UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION III
2443 WARRENVILLE ROAD, SUITE 210
LISLE, ILLINOIS 60532-4352

November 13, 2018

EN 53574
NMED No. 180415 (Closed)

Mr. John Applegate
Executive Vice President for University
Academic Affairs
Indiana University-IUPUI/IU Medical
Center Campus
1120 W. Michigan St.
Radiation Safety Room 159
Indianapolis, IN 46202-5111

SUBJECT: NRC REACTIVE INSPECTION REPORT NO. 03001609/2018002(DNMS) – INDIANA UNIVERSITY-IUPUI/IU MEDICAL CENTER CAMPUS

Dear Mr. Applegate:

On September 27 and 28, 2018, an inspector from the U.S. Nuclear Regulatory Commission (NRC) conducted a reactive inspection at your IU Health Methodist Hospital in Indianapolis, Indiana, with continued in-office review through October 25, 2018. The purpose of the inspection was to review the circumstances, root and contributing causes, and proposed corrective actions for a medical event that occurred on August 31, 2018; your staff reported this medical event to the NRC on the same day. The medical event involved an underdose to the treatment site during an administration of TheraSphere® yttrium-90 (Y-90) microspheres. The in-office review included a review of your written report and proposed corrective actions taken in response to the reported medical event. Our in-office review also included a review of the device manufacturer's analysis of the equipment and followup discussions with the device manufacturer. A final exit meeting was held between Ms. Deborah A. Piskura of my staff, and Dr. Michael Martin and Messrs. Scott Adams and Lee Stone of your staff by telephone on October 25, 2018, to discuss the inspection findings. The enclosed report presents the results of this inspection.

During this inspection, the NRC staff examined activities conducted under your license related to public health and safety. Additionally, the staff examined your compliance with the Commission's rules and regulations as well as the conditions of your license. Within these areas, the inspection consisted of selected examination of procedures and representative records, observations of activities, and interviews with personnel.

A medical event occurred as a result of a loss of flow within the TheraSphere® Administration Set. The physician observed an unusually low pressure within the device during attempts to infuse the Y-90 microspheres into the patient. As saline was injected into the system, the physician noted an unusual amount of saline collecting in the excess vial with little to no microspheres infusing into the patient. The physician terminated the treatment after two unsuccessful attempts. The licensee returned the portion of the TheraSphere® Administration Set that infused the dosage directly into the patient to the device manufacturer for analysis.

Based on the components that were returned, the manufacturer indicated that there may have been a kink or obstruction within the treatment catheter. However, because only a portion of the administration set was returned to the manufacturer, the manufacturer could not evaluate the system as a whole. Therefore, all factors that could have attributed to the medical event are unknown. After reviewing the data provided by the device manufacturer and our inspection findings, we have determined there is not sufficient information to conclude the exact cause of the loss of flow of microspheres within the TheraSphere® Administration Set that could have resulted in this medical event.

Based on these findings, the NRC has no further questions regarding this matter. No violations of NRC requirements were identified during this inspection. The NRC has concluded that the information regarding the device manufacturer's analysis of the returned components of the TheraSphere® Administration Set is already adequately addressed in the enclosed inspection report. You are not required to respond to this letter or its enclosure unless they do not accurately reflect your understanding of the issue or your position. If you choose to reply, mark your response as a "Reply to NRC Inspection Report No. 03001609/2018002(DNMS)" and send it to the U.S. Nuclear Regulatory Commission, ATTN: Document Control Desk, Washington, DC 20555-0001, with a copy to the Regional Administrator, Region III within 30 days of the date of this letter.

In accordance with Title 10 of the *Code of Federal Regulations* (CFR) 2.390 of the NRC's "Rules of Practice," a copy of this letter, its enclosure, and any response you provide will be made available electronically for public inspection in the NRC's Public Document Room or from the NRC's Agencywide Documents Access and Management System (ADAMS), accessible from the NRC's website at http://www.nrc.gov/reading-rm/adams.html. To the extent possible, your response should not include any personal privacy, proprietary, or safeguards information so that it can be made publicly available without redaction.

Please feel free to contact Ms. Piskura if you have any questions regarding this inspection. Ms. Piskura can be reached at 630-829-9867.

