

May 22, 2008

Mitzi Pennington, Site Director
Mallinckrodt, Inc.
2703 Wagner Place
Maryland Heights, MO 63043

SUBJECT: NRC SPECIAL INSPECTION REPORT NO. 030-00001/08-01(DNMS) AND
NOTICE OF VIOLATION – MALLINCKRODT, INC.

Dear Ms. Pennington:

This refers to the ongoing special inspection conducted on February 5 through 8, 2008, and March 10 through 13, 2008, at the Maryland Heights, Missouri facility, with continued NRC in-office review through April 22, 2008. The in-office review included receipt and review of information that was unavailable during the onsite inspection. The purpose of the inspection was to evaluate the facts, circumstances, and actions taken in response to the increased number of customer complaints that you received regarding the results of molybdenum-99 breakthrough tests conducted on technetium-99m generators and to evaluate the actions taken in response to the February 1, 2008, Confirmatory Action Letter (CAL 3-08-001). The enclosed report presents the results of the inspection to date. The special inspection will continue until the NRC has verified that all of the actions described in CAL 3-08-001 have been completed.

Based on your request to withhold proprietary information from public disclosure in accordance with the provisions of 10 CFR 2.390, the inspection report identifies components, equipment, chemicals, and other proprietary-related items in generic terms, such as Component 1 or Equipment 1.

Robert Gattone of my staff discussed the preliminary inspection findings with James Schuh of your staff during a telephone conference on April 10, 2008. In addition, the final exit meeting to discuss the inspection findings was held with you and other members of your staff at the Maryland Heights, Missouri facility on April 24, 2008. On May 23, 2008, members of my staff contacted you and other members of your staff to discuss the inspection findings.

This inspection was an examination of activities conducted under your license as they relate to safety and compliance with the Commission's rules and regulations and with 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.

Based on the results of the inspection, the NRC has determined that one 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 Web site at <http://www.nrc.gov/about-nrc/regulatory/enforcement/enforcement-pol.html>. The violation involves your failure to develop, implement, and maintain adequate Corrective Action Program procedures in accordance with Condition 20 of your license. The violation of Condition 20 of your license is cited in the enclosed Notice of Violation (Notice) and the circumstances

surrounding it are described in detail in the subject inspection report. The violation is being cited in the Notice because it was identified by the inspectors.

You are required to respond to this letter and should follow the instructions specified in the enclosed Notice when preparing your response. For your consideration and convenience, an excerpt from NRC Information Notice 96-28, "Suggested Guidance Relating to Development and Implementation of Corrective Action," is enclosed. The NRC will use your response, in part, to determine whether further enforcement action is necessary to ensure compliance with regulatory requirements.

Additionally, the NRC is reviewing the applicability of NRC notification requirements as they pertain to increased customer complaints that you received regarding the results of molybdenum-99 breakthrough tests conducted on technetium-99m generators. The applicability of the notification requirements remains an Open Item. The results of our review of the Open Item will be discussed in separate correspondence.

Furthermore, the NRC is concerned about Mallinckrodt, Inc.'s safety culture as it pertains to its response to increased customer complaints received regarding the results of molybdenum-99 breakthrough tests conducted on technetium-99m generator eluates, as exemplified by the following:

1. In October 2007, you identified that a generator component lot, that had not been used to produce generators (Lot A), contained a high concentration of a chemical that you suspected as a cause of molybdenum-99 breakthrough complaints. You were informed that the concentration of the chemical in Lot A was similar to the concentration in another lot of the same component that had been previously used to produce generators associated with molybdenum-99 breakthrough complaints. Nonetheless, you proceeded to use Lot A to produce generators, and you received a very high number of molybdenum-99 breakthrough complaints in January 2008.
2. You did not request customers to return a representative sample of generators associated with the very high number of molybdenum-99 breakthrough complaints received in January 2008 as a means of investigating the cause(s) of the problem.
3. You missed an opportunity to obtain additional information regarding the extent of condition associated with the molybdenum-99 breakthrough problem. Specifically, you presumed that all of the molybdenum-99 breakthrough complaints you received represented the extent of the problem without conducting an independent assessment, such as contacting other customers who received generators from the affected lots to verify the extent of the problem.
4. You missed opportunities to identify the cause(s) of the molybdenum-99 breakthrough problem during your change analysis. Specifically, as of March 10, 2008, your change analysis did not evaluate the safety consequences of "like-for-like" changes that occurred on the generator production line. For example, if a piece of production line equipment was replaced with the same make and model number, your staff did not evaluate the replacement part as a potential cause. Replacement parts may have been

modified by the manufacturer resulting in a change in operability, possibly contributing to the cause of the problem.

