UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION II
101 MARIETTA STREET, N.W., SUITE 2900
ATLANTA, GEORGIA 30323-0199

Report No. 47-23066-02/94-01

License No. 47-23066-02 Docket No. 030-20233

Licensee: West Virginia University Hospitals, Inc.
Morgantown, West Virginia

Inspection Conducted: August 1-2 and September 14, 1994

Inspector: _____ 10/13/94
H. Bermúdez, Sr. Radiation Specialist Date Signed

Accompanying NRC personnel on August 1-2, 1994: D. Howe, Health Physicist, Office of Nuclear Materials Safety and Safeguards

Approved By: _____
C. Hosey, Chief Date Signed
Nuclear Materials Inspection Section
Nuclear Materials Safety and Safeguards Branch
Division of Radiation Safety and Safeguards

SUMMARY

Scope:

This special, announced inspection of activities conducted under NRC License No. 47-23066-02 was initially performed to review the circumstances and events surrounding seven reported therapeutic misadministrations involving the use of strontium-89. The scope of the inspection was expanded to review the licensee's use of phosphorus-32 and the Quality Management Program applicable to the use of pure beta-emitting therapeutic radiopharmaceuticals.

Results:

The inspection revealed that no misadministrations occurred because several sources of error associated with the licensee's methodology of assaying dosages of pure beta-emitting radiopharmaceuticals offset each other. The sources of error in the licensee's methodology resulted from weaknesses in the licensee's Quality Management Program (QMP). Specifically, the licensee's inadequate methodology of assaying dosages of pure beta-emitting radiopharmaceuticals resulted from an inadequate procedure in the licensee's QMP and inadequate supervision and technical support provided to the licensee's technologists who were implementing the program. Of particular concern was the

failure of the licensee's QMP applicable to the use of pure beta-emitting radiopharmaceuticals to (1) account for the error induced in dose calibrator readings by the change in geometry and container material from glass vial to plastic syringe, and (2) specify how to obtain the proper dose calibrator setting in which to perform the assays.

Within the scope of the inspection, the following apparent violations were identified:

- Failure of the licensee's QMP applicable to the use of pure beta-emitting radiopharmaceuticals to (1) account for the error induced in dose calibrator readouts by the change in geometry and container material from glass vial to plastic syringe, and (2) specify how to obtain the proper dose calibrator setting in which to perform the assays. (Sections 4 and 5)

- Failure of the licensee's QMP applicable to the use of pure beta-emitting radiopharmaceuticals to require that written directives include the route of administration. (Section 5)

REPORT DETAILS

1. Persons Contacted

+K. Douglass, Acting Hospital Radiation Safety Officer
L. Evans, Vice President for Human Resources
*+M. Frick, Chairman, Radiology Department
+N. Gupta, Chief of Nuclear Medicine
+S. Keener, Chief Nuclear Medicine Technologist
*+L. Korb, Chief of Radiation Oncology
+E. Rauderbush, Acting University Radiation Safety Officer
*+P. Royce, Chief Radiation Oncology Technologist
+C. Saw, Physicist
+D. Shock, Administrative Director, Radiology Department
*S. Slack, Radiation Safety Officer
*S. Tancin, Vice President for Ancillary Services
D. Wald, Nuclear Medicine Physician

Other licensee personnel contacted included physicians, technologists, and clerical and security personnel.

*Attended preliminary exit interview on August 2, 1994.
+Attended exit interview on September 14, 1994.

2. Program Scope and Licensee Organization

License No. 47-23066-02, a medical broad-scope license, was originally issued to West Virginia University Hospitals, Inc., the licensee, on April 19, 1985, after separating the hospitals' functions from those of the university. The license was most recently renewed on November 27, 1991, and was most recently amended on July 28, 1994. The license authorized the use of byproduct materials in diagnostic and therapeutic nuclear medicine, brachytherapy, clinical and laboratory in-vitro studies, instrument calibrations, radioactive waste storage incident to disposal, and in sealed sources contained in a blood products irradiator.