Sincerely,

/RA/

Aaron T. McCraw, Chief
Materials Inspection Branch
Division of Nuclear Materials Safety

Docket No. 030-01609
License No. 13-02752-03

Enclosure:
IR 03001609/2018002(DNMS)

cc w/encl: Dr. Michael Martin, Radiation
Safety Officer
Dr. Harold O. Longe
State of Indiana

Letter to John Applegate from Aaron McCraw, dated November 13, 2018.

SUBJECT: NRC REACTIVE INSPECTION REPORT NO. 03001609/2018002(DNMS) –
INDIANA UNIVERSITY-IUPUI/IU MEDICAL CENTER CAMPUS

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DATE	11/13/2018		11/13/2018					

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U.S. Nuclear Regulatory Commission
Region III

Docket No.	030-01609
License No.	13-02752-03
Report No.	03001609/2018002(DNMS)
EN/NMED Nos.	53574 / 180415
Licensee:	Indiana University-IUPUI/IU Medical Center Campus
Address:	1120 W. Michigan St. Indianapolis, IN 46202-5111
Location Inspected:	IU Health Methodist Hospital Campus I-65 and 21st Street Indianapolis, Indiana
Inspection Dates:	September 27-28, 2018
Exit Meeting Date:	October 25, 2018
Inspector:	Deborah A. Piskura, Senior Health Physicist
Approved By:	Aaron T. McCraw, Chief Materials Inspection Branch Division of Nuclear Materials Safety

Enclosure

EXECUTIVE SUMMARY

Indiana University-IUPUI/IU Medical Center Campus
NRC Inspection Report 030-0160901609/2018002(DNMS)

The U.S. Nuclear Regulatory Commission (NRC) conducted a reactive inspection on September 27 and 28, 2018, to review the circumstances, causes, and licensee corrective actions regarding a medical event that occurred on August 31, 2018, at the IU Methodist Hospital, a location of use for the Indiana University-IUPUI/IU Medical Center Campus (the licensee). The licensee reported the medical event to the NRC on August 31, 2018. The medical event involved an underdose to the prescribed treatment site using yttrium-90 microspheres in a BTG International Canada, Inc. TheraSphere® Administration Set. The inspection included in-office review through October 25, 2018, to review the results of the device manufacturer's analysis of the returned equipment.

During a palliative treatment of a primary liver tumor on August 31, 2018, the licensee was only able to deliver approximately 16.6 percent of the prescribed dosage of TheraSphere® yttrium-90 (Y-90) microspheres, representing an underdose to the treatment site by approximately 83.4 percent. The authorized user prescribed the treatment to a tumor in the right lobe of the liver with a dose of 120 Gray using a single dosage of 86.9 millicuries. During the administration of the dosage, the authorized user noted an unusually low pressure within the delivery set as he injected saline in the system to infuse the microspheres. As the authorized user injected saline in the system, he noted that the saline flowed through the system with no resistance, appeared to bypass the v-vial containing the Y-90 microspheres, and collected into the "excess" vial. After two attempts to inject saline through the system with the same outcome, the authorized user terminated the treatment.

The direct cause of the medical event was initially attributed to a low pressure within the pressure relief valve leading to the saline excess vial on the "cold" portion of the administration set, preventing the Y-90 microspheres from being delivered to the treatment site. Upon further review, the licensee suspected that the microcatheter was kinked and obstructed the flow of the microspheres to the patient. The licensee concluded that the medical event would not result in adverse health consequences for the patient.

The licensee held the "hot" portion of the administration set for decay prior to returning the system to the device manufacturer for analysis on October 4, 2018. In addition, the licensee removed all administration sets under the same lot number from its inventory. Because only the "hot" portion of the administration set was returned, the device manufacturer could not perform a complete analysis to attempt to determine the cause of the medical event. The device manufacturer attributed the cause of the medical event to a kink in the microcatheter that created an obstruction within the line and prevented the flow of the Y-90 microspheres to the patient. In light of the information provided by the manufacturer, the licensee implemented additional corrective actions to the medical event to include revising its process to include the "cold" portion of the administration set with the "hot" portion for any future medical events involving the TheraSphere® Administration Set.

