U.S. NUCLEAR REGULATORY COMMISSION
REGION I

INSPECTION REPORT

Inspection No.	03001303/2011001
Docket No.	03001303
License No.	07-12153-02
NMED No.	110412
Event No.	47158
LER No.	2011-016
Licensee:	Christiana Care Health Services
Location:	4755 Ogletown-Stanton Road Newark, Delaware 19718
Inspection Date:	August 19, 2011, with in-office review through December 14, 2011, with telephonic exit on January 6, 2012
Date Followup Information Received:	August 26 and November 3, 2011

Inspector: ***Original Signed by:*** ***01/17/12***

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EXECUTIVE SUMMARY

Christiana Care Health Services
NRC Inspection Report No. 03001303/2011001

An announced, special inspection was conducted on August 19, 2011, at Christiana Care Health Services (CCHS) in Newark, Delaware. The special inspection reviewed the circumstances surrounding a possible medical event that was identified by CCHS on August 16, 2011, and reported to the NRC on the same day. The possible medical event involved a patient enrolled in a clinical research study of an investigational radioimmunotherapy agent for pancreatic cancer. On August 9, 2011, the patient was to receive the first of three separate treatments (one dosage per week) containing 10.5 mCi (0.39 GBq) of a Yttrium-90 labeled monoclonal antibody (DOTA-hPAM4). Instead, the patient received 31.5 mCi (1.17 GBq) during a single treatment (NMED# 110412). On August 16, 2011, when the patient was to receive her second dosage in the protocol, the supplying radiopharmacy realized that they inadvertently provided all three fractionated dosages in a single dosage and notified CCHS. CCHS identified that they relied on the label provided by the radiopharmacy during preparation of the written directive and documented 31.0 mCi on the written directive, which was approved and signed by the authorized user. The patient's physician and the patient were notified of the event on the same day.

In this event, the administered dosage differed from the intended fractionated dosage specified in the clinical protocol by 20 percent or more, and would appear to meet the medical event reporting requirements in 10 CFR 35.3045(a)(1)(ii). However, since the written directive was erroneously filled out to deliver the entire dosage at once, the administration was in accordance with the written directive; and therefore, did not constitute a medical event. The licensee retracted the event on November 1, 2011.

It was decided that the patient would not receive any further Y-90hPAM4 dosages for this retreatment cycle per decision of the medical director in consultation with the medical director of the study sponsor.

Within the scope of this special inspection, one violation of NRC regulations was identified. The licensee's written procedures did not provide high confidence that each administration is in accordance with the treatment plan, as required by 10 CFR 35.41(b)(2). Specifically, the licensee's procedures did not require the authorized user to fully review the treatment plan data that documented the fractionated dosage to be delivered prior to the dosage administration.

REPORT DETAILS

I. Event Details

a. Inspection Scope

The inspector reviewed the circumstances surrounding an August 9, 2011, administration of a Yttrium-90 clinical trial therapy for unresectable pancreatic cancer (ClinicalTrials.gov Identifier NCT00603863, IND Number 11380), which resulted in a possible medical event (Event Notification 47158) at Christiana Care Health Services (Newark, Delaware). The event was reported to the NRC Operations Center on August 16, 2011. The inspector followed NRC Management Directive 8.10, "NRC Medical Event Assessment Program" and DNMS Directive 0310.1, Revision 1, "Response to Medical Events." The inspector conducted interviews with staff, including the authorized user (AU), nuclear medicine technologist (NMT), Radiation Safety Officer (RSO), Medical Director, and the Manager of Nuclear Medicine/PET; and reviewed patient records, written directives, and therapy policy and procedures. The inspector also reviewed the records for all other patients enrolled in the same clinical trial (18 additional patients) and for a similar clinical trial utilizing Yttrium-90 hLL2. The inspector determined that all other administrations were in accordance with their treatment plans.

b. Observations and Findings

Therapy Program

CCHS is authorized to perform 10 CFR 35.300 therapies at Christiana Hospital, located at 4755 Ogletown-Stanton Road, Newark, Delaware, and Medical Arts Pavillion, 4735 Ogletown-Stanton Road, Newark, Delaware. This announced, special inspection was limited to clinical trial therapies authorized by 10 CFR 35.300 at Christiana Hospital and reviewed the circumstances surrounding a possible medical event that involved a patient enrolled in a clinical research study of an investigational radioimmunotherapy agent for pancreatic cancer. Patients receive a 4-week treatment cycle with once-weekly 30-minute chemotherapy agent gemcitabine infusions beginning one week prior to the first 90Y-hPAM4 dosage and continuing during the 3 consecutive weeks over which once weekly 90Y-hPAM4 dosages are given. Depending on toxicity, patient cohorts will receive one of several possible 90Y and gemcitabine dosage combinations. Post-treatment evaluations are conducted until instituting another 90Y-hPAM4 treatment cycle, maintenance gemcitabine, or for a maximum period of 12 weeks. The patient involved in the August 9, 2011 incident was beginning her second 90Y-hPAM4 treatment cycle.