At the time of the inspection the licensee was performing approximately 15 nuclear medicine procedures per day, 2 phosphorus-32 (P-32) therapeutic administrations per year, 2 strontium-89 (Sr-89) therapeutic administrations per month, and 6 brachytherapy procedures per year, in addition to approximately 45 treatments per day involving the use of a linear accelerator not licensed by the NRC. The Radiology Department consisted of, among others, the Nuclear Medicine, Radiation Oncology, Medical Physics, and Radiation Safety Sections. Three technologists, one program director and the chief technologist reported to the Chief of Nuclear Medicine. Six technologists, one dosimetrist, one program director and the chief technologist reported to the Chief of Radiation Oncology. The Radiation Safety Officer (RSO), who was also the university's RSO under a separate NRC license, resigned his position between the August and September

inspections and was replaced in the interim by one of two of the licensee's physicists. The acting RSO was assisted by the acting RSO of the university and his staff. During the September inspection licensee representatives indicated they were actively recruiting an RSO and were trying to augment the radiation safety staff.

3. Circumstances Surrounding the Reported Misadministrations

Through interviews with licensee representatives, reviews of records, demonstrations by licensee representatives and direct observations, the inspector determined the following:

In 1993, the licensee began providing palliative therapy with a new radioactive drug which contained strontium-89 (Sr-89), a pure beta-emitting radionuclide. The standard treatment dosage was established to be four millicuries (mCi). It was also decided that such therapy services were going to be provided by the licensee's Radiation Oncology staff. The Oncology Chief Technologist had experience in handling sealed sources in brachytherapy and using the linear accelerator but had little experience in handling and assaying unsealed radiopharmaceuticals. The technologist used the drug manufacturer's instructions and, with the assistance of the Nuclear Medicine Chief Technologist, developed a procedure for assaying the Sr-89 dosages in the dose calibrator of the Nuclear Medicine laboratory. During the development stages of the new therapy program and the first three administrations, the RSO provided guidance to the technologist regarding the handling of unsealed radioactive materials and other personnel radiation safety matters. Neither the RSO nor any other individual at the facility other than the Nuclear Medicine Chief Technologist reviewed the assay procedure to ensure that it was in accordance with the manufacturer's instructions. Although the Oncology Chief Technologist had difficulty understanding the manufacturer's instructions when developing the assay procedure, she felt the procedure was adequate since she was being helped by the Nuclear Medicine Chief Technologist and supervised by the RSO, who was a physicist.

The new assay procedure followed the guidance provided in the licensee's Nuclear Medicine Policy No. IV.03, "Injection of Radiopharmaceuticals and Medications Associated with Nuclear Radiology Imaging." Items J and K of Policy No. IV.03 require that, based on the prescribed dosage, the required volume of a radiopharmaceutical be withdrawn from the vial

containing the radiopharmaceutical using a syringe, be measured in the syringe in a dose calibrator and then adjusted until the necessary dose calibrator reading is obtained. Radiopharmaceuticals routinely used in nuclear radiology imaging are gamma-emitters whose radiation is directly detected in the dose calibrator. Contrary to imaging radiopharmaceuticals, beta-emitters are assayed mainly by detecting the radiation generated in the container that houses the dosage as a result of the interaction of the beta radiation with the material, after applying a correction factor (i.e., a 4 mCi dosage of a pure beta-emitting radiopharmaceutical will produce reading of 40 microcuries in a properly used and calibrated dose calibrator).

While developing the assay procedure the technologist sought advice from the nuclear pharmacy that supplied the dosages regarding the proper dose calibrator setting to be used to perform the assays. Pharmacy personnel advised the technologist to use the same dose calibrator setting used in the pharmacy. The technologist followed the pharmacy's advice without verifying the adequacy of the setting in producing accurate readings. The technologist did not note that the drug manufacturer's instructions indicated that the dose calibrator setting was dependent on the type of dose calibrator possessed by the licensee and the type of container that houses the dosage.