No violations of NRC requirements were identified during the review of this medical event.

REPORT DETAILS

1 Program Overview and Inspection History

The Indiana University-IUPUI/IU Medical Center Campus (licensee) was a large medical institution that conducted licensed activities at six locations in the Indianapolis area. Under License Number 13-02752-03, the licensee operated a Type A medical broadscope program with authorization to use licensed materials with atomic numbers 3-83 and Y-90 microspheres. The licensee administered Y-90 microsphere treatments using the BTG International Canada, Inc. TheraSphere® Administration Set at its University Hospital and IU Methodist Hospital. The U.S. Food and Drug Administration granted the manufacturer of TheraSphere® Y-90 microspheres a Humanitarian Device Exemption, allowing the use of new technologies that otherwise would not be available through more conventional processes to encourage research and development of treatments for rare diseases. The device exemption of TheraSphere® Y-90 microspheres was limited to the treatment of unresectable liver cancer. The licensee established a Radiation Safety Committee (RSC) to review and approve users, uses, and facilities as required for a medical broad scope licensee. All human research protocols, including the use of TheraSphere® Y-90 microspheres, were reviewed by the licensee's Institutional Review Board. The daily radiation safety activities were managed by a dedicated, full-time Radiation Safety Officer (RSO), three staff health physicists (functioning as Assistant RSOs), one student health physics technician, and two office assistants.

The nuclear medicine department at the IU Methodist Hospital performed approximately 25-30 Y-90 microsphere administrations annually, using the TheraSphere® Administration Set. The licensee's RSC approved four interventional radiologists as authorized users for Y-90 microspheres. The licensee developed protocols for the administration of TheraSphere® Y-90 microspheres, based on patient anatomy, vasculature, tumor volume, and liver volume. The licensee instituted a multi-departmental approach for the use of Y-90 microspheres. The team consisted of an interventional radiologist/authorized user, a nurse, a nuclear medicine technologist, a radiology technician, and a health physicist from the radiation safety office. The licensee received unit dosages of the Y-90 microspheres from the vendor from which it assayed and stored the prepared dosages within the nuclear medicine hot lab. The team administered all Y-90 microspheres treatments within the interventional radiology suite. Following the treatment, the licensee imaged the patient to verify that the treatment was performed in accordance with the written directive.

2 Sequence of Events and Licensee Investigation

2.1 Inspection Scope

The inspector reviewed the licensee's investigation of the medical event. The inspector also interviewed selected licensee personnel, reviewed the licensee's written policies and procedures for Y-90 administrations, and observed equipment and facilities.

2.2 Observations and Findings

The TheraSphere® Administration Set is a prepackaged, single use Administration Set, to be used with the Y-90 dose vial to inject the microspheres into the patient, and the Lucite Administration Accessory Kit to be used as shielding. A schematic depicting the TheraSphere® Administration Set is included as the Attachment to this report. Once the

Administration Set is assembled for patient treatment, tubing after “B” on the diagram depicts the “hot” portion or the radiation component of the set where the Y-90 microspheres would flow to the patient. All components depicted after “B” would be potentially contaminated and contained within the Administration Accessory Kit for shielding and contamination control. The components of the Administration Set depicted to the left of “A” are non-radioactive or “cold.” Upon completion of the treatment, the licensee staff would cut the tubing depicted on the Attachment as “Cut Here.” The “cold” components depicted to the left of “A” would be treated as medical waste; the “hot” components depicted to the right of “B” would be collected as radioactive waste and held for decay.

The licensee planned the patient treatment according to the tumor volume and ordered a pre-calibrated unit dosage of Y-90 microspheres, corrected for radiological decay, in order to deliver the prescribed dose to the treatment site. Based on the patient’s anatomy and the vasculature to the tumor, the authorizer user prescribed a dose of 120 Gray (equivalent to 120 Sievert or 12,000 rem). The medical physics staff planned the treatment according to the authorized user’s prescribed dose to the tumor volume in the right lobe and calculated a dosage of Y-90 microspheres at 86.9 millicuries for the treatment site. On the morning of August 31, 2018, the nuclear medicine technologist prepared and assayed the dosage in the hot lab. Then, the nuclear medicine and interventional radiology personnel prepared and assembled the TheraSphere® delivery system, including the Administration Set, the dosage, and the Administration Accessory Kit in preparation for treatment.

