

November 13, 2009

NMED No. 090786

Mark L. Driscoll
Radiation Safety Officer
Regents of the University of Michigan
Radiation Safety Service
Occupational Safety & Environmental Health
1239 Kipke Drive
Ann Arbor, MI 48109-1010

SUBJECT: NRC REACTIVE INSPECTION REPORT NO. 030-01988/2009-002(DNMS) AND
NOTICE OF VIOLATION – THE REGENTS OF THE UNIVERSITY OF
MICHIGAN

Dear Mr. Driscoll:

On October 29, 2009, a U.S. Nuclear Regulatory Commission (NRC) inspector conducted an inspection at the University of Michigan Medical Center in Ann Arbor, Michigan. The purpose of the inspection was to review the circumstances, root and contributing causes, and proposed corrective actions to a reported medical event that occurred on October 14, 2009. The findings of the inspection were discussed with you and selected members of your staff at a preliminary exit meeting on October 29, 2009, and at a final, telephonic, exit meeting on November 5, 2009. The enclosed report presents the results of this inspection.

Based on the results of this inspection, the NRC has determined that a Severity Level IV violation of NRC requirements occurred. The violation was evaluated in accordance with the NRC Enforcement Policy. The current Enforcement Policy is included on the NRC's website at (<http://www.nrc.gov/about-nrc/regulatory/enforcement/enforce-pol.html>). The violation is cited in the enclosed Notice of Violation (Notice) and the circumstances surrounding it are described in detail in the subject inspection report (enclosed).

The NRC has concluded that information regarding the reason for the violation, the corrective actions taken and planned to correct the violation and prevent recurrence is already adequately addressed on the docket in the subject inspection report and in your letters dated October 27 and November 12, 2009. Therefore, you are not required to respond to this letter unless the description herein does not accurately reflect your corrective actions or your position. In that case, or if you choose to provide additional information, you should follow the instructions specified in the enclosed Notice.

M. Driscoll

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In accordance with 10 CFR 2.390 of the NRC's "Rules of Practice," a copy of this letter, its enclosures, and your response, if you choose to provide one, will be made available electronically for public inspection in the NRC Public Document Room or from the NRC's Agencywide Documents Access and Management System (ADAMS), accessible from the NRC 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 available to the Public without redaction.

Sincerely,

/RA/

Tamara E. Bloomer, Chief
Materials Inspection Branch

Docket No. 030-01988
License No. 21-00215-04

Enclosures:

1. Notice of Violation
2. Inspection Report No. 030-01988/2009-002(DNMS)

cc w/encls: State of Michigan

M. Driscoll

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In accordance with 10 CFR 2.390 of the NRC's "Rules of Practice," a copy of this letter, its enclosures, and your response, if you choose to provide one, will be made available electronically for public inspection in the NRC Public Document Room or from the NRC's Agencywide Documents Access and Management System (ADAMS), accessible from the NRC Web site 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 available to the Public without redaction.

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NOTICE OF VIOLATION

The Regents of the University of Michigan
Ann Arbor, Michigan

Docket No. 030-01988
License No. 21-00215-04

During an NRC inspection conducted on October 29, 2009 a violation of NRC requirements was identified. In accordance with the NRC Enforcement Policy, the violation is listed below:

10 CFR 35.41(a)(2) requires, in part, that for any administration requiring a written directive, licensees must develop, implement, and maintain written procedures to provide high confidence that each administration is in accordance with the written directive. Procedures must meet the requirements described in 10 CFR 35.41(b).

10 CFR 35.41(b) requires, in part, that the procedures required by 10 CFR 35.41(a) must address methods for verifying that the administration of byproduct material is in accordance with the treatment plan, if applicable, and the written directive.

Contrary to the above, as of October 14, 2009, the licensee's procedure for radiopharmaceutical procedures requiring a written directive did not provide high confidence that each administration is in accordance with the written directive. Specifically, the licensee's procedure did not require verification of the physical volume of iodine-131 metaiodobenzylguanidine sulfate (mIBG) to be administered or provide a means for recovery and administration of the complete dose in the event that air was detected in the intravenous line.

This is a Severity Level IV violation (Supplement VI).