The licensee began administering Sr-89 dosages on November 15, 1993. The licensee requested from the nuclear pharmacy that the dosages be supplied in glass vials in order to follow the procedure based on Nuclear Medicine Policy No. IV.03. The vials were calibrated by the pharmacy to have the prescribed amount of material on the day the licensee needed it for an administration. Due to the difference in the dose calibrator reading caused by the change in geometry and container material from glass vial to plastic syringe, the calibrated dosages transferred from the vials to the syringes produced readings in the dose calibrator higher than the ones expected. Based on the higher readings, the technologist routinely withdrew material from the syringes until obtaining the desired readings. This resulted in the licensee administering lower dosages than the ones prescribed.

As of July 8, 1994, the licensee had performed 14 therapeutic administrations of the Sr-89 radiopharmaceutical. On that day, the licensee had scheduled its 15th administration. The pharmacy erroneously supplied the licensee a calibrated dosage

with the prescribed activity in a syringe instead of a vial. When the technologist assayed the syringe she noted that the dose calibrator reading was substantially higher than the one expected. The technologist contacted the pharmacy to resolve the discrepancy in the measured activity. As a result of discussions with pharmacy personnel, the technologist suspected that all previous dosages had been improperly assayed, and so informed her management.

The next patient to be administered the Sr-89 radiopharmaceutical was scheduled for July 19, 1994. On that day, suspecting that the previous dosages may have been assayed improperly, the RSO and the physicist were directly involved in the assay. They received a dosage in a vial labeled by the pharmacy to contain 4.00 ± 10% mCi. The RSO and physicist measured the vial to contain 4.00 mCi and withdrew the dosage into a syringe. They then measured the residual activity in the vial to determine the actual activity transferred to the syringe. When they measured the activity in the syringe, they noted that the reading was 20.25% greater than expected and concluded that all previous administered dosages except the one that accidentally came from the pharmacy in a syringe had been reduced by the same factor prior to administration.

Pursuant to 10 CFR 35.2, "misadministration" means, in part, the administration of a therapeutic radiopharmaceutical when the administered dosage differs from the prescribed dosage by more than 20% of the prescribed dosage. The licensee reviewed the records of all previous administrations of Sr-89 radiopharmaceuticals and, after applying the calculated correction factor to each recorded dosage administered, determined that seven of the previous administrations met the definition of misadministration. At 4:46 p.m. on the same day the licensee notified the NRC Operations Center of the misadministrations. On July 20, 1994, the NRC issued a Confirmatory Action Letter (CAL) which documented the suspension of Sr-89 administrations until corrective actions resulting from the review of procedures were discussed with the NRC. The CAL also discussed required notifications of patients and referring physicians.

4. Inspection Findings

The inspector arrived at the licensee's facility on August 1, 1994, to review the circumstances surrounding the reported misadministrations and the licensee's corrective actions. While reviewing the drug manufacturer's literature

the inspector noted that, in accordance with the Food and Drug Administration's "Good Manufacturing Practices," the manufacturer was able to certify the accuracy of the stated radioactive contents in the product to within 1.5% by using techniques traceable to the National Institute of Standards and Technology. Licensee representatives were unable to explain to the inspector why the dosages they were receiving from the pharmacy were rated to an accuracy of ± 10%.