On August 9, 2011, the patient was to receive the first of three separate treatments (one dosage per week) containing 10.5 mCi (0.39 GBq) of a Yttrium-90 labeled monoclonal antibody (DOTA-hPAM4). Instead, the patient received 31.5 mCi (1.17 GBq), which was the total prescribed dosage for that treatment cycle in a single dosage, rather than as 3 fractionated dosages as specified by the research protocol. The dosage was ordered from Cardinal Health using forms supplied by Immunomedics, the study sponsor. The order form was a two page form, which listed the weekly fractionated dosage on the first

page, and the total prescribed dosage for the treatment cycle on the second page. When received at CCHS, the NMT performed routine package receipt procedures for receiving a radioactive package and then assayed the dosage as 31.5 millicuries. The technologist checked the assayed amount to the syringe label, rather than the dose calculation worksheet/treatment plan. The NMT then provided the assayed amount to the Authorized User (AU) so that he may fill out the written directive immediately prior to administering the therapy treatment. The NMT and AU did not recognize the error made by the radiopharmacy. The AU wrote the written directive for 31 millicuries Y-90 hPAM4 I.V. x 1 over 10 minutes; this dosage was administered by the AU in accordance with the written directive.

The event was discovered when the Cardinal Health pharmacist notified the nuclear medicine manager on August 16, 2011, that he had dispensed the full cycle dose on August 9, 2011. The nuclear medicine manager made the appropriate notifications to CCHS staff and to Immunomedics. The patient's referring physician and the patient herself were notified by the Medical Director on the morning of August 16, 2011.

It was decided that the patient would not receive any further Y-90hPAM4 dosages for this retreatment cycle per decision of the medical director in consultation with the medical director of the study sponsor. However, the patient had recovered and was able to continue her regime of chemotherapy agent Gemcitabine per the trial protocol.

On September 8, 2011, a conference call was held with Frank Costello and Elaine Crescenzi of Pennsylvania Department of Environmental Protection and Peter Boncross of Cardinal Health to review the incident and to learn Cardinal Health's corrective actions (see Section e.).

On September 9, 2011, a conference call was conducted with NRC Region I, NRC FSME Headquarters, and the FDA to determine if this was a medical event. In this event, the administered dosage differed from the intended fractionated dosage specified in the clinical protocol by 20 percent or more, and would appear to meet the medical event reporting requirements in 10 CFR 35.3045(a)(1)(ii). However, since the written directive was erroneously filled out to deliver the entire dosage at once, it was determined that the administration was in accordance with the written directive; and therefore, not a medical event. NRC FSME concurred with the decision that this was not a medical event on September 12, 2011. This information was communicated to CCHS on November 1, 2011, and the event was retracted that day.

Event Chronology

August 9 The patient was to receive the first of three separate treatments (one dosage per week) containing 10.5 mCi (0.39 GBq) of a Yttrium-90 labeled monoclonal antibody (DOTA-hPAM4). Instead, the patient received 31.5 mCi (1.17 GBq), which was the total prescribed dosage for that treatment cycle in a single dosage, rather than as 3 fractionated dosages as specified by the research protocol.

August 16 The event was discovered when the Cardinal Health pharmacist notified the nuclear medicine manager that he had dispensed the full cycle dose on August 9, 2011. The nuclear medicine manager made the appropriate notifications to CCHS staff and to Immunomedics. The patient's referring physician and the patient herself were notified by the Medical Director. The RSO notified the NRC Operations Center of the possible medical event. Upon consultation with Immunomedics, it was determined that the patient had received the total prescribed treatment dosage of Y-90 hPAM4 at once so she would not receive any more.

Immunomedics revised their two page Radiolabeling Dose Calculation Worksheet and Request for Y90-hPAM4IgG Radiolabeled Antibody forms into a one page Radiolabeling Dose Request and Calculation Worksheet. The new form lists only the single fractionated dosage to be given for each treatment visit (not the total prescribed dosage) and the intended infusion dates.

August 19 The on-site special inspection was conducted by NRC Region I.

August 26 The 15 day report was received by the NRC Region I office.

September 9 A conference call was held with NRC Region I, NRC FSME Headquarters, and the FDA to determine if this was a medical event since the administration was in accordance with the written directive even though the written directive was filled out erroneously to deliver the entire treatment dosage at once.

September 12 NRC FSME Headquarters concurred that this was not a medical event.

November 1 NRC Region I informed CCHS that this was not believed to be a medical event; CCHS retracted the event that day.

November 3 CCHS submitted their revised procedures regarding the ordering, verification, and administration of therapeutic radiopharmaceuticals

Notification of the Event

Although the event occurred on August 9, 2011, the licensee did not identify that a reportable event had occurred until August 16, 2011. The NRC Operations Center was notified by the licensee on the same day of the identification. The AU notified the referring physician and the patient. The licensee also submitted a 15-day report written report, which was received in Region I on August 26, 2011. Since it was determined that a medical event did not occur, the licensee retracted the event on November 1, 2011.