The authorized user positioned the microcatheter in the patient. The authorized user used a high-flow, 3-French microcatheter with an inner diameter of 0.027 inches to administer the microspheres to the patient. According to the manufacturer’s package insert, a catheter with a diameter of greater than or equal to 0.02 inches was required to avoid any possible occlusions or retention of microspheres within the line; the licensee’s use of a 0.027 inch catheter was within the general guidelines of instructions in the package insert. In preparation for the treatment, the authorized user primed the system to purge air within the tubing. The authorized verified the positioning of the microcatheter within the treatment site using contrast media under angiography. This action also verified the flow through the microcatheter to the patient to ensure that the microspheres had an unobstructed path to the treatment site.

At the start of the administration of the Y-90 microspheres, the authorized user noted an unusually low pressure within the system. As the authorized user injected saline in the system, he noted that the saline flowed through the system with little resistance, appeared to bypass the v-vial containing the Y-90 microspheres, and collected directly into the “excess” vial. After two attempts to inject saline through the system with the same outcome, the authorized user terminated the treatment.

Surveys of the patient indicated that very little of the dosage had been administered to the treatment site. The staff surveyed near the dose vial within the Administration Accessory Kit and noted that the readings were high indicating that a significant amount of the dosage remained in the v-vial. A visual examination of the v-vial confirmed that a significant amount of microspheres remained in the v-vial. The staff cut the tubing marked “B” separating the “cold” portion from the “hot” portion of the Administration Set, and placed the hot portion including the dose vial into a waste container. The waste container was secured within the hot lab. The “cold” portion of the Administration Set was disposed as normal medical waste.

Based on the licensee's calculations, the patient received a dosage of approximately 14.4 millicuries of Y-90 microspheres and 20 Gray (20 Sievert), equivalent to 2,000 rem or only 16.6 percent of the prescribed dose to the right lobe of the liver; approximately 83.4 percent of the dosage remained in the v-vial and tubing of the Administration Set. The administered dose differed from the prescribed dose by 50 rem to an organ or tissue, and the total dose differed by greater than 20 percent from the prescribed dose. Therefore, the administration fit the criteria as a reportable medical event to the NRC under 10 CFR 35.3045.

The licensee's initial investigation could not determine the cause of the medical event. The radiation safety staff discussed this incident with representatives of the device manufacturer. From the licensee's description of the incident, the device manufacturer initially suspected an occlusion either within the tubing of the "hot" portion of the administration set or the microcatheter to the patient prevented the microspheres from flowing to the treatment site. The licensee awaited the results of the manufacturer's analysis.

The licensee held the "hot" portion of the Administration Set for decay prior to shipping it to the device manufacturer for analysis on October 4, 2018. The manufacturer confirmed receipt on October 9, 2018.

The licensee concluded that the medical event would not result in adverse health consequences for the patient. On September 7, 2018 the licensee administered a compensating dose to the patient; the dose was administered in accordance with the written directive.

2.3 Conclusions

The licensee identified that a Y-90 microspheres administration on August 31, 2018, met the criteria for an NRC medical event, because the administration resulted in an underdose to the treatment site that differed from the prescribed dose by 50 rem to an organ or tissue, and the total dose differed by greater than 20 percent from the prescribed dose. The licensee delivered 16.6 percent of the prescribed dose to the patient. The licensee sent the "hot" portion of the Administration Set used for this patient treatment to the device manufacturer for analysis to gain insights into the possible causes of the medical event.

3 Device Manufacturer's Analysis

3.1 Inspection Scope

The inspector reviewed the device manufacturer's analysis of equipment involved in the medical event. The inspector also interviewed selected representatives of the device manufacturer, and reviewed excerpts of the investigation report provided to the licensee.