Through discussions with pharmacy personnel the inspector was able to resolve the apparent discrepancy regarding the accuracy in the amount of material contained in the dosages. Pharmacy personnel indicated that their stock of Sr-89 dosages obtained from the manufacturer may contain both dosages that are calibrated to contain four mCi sometime in the future and dosages calibrated to have four mCi sometime in the recent past. Pharmacy personnel indicated that, when they dispensed a four mCi dosage prepared from a dosage that was calibrated to be four mCi in the past, i.e., a post-calibrated dosage, they added material from another dosage in their stock to replace the decayed activity in the post-calibrated dosage. Pharmacy personnel further indicated that they used volumetric and dose calibrator measurements to determine the amount of material to be added, and that this technique increased the uncertainty in the accuracy of the stated radioactive contents to ± 10%. Through review of records and discussions with pharmacy personnel the inspector determined that the dosage used on July 19, 1994, to determine that misadministrations occurred was a post-calibrated dosage with a 10% uncertainty in its activity content. The inspector performed independent calculations that revealed that the uncertainty in the dosage used to determine that misadministrations occurred was high enough to cover the range of possibilities from that in which there were no misadministrations to that in which all administrations were misadministrations. The inspector also indicated that he agreed that the best estimate available at the time pointed to the likelihood that there were seven misadministrations.

Since the Sr-89 assay procedure was developed with the assistance of the Nuclear Medicine Chief Technologist based on a nuclear medicine procedure, the inspector inquired whether the nuclear medicine staff administered pure beta-emitting radiopharmaceuticals. Licensee representatives indicated that the nuclear medicine staff administered radiopharmaceuticals containing phosphorus-32 (P-32) on an infrequent basis. At the licensee's nuclear medicine laboratory the inspector noted that the licensee's dose calibrator had a label provided by the manufacturer of the dose calibrator indicating the setting for assaying P-32. After a second and closer look, the inspector noted that the

label had an asterisk next to "P-32" that led to a footnote which, in fine print, provided a warning indicating that up to a 20% correction factor may be necessary for assaying dosages contained in syringes. A nuclear medicine technologist indicated to the inspector that P-32 dosages were assayed in syringes in the setting specified in the label and prepared in the same manner in which Sr-89 dosages were prepared, i.e., by adjusting syringe volumes until the desired reading was obtained. Based on that discussion, the inspector determined that P-32 dosages were assayed in an incorrect dose calibrator setting, and the assay procedure did not account for the difference in dose calibrator reading caused by the change from vial to syringe.

On August 2, 1994, the inspector discussed with licensee management the inadequacies in its assay procedure when it was applied to pure beta-emitting radiopharmaceuticals. Specifically, the inspector pointed out that the procedure (1) failed to account for the error induced in the dose calibrator reading by the change in geometry and container material from glass vial to plastic syringe, and (2) did not specify how to obtain the proper dose calibrator setting in which to perform the assays. The inspector indicated to licensee management that, based on such inadequacies, there was a possibility that misadministrations involving the use of P-32 may have occurred, and the best estimate available pointed at the likelihood that seven misadministrations involving Sr-89 occurred. Licensee representatives indicated that they would pursue the issue further and would report to the NRC their findings.

In two letters to the NRC dated August 8 and 12, 1994, the licensee documented a systematic investigation of their assay techniques applicable to pure beta-emitting radiopharmaceuticals which revealed that no misadministrations occurred. Regarding Sr-89, the licensee obtained a pre-calibrated dosage directly from the manufacturer with a rated accuracy of ± 1.5%. The licensee's reported measurements revealed that the overall error resulting from the use of the wrong dose calibrator setting and the change from vial to syringe configuration was 6.6%. Based on the calculations, the licensee indicated that the worst case administration resulted in a patient receiving a dose which was 8.75% less than the prescribed dose. Regarding P-32, the licensee's reported measurements with a precalibrated dosage with a rated accuracy of ± 5% revealed that the overall error resulting from the use of the wrong dose calibrator setting and the change from vial to syringe configuration was 9.5%. Based on the calculations the licensee indicated that the worst case administrations resulted in four patients receiving a dose which was 9.5% less than the prescribed dose.