Corrective and Preventative Actions Taken by CCHS

During the inspection conducted on August 19, 2011, and in subsequent correspondence dated August 26 and November 3, 2011, the licensee described the following corrective and preventive actions:

1. CCHS implemented the use of Immunomedics' revised Radiolabeling Dose Request and Calculation Worksheet.

2. CCHS stated they would implement the following corrective actions regarding research therapeutic procedures:

    i. A designated technologist and AU are assigned the day prior to performing the research procedure.
    ii. The therapy dosage is reviewed by the AU and the technologist the day before the procedure to verify the accuracy of the dosage to be ordered.
    iii. The technologist or the NM manager confirm the dosage and activity with the radiopharmacy compounding the product.
    iv. Upon receipt of the dosage, the technologist performs the normal opening procedure upon receiving a radioactive package.
    v. The technologist verifies the patient's name, radiopharmaceutical, and dosage amount, and cross checks this information with the Immunomedics radiolabeling dosage request and calculation worksheet. Any discrepancies are directly brought to the attention of the AU.
    vi. The AU checks the dosage label on the lead pig and syringe for accurate patient and dosage information. The AU supervises the dosage assay in the dose calibrator prior to administration.

3 CCHS developed a new radiopharmaceutical quality management form and a form for therapeutic radiopharmaceutical request for non-thyroid therapeutic doses. Both forms were put into use on August 29, 2011.

4. CCHS revised their procedures regarding the ordering, verification, and administration of therapeutic radiopharmaceuticals. The revised procedures include a final time-out prior to dosage administration for the AU and NMT to confirm patient identity, correct radiopharmaceutical, correct dosage, and to address any other concerns. This time-out is documented on the revised quality management form.

5. CCHS provided staff members training on the updated policies and procedures.

Corrective Actions Taken by Immunomedics

Immunomedics revised their two page Radiolabeling Dose Calculation Worksheet and Request for Y90-hPAM4IgG Radiolabeled Antibody forms into a one page Radiolabeling Dose Request and Calculation Worksheet. The new form lists only the single

fractionated dosage to be given for each treatment visit (not the total prescribed dosage) and the intended infusion dates. The form was revised for the Y-90 hPAM4 clinical trial, as well as a Y-90 hLL2 clinical trial, which utilized a similar form. The revised forms were sent out to all trial participants and to the Cardinal Health radiopharmacists.

Corrective Actions Taken by Cardinal Health

When the order form is received from CCHS, the pharmacist puts the fractionated dosages into the system for three separate dates, highlighting the dosage dates and amounts. Immediately prior to compound, a second radiopharmacist is brought over to verify all information. The Pharmacy Manager drafted a memorandum on this incident and outlined their corrective actions. He had planned to send this Lessons Learned statement to the other Cardinal Health pharmacies.

Additional Information

On September 22, 2011, the FDA put a partial hold on Immunomedics's pancreatic cancer drug trial after the patient was given the incorrect dosage. On November 2, 2011, the FDA announced that the clinical trial could resume, provided that the radiopharmacies and clinical sites involved complete and document retraining on the radiopharmaceutical dosing, ordering, and administration process.

c. Conclusions

Within the scope of this special inspection, one violation of NRC regulations was identified. The licensee's written procedures did not provide high confidence that each administration is in accordance with the treatment plan, as required by 10 CFR 35.41(b)(2). Specifically, the licensee's procedures did not require the authorized user to fully review the treatment plan data that documented the fractionated dosage to be delivered prior to the dosage administration.

II. Exit Meeting

A preliminary exit meeting was held on August 19, 2011, to discuss the scope of the inspection and the inspector's initial observations. On January 6, 2012, a telephonic exit meeting was held to discuss the inspection results with Patrick Grusenmeyer, Senior Vice President of CCHS and other members of the licensee's staff.

PARTIAL LIST OF PERSONS CONTACTED

Licensee

* Theresa Riggle, Nuclear Medicine Technologist
*+ Timothy Manzone, M.D., Authorized User, Medical Director, Chair of Radiation Safety Committee
Hung Q. Dam, M.D., Authorized User
*+ Patrick Grusenmeyer, Senior Vice President
*+ Joseph F. Solge, Jr., Radiation Safety Officer
* Anthony Gialloreto, Director of Non-Invasive Services
* Penny Vigneau, Senior Vice President of Cardiovascular Services
*+ Cindy Knotts, Manager of Nuclear Medicine/PET

*Present at preliminary exit meeting on August 19, 2011
+Participated in telephonic exit meeting conducted on January 6, 2012

Cardinal Health

Lisa Leslie, Radiopharmacist
Peter Boncross, Radiopharmacist, Pharmacy Manager

Immunomedics

Sue Garl, Senior Clinical Research Associates
Heather Horne, Director, Clinical Research