3.2 Observations and Findings

The device manufacturer, BTG International Canada, Inc., initiated its investigation of the licensee's returned Administration Set on October 12, 2018. The manufacturer's investigation included a visual inspection, radiation exposure rate surveys, digital microscopy and pressure/flow testing. The manufacturer confirmed through visual inspection and surveys that the majority of microspheres remained in the dose vial and were not delivered to the patient during the treatment. The manufacturer noted residual microspheres along the flow path, from the outlet tubing to the microcatheter. Kinks were identified on the microcatheter and radiation surveys at these locations were elevated in comparison to other sections of microcatheter that appeared normal or unkinked. The manufacturer could not confirm whether these kinks in the microcatheter were present during the patient treatment. Pressure/Flow tests determined that Administration Set and tubing appeared functional with no resistance to flow. The manufacturer's tests revealed significant resistance in flow within the microcatheter which was used to deliver to dosage to the patient; this resistance indicated a possible occlusion or kink that could prevent the microspheres from flowing to the treatment site.

The "cold" portion of the Administration Set, where the authorized user observed the flow of saline to the excess vial, was not returned to the manufacturer. The licensee staff was not instructed to include the "cold" portion of the Administration Set with their return. Without the "cold" portion of the Administration Set, the manufacturer's analysis was inconclusive on any defects or issues with this Administration Set. According to the manufacturer's production records, the lot from which this Administration Set came passed all quality tests.

3.3 Conclusions

Based on the components that were returned, the manufacturer indicated that there may have been a kink obstruction within the treatment catheter. The manufacturer could not performed a complete analysis of the Administration Set, because not all of the components were returned.

4 Licensee Corrective Actions

4.1 Inspection Scope

The inspection included an assessment of the licensee's proposed corrective actions to prevent similar events. The inspector reviewed the licensee's September 10, 2018 written report of the medical event and interviewed the RSO, selected radiation safety and radiology staff, and the authorized user.

4.2 Observations and Findings

The licensee removed all Administration Sets under the same lot number from its inventory. Discussions with the authorized user revealed that, on September 2, 2018, he experienced another incident while performing an interventional procedure (non-NRC licensed activity) using the same type of microcatheter. During this procedure, the authorized user experienced difficulty with the microcatheter, and he suspected that the catheter had a kink. The authorized user recalled the difficulty he had with the August 31, 2018 Y-90 medical

event and suspected that this catheter lot could be defective. As such, the licensee pulled all microcatheters under this lot number from its inventory.

During its initial discussions with the device manufacturer on this medical event, the licensee staff was not instructed to include the “cold” portion of the kit with their return. Upon completion of the procedure, the “cold” portion was detached from the Administration Kit and discarded as medical waste according to the licensee’s routine practice. The staff did not consider isolating the entire Administration Set for return. The licensee revised its process to include returning the “cold” portion of the Administration Set, along with the “hot” portion, for any future events involving TheraSphere® Y-90 microspheres.

4.3 Conclusions

The licensee implemented immediate corrective actions to address the suspected cause of the medical event to prevent similar events by taking Administration Sets and microcatheters from the same lot out of its inventory. The licensee also revised its process to include returning the “cold” portion of the Administration Set, along with the “hot” portion, for any future events involving TheraSphere® Y-90 microspheres.

5 Notifications and Reports

5.1 Inspection Scope

The inspector reviewed the licensee's notifications to the NRC Operations Center, the referring physician, and the patient. In addition, the inspector reviewed the licensee’s written report describing the medical event.

5.2 Observations and Findings

On August 31, 2018, the day of the microspheres administration, the licensee notified the NRC Operations Center of the medical event (Event Number 53574). The confirmed that the licensee notified the patient and the patient's referring physician. In addition, the licensee provided the authorized user and the referring physician a copy of its written report on the medical event. The licensee provided its written report of the medical event to the NRC in a report dated September 10, 2018, detailing its initial actions taken in response to the medical event. The report included the information required by 10 CFR 35.3045(d)(1).

5.3 Conclusions

The licensee made all of the notifications and reports as required by 10 CFR 35.3045 within the specified time period. The licensee’s written report included all of the required information.

6 Other Areas Inspected

6.1 Inspection Scope

The inspector reviewed other aspects of the licensee’s radiation protection program, related to the licensee’s use of Y-90 microspheres. The inspector interviewed selected individuals, toured the licensee’s facilities, and reviewed selected records.