5. Your customer complaint receipt form did not include information necessary for you to identify molybdenum-99 breakthrough test failures that occurred after the first elution.
6. You did not have a procedure to assist staff in identifying trends in customer complaints, which impact safety, and formally communicate noted trends to management.

As stated in the enclosed NRC Regulatory Issue Summary 2005-18, "Guidance for Establishing and Maintaining a Safety Conscious Work Environment" (RIS), a strong safety culture is described as the "necessary full attention to safety matters." A strong safety culture is also often described as having a "safety-first focus." Attributes include the safety-over-production principle, procedural adherence, and conservative decision-making. Therefore, in addition to responding to the violation cited in the Notice, the NRC is requesting that you provide specific actions that have been or will be taken to enhance Mallinckrodt, Inc.'s safety culture in response to the increased number of customer complaints associated with technetium-99m generators. The enclosed RIS is provided for your consideration in developing your response to our concern.

In accordance with 10 CFR 2.390 of the NRC's "Rules of Practice," a copy of this letter, its enclosures, and your response, will be made available electronically for public inspection in the NRC Public Document Room or from the NRC's document system (ADAMS), accessible from the NRC Web site at <http://www.nrc.gov/readingrm/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/

Steven A. Reynolds, Director
Division of Nuclear Materials Safety

Docket No. 030-00001
License No. 24-04206-01

Enclosures:

1. Notice of Violation
2. Inspection Report 030-00001/08-01(DNMS)
3. Excerpt from NRC Information Notice 96-28
4. NRC Regulatory Issue Summary 2005-18

cc: J. Schuh, Radiation Safety Officer
State of Missouri
Orhan Suleiman, Food and Drug Administration
Michele Perry-Williams, Food and Drug Administration

DISTRIBUTION:

See next page

Letter to Mitzi Pennington from Steven A. Reynolds dated May 22, 2008

SUBJECT: NRC SPECIAL INSPECTION REPORT NO. 030-00001/08-01(DNMS) AND NOTICE OF VIOLATION – MALLINCKRODT, INC.

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NOTICE OF VIOLATION

Mallinckrodt Inc.
Maryland Heights, Missouri

Docket No. 030-00001
License No. 24-04206-01

During an NRC inspection conducted on February 5 through 8, 2008, and March 10 through 13, 2008, a violation of NRC requirements was identified. In accordance with the NRC Enforcement Policy, the violation is listed below:

Condition 20 of License No. 24-04206-01 requires that the licensee maintain a corrective action program (CAP) to identify and correct deficiencies associated with radiation safety, and that:

- A. It develop, implement, and maintain procedures to assure that conditions adverse to radiation safety, such as failures, malfunctions, deficiencies, deviations, defective material and equipment, and non-conformances that could reasonably affect exposures to workers or the public, or releases of radioactive material in effluents or to the sanitary sewer system, are promptly identified and corrected. In the case of significant conditions adverse to radiation safety, the measures shall assure that the cause of the condition is determined and corrective action taken to preclude repetition. The identification of the significant condition adverse to radiation safety, the cause of the condition, and the corrective action taken shall be documented and reported to appropriate levels of management. The procedures shall include appropriate quantitative or qualitative acceptance criteria for determining that the procedures have been satisfactorily accomplished; and
- B. The procedure(s) shall include provisions for: 1) defining conditions that are adverse to radiation safety; 2) identifying conditions that are adverse to radiation safety; 3) reporting the conditions to appropriate management levels; 4) investigating adverse conditions in sufficient detail to identify root causes; 5) developing and implementing corrective actions to address the identified root cause(s) and to prevent recurrence; and 6) establishing time tables (milestones) for each provision, commensurate with the significance of the adverse condition.

Contrary to the above, as of April 24, 2008, the licensee did not develop, implement, and maintain CAP procedures that included actions to assure that conditions adverse to radiation safety were promptly identified and corrected. In addition, the licensee's CAP procedures did not include measures to be taken to assure that the cause of significant conditions adverse to radiation safety were determined and corrective action was taken to preclude repetition, and that the cause of the condition and the corrective action taken was documented and reported to appropriate levels of management. Specifically, the licensee developed, implemented, and maintained separate CAP procedures for Environmental Health and Safety issues and Product Quality issues, and the Product Quality CAP procedures did not include provisions for: 1) defining conditions that are adverse to radiation safety; 2) identifying conditions that are adverse to radiation safety; 3) reporting the conditions to appropriate management levels; 4) investigating adverse conditions, in sufficient detail to identify root causes; and 5) establishing time tables (milestones) for each provision, commensurate with the significance of the adverse condition.

