional Radiology Practice Parameter for Radioembolization with Microsphere Brachytherapy Device (Rmbd) for Treatment of Liver Malignancies" (https://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/RMBD.pdf?db=web) states that postprocedure bremsstrahlung planar imaging, SPECT and/or SPECT/CT *can be used* within 24 hours of the conclusion of the procedure to document the placement of the devices and assess for significant extrahepatic shunting. Similarly, the "European Association of Nuclear Medicine Procedure Guideline for the Treatment of Liver Cancer and Liver Metastases with Intra-Arterial Radioactive Compounds" (http://www.eanm.org/publications/guidelines/EANM_liver_treatment_guidelines_2012.pdf) states that bremsstrahlung images, or one or two frames of 30-min PET acquisition, performed a few hours after the administration *are useful* to locate the activity. It is our understanding that the majority of institutions performing radioembolization do not obtain post-administration imaging routinely. Accordingly, in concert with the package inserts and professional society guidance documents, we assert that such imaging is not standard of care.

Furthermore, as more medical licensees implement some kind of post-administration imaging of Y-90 microsphere patients, more incidents similar to our Y-90 incident will be identified that would have otherwise gone unnoticed in the past. We encourage the NRC to

consider what level of regulatory response is appropriate so as not to discourage a licensee from performing post-administration imaging, which may indeed provide useful information that could help to shape future practice of radioembolization.

Consideration for NRC Final Enforcement Determination

We recognize from review of the NRC Enforcement Manual (ML102630150) that failure to report a medical event is normally categorized at Severity Level III. As noted in the NRC Enforcement Policy (ML16271A446) Section 3:

> "The NRC may choose to exercise discretion and either escalate or mitigate enforcement sanctions or otherwise refrain from taking enforcement action within the Commission's statutory authority. The exercise of discretion allows the NRC to determine what actions should be taken in a particular case, notwithstanding the guidance contained in this statement of policy. After considering the general tenets of this Policy and the safety and security significance of a violation and its surrounding circumstances, judgment and discretion may be exercised in determining the severity levels of violations and the appropriate enforcement sanctions to be taken."

Washington University originally determined the Y-90 incident to not be a reportable medical event based on the conclusion that patient intervention was the likely cause of the Y-90 microspheres being deposited in the wrong site. We ask that the NRC categorize this apparent violation at Severity Level IV or lower based on the circumstances of the Y-90 incident, our prompt and comprehensive corrective actions, and other mitigating factors described herein.

Again, we appreciate the opportunity to respond to the apparent violation and to review the NRC inspection report prior the NRC's final enforcement decision on the matter. You may contact me at (314) 362-2988 or at slanghorst@wustl.edu if you have any questions regarding this written response.

Sincerely,

Susan M. Langhorst, Ph.D., CHP
Radiation Safety Officer

Cc: Barry A. Siegel, M.D., Radiation Safety Committee Chairman
Bruce D. Backus, P.E., Environmental Health & Safety
Christopher W. Goddard, Associate General Counsel

FedEx.
TRK# 0200 8580 5334 8861

FRI - 21 JUL AA
STANDARD OVERNIGHT

XH ENLA

60532
IL-US
ORD

RECEIVED JUL 21 2017

FID 5043819 20JUL17 CPSA 546C1/C0C2/0C8A

8580 5334 8861

0200 Form ID No.

FedEx Retrieval Copy

5-6608-6

Phone 314 362-2476

Dept./Floor/Suite/Room

City SAINT LOUIS State MO ZIP 63110

2 Your Internal Billing Reference

3 To
Recipient's Name JOHN B. GIESSNER Phone 630 829-9500

Company US NRC - REGION III

Recipient's Address DIVISION OF NUCLEAR MATERIALS SAFETY
We cannot deliver to P.O. boxes or P.O. ZIP codes.
Dept./Floor/Suite/Room

Address 2443 WARRENVILLE ROAD SUITE 210
To request a package be held at a specific FedEx location, print FedEx address here.

City LISLE State IL ZIP 60532-4352

fedex.com 1.800.GoFedEx 1.800.463.3339

4a Express Package Service — Packages up to 150 lbs.
1 ☐ FedEx Priority Overnight — Next business morning.* Friday shipments will be delivered on Monday unless SATURDAY Delivery is selected.
5 ☑ FedEx Standard Overnight — Next business afternoon.* Saturday Delivery NOT available.
6 ☐ FedEx First Overnight — Earliest next business morning delivery to select locations.* Saturday Delivery NOT available.
3 ☐ FedEx 2Day — Second business day.* Thursday shipments will be delivered on Monday unless SATURDAY Delivery is selected.
FedEx Express Saver — Third business day.* Saturday Delivery NOT available.
* To most locations.

4b Express Freight Service — Packages over 150 lbs.
7 ☐ FedEx 1Day Freight
83 ☐ FedEx 3Day Freight — Third business day.** Saturday Delivery NOT available.
** To most locations.

5 Packaging
6 ☑ FedEx Envelope*
2 ☐ FedEx Pak*
FedEx Tube
1 ☐ Other
* Declared value limit $500.

6 Special Handling
3 ☐ SATURDAY Delivery — Not available for FedEx Standard Overnight, FedEx First Overnight, FedEx Express Saver, or FedEx 3Day Freight.
1 ☐ HOLD Weekday at FedEx Location — Not available for FedEx First Overnight.
31 ☐ HOLD Saturday at FedEx Location — Available ONLY for FedEx Priority Overnight and FedEx 2Day to select locations.

Does this shipment contain dangerous goods? One box must be checked.
☑ No
4 ☐ Yes — As per attached Shipper's Declaration.
☐ Yes — Shipper's Declaration not required.
6 ☐ Dry Ice — Dry Ice, 9, UN 1845 ___ x ___ kg
☐ Cargo Aircraft Only
Dangerous goods (including dry ice) cannot be shipped in FedEx packaging.

7 Payment Bill to: Enter FedEx Acct. No. or Credit Card No. below.
1 ☑ Sender — Acct. No. in Section 1 will be billed.
2 ☐ Recipient
3 ☐ Third Party
4 ☐ Credit Card
5 ☐ Cash/Check
Obtain Recip. Acct. No. ☐

[redacted]

Total Packages 01 | Total Weight [redacted] | Total Charges

Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See the current FedEx Service Guide for details.

8 NEW Residential Delivery Signature Options — If you require a signature, check Direct or Indirect.
☐ No Signature Required — Package may be left without obtaining a signature for delivery.
10 ☑ Direct Signature — Anyone at recipient's address may sign for delivery. Fee applies.
34 ☐ Indirect Signature — If no one is available at recipient's address, anyone at a neighboring address may sign for delivery. Fee applies.

520

Rev. Date 6/05 Part #156297 ©1994–2005 FedEx PRINTED IN U.S.A. SRY

RT 797 FZ
1 16:00 D 8861 07.21

8580 5334 8861

▼ Insert shipping document here.