The NRC has concluded that information regarding the reason for the violation, the corrective actions taken and planned to be taken to correct the violation and prevent recurrence, and the date when full compliance will be achieved, is already adequately addressed on the docket in Inspection Report No. 030-01988/2009-002(DNMS), and the letter from the Licensee dated October 27, 2009. However, you are required to submit a written statement or explanation pursuant to 10 CFR 2.201 if the description, therein, does not accurately reflect your corrective actions or your position. In that case, or if you choose to respond, clearly mark your response as a "Reply to a Notice of Violation," 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 the letter transmitting this Notice of Violation (Notice).

If you choose to respond, in accordance with 10 CFR 2.390 of the NRC's "Rules of Practice," your response along with this letter and its enclosures will be made available electronically for public inspection in the NRC Public Document Room or from the Publicly Available Records (PARS) component of the NRC's Agencywide Documents Access and Management System (ADAMS). ADAMS is accessible from the NRC website at <http://www.nrc.gov/reading-rm/adams.html>. Therefore, to the extent possible, the response should not include any personal privacy, proprietary, or safeguards information so that it can be made available to the Public without redaction.

In accordance with 10 CFR 19.11, you may be required to post this Notice within two working days.

Dated this 13th day of November 2009

U.S. NUCLEAR REGULATORY COMMISSION

REGION III

Docket No.: 030-01988

License No.: 21-00215-04

Report No.: 030-01988/2009-002(DNMS)

Licensee: The Regents of the University of Michigan

Location: University of Michigan Medical Center
Ann Arbor, Michigan

Date: October 29, 2009

Inspectors: Geoffrey M. Warren, Health Physicist
Jose Macatangay, Health Physicist

Reviewed by: Tamara E. Bloomer, Chief
Materials Inspection Branch
Division of Nuclear Materials Safety

EXECUTIVE SUMMARY

**The Regents of the University of Michigan
Ann Arbor, Michigan
NRC Inspection Report No. 030-01988/2009-002(DNMS)**

The purpose of this inspection was to review the circumstances, root and contributing causes, and corrective actions associated with a medical event that occurred on October 14, 2009, at the University of Michigan Medical Center in Ann Arbor, Michigan, involving the administration of a therapeutic quantity of iodine-131 (I-131) metaiodobenzylguanidine sulfate (mIBG).

The authorized user's written directive prescribed a dosage of 180.5 millicuries (mCi) of I-131 mIBG for a three-year-old patient under a clinical trial for pediatric patients with resistant or recurrent neuroblastoma. The dosage was prepared in accordance with the guidelines provided by the manufacturer of the material, except that the prepared dosage volume was 40 milliliters (ml) instead of the recommended 50 ml because the pharmacist miscalculated the volume of saline solution to be added.

The dosage was administered through an infusion pump, which was set to alarm when 45 ml of the dosage had been delivered so that the technologist could watch for air in the line from the dosage to the pump. However, because of the reduced volume, the infusion pump alarmed to indicate air in the line from the pump to the patient before 45 ml had been delivered. Because air was in that line, the technologist terminated the procedure to avoid injecting air into the patient's bloodstream, and was unable to flush the line with saline to deliver the residual material in the line to the patient. As a result, only 76.5 percent of the prescribed dosage was administered to the patient.

Because this differed from the prescribed dosage by more than 20 percent and the patient's whole-body dose differed by more than 5 rem from the expected dose, this qualified as a medical event. Both the authorized user and the principal investigator for the clinical trial, who was also the referring physician, determined that an adequate dosage was given to the patient to provide an adequate therapeutic dose. As such, they determined that there was no significant medical effect to the patient as a result of the underdose.

The inspector identified one violation of NRC requirements, involving the failure to develop, implement, and maintain written procedures to provide high confidence that each administration is in accordance with the written directive for therapeutic radiopharmaceutical treatments under this clinical trial, as required by 10 CFR 35.41(a). Specifically, the procedure did not provide for verification of the volume of the dose or provide a means to recollect the dosage in case of air in the line so that the complete dosage could be given to the patient.

The licensee's corrective actions included: (1) revising the procedure for therapeutic radiopharmaceuticals performed under this clinical trial to require verification of the volume of the dosage by a second individual prior to administration, and setting the IV infusion pump to alert at 40 ml instead of 45 ml; and (2) designing a means of purging air bubbles back into the dosage vial from the line from the infusion pump to the patient in the event of a similar event. Based on the letter from the licensee dated November 12, 2009; the corrective actions will be completed by December 1, 2009.