On September 14, 1994, the inspector met with licensee representatives to review and discuss in detail the licensee's investigation reported in its August 8 and 12, 1994 letters. Licensee representatives indicated that for both radionuclides, especially for P-32, the error resulting from assaying the dosages in the wrong dose calibrator setting offset the error resulting from the change from vial to syringe, with an overall effect of a slight underdosing of patients. The inspector performed independent calculations using the licensee's data and agreed with the licensee's results regarding Sr-89. The inspector also compared the most recent calculations with the methodology used on July 19, 1994, used to justify reporting seven misadministrations. The inspector concluded that the more recent evaluations were more reliable, in that significant sources of error had been minimized to more accurately estimate the actual doses administered. Regarding the calculations involving P-32, the inspector's independent calculations were in close agreement with the licensee's, with an estimated 12.1% overall error. Based on this, the inspector determined that, since April 1992, there were four administrations of P-32 in which the patients were underdosed by as much as 12.1%.

Pursuant to 10 CFR 35.2, "recordable event" means, in part, the administration of a therapeutic radiopharmaceutical dosage when the administered dosage differs from the prescribed dosage by more than 10% of the prescribed dosage. Although the inspector's and the licensee's calculations were in close agreement, i.e., 9.5% vs. 12.1% underdose, the inspector's calculations showed that there were four recordable events involving the use of P-32 while the licensee's calculations showed there were none. After discussing this finding with licensee representatives, they indicated that they have considered the whole issue regarding the improper assaying of pure beta-emitting radiopharmaceuticals as a recordable event and have been aggressively pursuing it accordingly.

5. Regulatory Issues

10 CFR 35.32(a) requires, in part, that the licensee establish and maintain a written Quality Management Program (QMP) to provide high confidence that byproduct materials will be administered as directed by the authorized user.

Item 3 of the licensee's Nuclear Medicine QMP requires that radiopharmaceutical dosages be measured in the dose calibrator prior to administration in accordance with licensee Policy No. IV.03. Items J and K of licensee Policy No. IV.03 require that the required volume of a radiopharmaceutical be withdrawn with a syringe from the

vial containing the radiopharmaceutical, measured in a dose calibrator and adjusted until the necessary dose calibrator reading is obtained. The failure of licensee Policy No. IV.03 for assaying dosages of pure beta-emitting radiopharmaceuticals (1) to account for the error induced in the dose calibrator reading by the change in geometry and container material from glass vial to plastic syringe, and (2) to specify how to obtain the proper dose calibrator setting in which to perform the assays was identified as an example of a violation of 10 CFR 35.32(a).

Item 1 of the licensee's Nuclear Medicine QMP requires that an authorized user date and sign a written directive prior to administration of a therapeutic dosage of a radiopharmaceutical. For a therapeutic administration of a radiopharmaceutical other than sodium iodide I-131 or I-125, 10 CFR 35.2 defines "written directive" as an order in writing for a specific patient dated and signed by an authorized user prior to administration, containing the radiopharmaceutical, dosage, and route of administration. While reviewing the licensee's records associated with the administrations of Sr-89 radiopharmaceuticals the inspector noted that the written directives did not include the route of administration. The inspector then reviewed the licensee's QMP applicable to the administration of pure beta-emitting therapeutic radiopharmaceuticals, which are radiopharmaceuticals other than sodium iodide I-131 or I-125, and determined that the QMP was inadequate in that it did not require that written directives include the route of administration. The failure of the licensee's QMP to require that the route of administration be included in the written directives was identified as another example of a violation of 10 CFR 35.32(a).

6. Exit Interview

The inspection scope and results were summarized in an exit interview on September 14, 1994, with those individuals identified in Section 1 above. The inspector reviewed the program areas inspected and discussed in detail the inspection findings. The inspector addressed inadequacies in the licensee's QMP and in the supervision and technical support provided to its technologists. The NRC's enforcement policy was also reviewed with licensee representatives. Licensee representatives provided no dissenting comments regarding the inspection findings and indicated that the necessary steps to correct the deficiencies discussed in this report would be taken. There is no proprietary information contained in this report.