6.2 Observations and Findings

The inspector reviewed selected RSC meeting minutes and documentation of training for physicians approved as authorized users for Y-90 microspheres. The inspector determined that the RSC established a quorum for its quarterly meetings and reviewed events and program audit results, as well as approved uses, facilities, and users. The licensee approved four interventional radiologists as authorized users of Y-90 microspheres and documented the training and experience for their approvals.

6.3 Conclusions

The inspector did not identify any issues or concerns with the licensee's oversight of the use of Y-90 microspheres.

7 Exit Meeting Summary

The NRC inspector presented the preliminary inspection findings following the onsite inspection on September 28, 2018. The licensee did not identify any documents or processes reviewed by the inspectors as proprietary. The licensee acknowledged the findings presented. The final exit meeting was subsequently conducted via telephone on October 26, 2018, and included a discussion of the additional corrective actions the licensee committed to implement as a result of the manufacturer's recommendations and analysis of the returned device.

LIST OF PERSONNEL CONTACTED

* Steve Adams, Director of Administration, Interim University Director of Environmental Health and Safety
John Bullock, Health Physicist
Sabah D. Butty, M.D., Interventional Radiologist/Authorized User
Christopher P. Harvey, M.S, Assistant RSO
* T. Michael Martin, Ph.D., CHP, Radiation Safety Officer
Cassie Lund, RT(R)(VI), Imaging Manager, IU Methodist Hospital
Rachel Schmidt, M.S., Assistant RSO
Timothy Kleyn, Assistant RSO
* Lee Stone, Interim Director, Environmental Health and Safety
John Applegate, Executive Vice President for University Academic Affairs

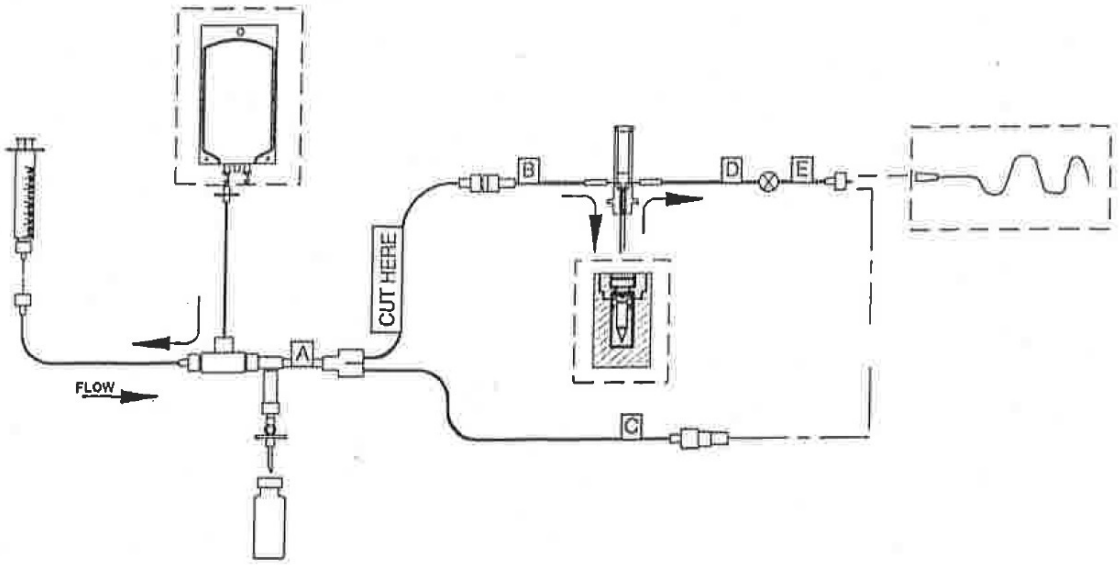
* Attended the on-site exit meeting on September 28, 2018 and the October 25, 2018 final exit teleconference

Representatives of BTG International Canada Inc. contacted by telephone on October 19 and 24, 2018:
Eric Li, Technical Specialist
Scott McGhee, Radiation Safety Officer

INSPECTION PROCEDURES (IP) USED

IP 87103, "Inspection of Material Licensees Involved in an Incident or Bankruptcy Filing"
IP 87134, "Medical Broad Scope Programs"

TheraSphere® Administration Set



Items in dashed boxes are not supplied with the Administration Set

Attachment