REPORT DETAILS

1 Program Scope and Inspection History

The University of Michigan operated a number of facilities throughout Michigan for medical and research uses as authorized by NRC License No. 21-00215-04. Among these facilities was the University of Michigan Medical Center on the university campus in Ann Arbor, Michigan. The Division of Nuclear Medicine at the medical center performed a variety of therapeutic and diagnostic procedures, including procedures in support of clinical research.

No violations of NRC regulatory requirements were cited during the two previous routine NRC inspections of the licensee's activities, conducted on January 22 – 26, 2007 and March 10 – 13, 2008, though one Severity Level IV violation of NRC requirements was cited as a result of the decommissioning inspection conducted on January 25, 2007.

2 Sequence of Events and Licensee Investigation

2.1 Inspection Scope

The inspector interviewed the nuclear pharmacist, the nuclear medicine technologist, the authorized user physician, the referring physician/principal investigator, and the radiation safety staff to determine the sequence of events that resulted in the medical event. In addition, the inspector reviewed selected records and procedures, and reviewed compliance with regulatory requirements relevant to the implant procedure.

2.2 Observations and Findings

The hospital was taking part in a clinical trial of the use of iodine-131 (I-131) mIBG to provide a palliative treatment for pediatric patients with recurrent or residual neuroblastoma. This trial was a FDA-regulated clinical trial, and had been approved by the University's Subcommittee on Human Use of Radioisotopes. As part of the trial, this treatment was scheduled to be given to a three-year-old patient on October 14, 2009. A written directive was prepared for the administration of 180.5 millicuries (mCi) of I-131 mIBG and signed by the authorized user. Before this treatment, hospital personnel had performed three treatments under this trial without incident.

The recommendations provided by the manufacturer of the I-131 mIBG described the process for preparing the dosage. This included the drawing of a calculated volume of the stock material to provide the prescribed dosage, and the addition of saline solution to bring the volume to 50 milliliters (ml). For this treatment, the volume of stock solution was approximately 17 ml; the nuclear pharmacist should have added 33 ml of saline solution, but miscalculated the quantity necessary and added only 23 ml instead. This resulted in a 40-ml dosage, though the pharmacist noted on the written directive that the dosage volume was 50 ml. The measured dosage was 186.99 mCi I-131 mIBG, within 10 percent of the prescribed dosage.

The Department of Nuclear Medicine's procedure for administrations requiring a written directive required that the activity of the dosage be verified, but did not require that the physical volume of the dosage be verified.

In accordance with the manufacturer's recommendations, the I-131 mIBG was administered intravenously via an infusion pump. A nurse set up the infusion pump and the nuclear medicine technologist connected the I-131 mIBG dose to the pump and set the pump to administer the dose at approximately 1 ml per minute. The technologist set the infusion pump to alarm when 45 ml of the intended 50 ml had been administered. The technologist performed additional monitoring duties in the patient room area, generally remaining away from the dosage during delivery to reduce her radiation dose. The manufacturer's recommendations suggested that the technologist start looking for air in the line from the dosage to the infusion pump (the secondary line) at the 45-ml alarm.

Because the dosage was a smaller volume than intended, air appeared in the line earlier than expected. The infusion pump alarmed and stopped the infusion when it detected air in the line, and the technologist determined that air had entered the line from the pump to the patient (the primary line). After determining through a conversation with a nurse that they had no means to recollect the material or remove the air from the primary line, the technologist gave as much of the I-131 mIBG as she could without injecting air into the patient's bloodstream, then terminated the procedure. Because air had entered the primary line, the technologist was unable to flush the line with saline to flush residual material into the patient.

After terminating the procedure, the technologist returned the dose vial and the tubing involved in the treatment to nuclear medicine and determined that the residual material totaled 49 mCi, indicating that 137.99 mCi was administered to the patient. Based on this, the quantity administered represented a 23.5 percent underdose, and the whole-body dose to the patient differed by more than 5 rem from the dose he would have received if the complete dosage had been given as intended. Because of this, the event qualifies as a medical event as described in 10 CFR 35.3045(a).

Title 10 Code of Federal Regulations (CFR) 35.41(a) states, in part, that, for any administration requiring a written directive, licensees are required to develop, implement, and maintain written procedures to provide high confidence that each administration is in accordance with the written directive. Procedures must meet the requirements described in 10 CFR 35.41(b). Title 10 CFR 35.41(b), provides, in part, that the procedures required by 10 CFR 35.41(a) must address methods for verifying that the administration of byproduct material is in accordance with the written directive. The licensee's failure to develop adequate procedures to provide high confidence that the I-131 mIBG treatment was performed in accordance with the written directive, specifically to address verification of the volume of the dosage or to address recovery of the dosage in the event that air gets into the primary line, is a potential violation of 10 CFR 35.41(a).

Both the authorized user and the principal investigator for the clinical trial, who was also the referring physician, determined that an adequate dosage was given to the patient to provide an adequate therapeutic dose. As such, they determined that there was no significant medical effect to the patient as a result of the underdose.

The licensee determined that the root cause of the medical event was the lack of an adequate procedure or system in place to purge air from the primary line in a safe and reliable manner which would have allowed the treatment to continue to completion, and that a contributing cause was the unintended departure from the routine protocol, in that the pharmacist miscalculated the volume of saline to be added to the dosage.

2.3 Conclusions

The inspector identified a potential violation of 10 CFR 35.41(a), concerning the licensee's failure to develop adequate procedures to provide high confidence that therapeutic radiopharmaceutical procedures performed under this clinical trial are performed in accordance with the written directive.

3 Notifications and Reports

3.1 Inspection Scope

The inspector interviewed the radiation safety officer (RSO), a senior health physicist, and the referring physician/principal investigator to determine what event notifications had been made. The inspector also reviewed the licensee's telephonic event notification to the NRC Operations Center on October 15, 2009, and the licensee's written report dated October 27, 2009.

3.2 Observations and Findings

The medical event occurred on October 14, 2009. The referring physician/principal investigator was notified about the medical event on October 14, and he notified the parents of the patient on October 15. The referring physician was employed by the University of Michigan, so no written report to the referring physician was required.

The RSO reported the medical event to the NRC Operations Center on October 15, the next calendar day after the medical event. The written report, dated October 27, 2009, was received by NRC on October 29, within 15 days of the initial report. The written report contained all required information.

3.3. Conclusions

The inspector did not identify any violations of NRC requirements concerning the reporting of the medical event.

4 Licensee Corrective Actions

4.1 Inspection Scope

The inspector interviewed selected licensee personnel concerning the licensee's proposed corrective actions and reviewed the corrective actions described in the licensee's written report.

4.2 Observations and Findings

The inspector determined that the licensee initiated corrective actions to prevent recurrence of a similar event. The corrective actions included:

- (1) Revising the procedure for therapeutic radiopharmaceuticals performed under this clinical trial to require verification of the volume of the dosage by a second individual prior to administration, and setting the IV infusion pump to alert at 40 ml instead of 45 ml; and
- (2) Designing a means of purging air bubbles back into the dosage vial from the primary line in the event of a similar event.

Based on the letter from the licensee dated November 12, 2009; the corrective actions will be completed by December 1, 2009.

4.3. Conclusions

The inspector determined that the licensee's proposed corrective actions are adequate to prevent recurrence of the medical event and the associated violation.

5 **Exit Meeting Summary**

The inspector discussed the conclusions described in this report with the licensee during a preliminary exit meeting conducted at the licensee's facility on October 29, 2009. The licensee did not identify any information provided to the inspector during this inspection as proprietary in nature. A final exit meeting was conducted by telephone with the licensee's RSO and Senior Health Physicist on November 4, 2009.

LIST OF PERSONS CONTACTED

- Anca Avram, M.D., Authorized User, Division of Nuclear Medicine
- * Mark Driscoll, Radiation Safety Officer, Occupational Safety & Environmental Health
- Kirk A. Fray, M.D., Ph.D., Chief, Division of Nuclear Medicine
- # David Hubers, Nuclear Pharmacist, Division of Nuclear Medicine
- #* Dennis Palmieri, Senior Health Physicist, Occupational Safety & Environmental Health
- # David Raffel, Ph.D., Director, Radiation Health Physics, Division of Nuclear Medicine
- # Denise Regan, Technologist, Division of Nuclear Medicine
- # Neil Whiteside, Health Physicist, Occupational Safety & Environmental Health
- Gregory Yanik, M.D., Clinical Professor, Department of Pediatrics, Referring Physician

- # Attended the Preliminary Exit Meeting
- * Contacted by telephone for Final Exit Meeting