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

Enclosure 1

Pursuant to the provisions of 10 CFR 2.201, Mallinckrodt Inc. is hereby required to submit a written statement or explanation 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). This reply should be clearly marked as a "Reply to a Notice of Violation" and should include for each violation: (1) the reason for the violation, or, if contested, the basis for disputing the violation or severity level; (2) the corrective steps that have been taken and the results achieved; (3) the corrective steps that will be taken to avoid further violations; and (4) the date when full compliance will be achieved. Your response may reference or include previous docketed correspondence, if the correspondence adequately addresses the required response. If an adequate reply is not received within the time specified in this Notice, an order or a Demand for Information may be issued as to why the license should not be modified, suspended, or revoked, or why such other action as may be proper should not be taken. Where good cause is shown, consideration will be given to extending the response time.

If you contest this enforcement action, you should also provide a copy of your response, with the basis for your denial, to the Director, Office of Enforcement, United States Nuclear Regulatory Commission, Washington, DC 20555-0001.

Because your response will be made available electronically for public inspection in the NRC Public Document Room or from the NRC's document system (ADAMS), accessible from the NRC Web site at <http://www.nrc.gov/reading-rm/adams.html> to the extent possible, it should not include any personal privacy, proprietary, or safeguards information so that it can be made available to the public without redaction. If personal privacy or proprietary information is necessary to provide an acceptable response, then please provide a bracketed copy of your response that identifies the information that should be protected and a redacted copy of your response that deletes such information. If you request withholding of such material, you must specifically identify the portions of your response that you seek to have withheld and provide in detail the bases for your claim of withholding (e.g., explain why the disclosure of information will create an unwarranted invasion of personal privacy or provide the information required by 10 CFR 2.390(b) to support a request for withholding confidential commercial or financial information). If safeguards information is necessary to provide an acceptable response, please provide the level of protection described in 10 CFR 73.21.

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

Dated this 22nd day of May 2008

U.S. NUCLEAR REGULATORY COMMISSION

REGION III

Docket No.: 030-00001

License No.: 24-04206-01

Report No.: 030-00001/08-01(DNMS)

Licensee: Mallinckrodt, Inc.

Facility: 2703 Wagner Place
Maryland Heights, Missouri

Inspection Dates: February 5 through 8, 2008
March 10 through 13, 2008
Continued in-office review through April 22, 2008

Preliminary Exit Meeting: March 13, 2008

Final Exit Meeting: April 24, 2008

Inspectors: Robert G. Gattone, Jr., Senior Health Physicist
Kevin G. Null, Senior Health Physicist

Approved By: Patricia J. Pelke, Chief
Materials Licensing Branch
Division of Nuclear Materials Safety

EXECUTIVE SUMMARY

Mallinckrodt, Inc. NRC Inspection Report 030-00001/08-01(DNMS)

This was a special inspection conducted at Mallinckrodt, Inc. (licensee) from February 5 through 8, 2008, and from March 10 through 13, 2008, to evaluate the facts, circumstances, and the licensee's actions taken in response to the increased number of customer complaints it received associated with technetium-99m generators that failed the molybdenum-99 breakthrough test. From approximately October 2006 through February 2007, and particularly in January 2008, the licensee received an increase in the number of customer complaints associated with technetium-99m generators that failed the molybdenum-99 breakthrough tests. Specifically, an increased number of generators produced elutions that exceeded the 0.15 microcurie of molybdenum-99 per millicurie of technetium-99m regulatory limit in Title 10 Code of Federal Regulations (CFR) 35.204, "Permissible Molybdenum-99 Concentration" at either the first or a subsequent generator elution. The inspectors also evaluated the actions associated with Confirmatory Action Letter (CAL) No. 3-08-001 dated February 1, 2008.

The licensee calculated the average and highest increased concentrations of molybdenum-99 for the January 2008 event. Based on this information, the licensee determined that the safety significance of administering radiopharmaceuticals with molybdenum-99 concentrations that exceeded the limits in 10 CFR 35.204 was very low. The licensee calculated that the average increased molybdenum-99 concentration identified in early 2008 would result in an additional 15 millirem Total Effective Dose Equivalent (TEDE) to a patient. In addition, the licensee calculated that the highest increased concentration of molybdenum-99 identified in early 2008 would result in an additional 200 millirem TEDE to a patient. The licensee also determined that the chemical hazard associated with administration of radiopharmaceuticals with molybdenum-99 in excess of the 10 CFR 35.204 limit was very low. Based on an independent assessment of this event, the NRC determined that the safety significance of administering radiopharmaceuticals with molybdenum-99 in excess of the 10 CFR 35.204 limit was low.

Based on the licensee's request to withhold proprietary information from public disclosure in accordance with the provisions of 10 CFR 2.390, the report identifies components, equipment, chemicals, and other proprietary-related items in generic terms, such as Component 1 or Equipment 1. The licensee's investigation into the cause(s) of the molybdenum-99 breakthrough problem is still ongoing. As of March 28, 2008, the licensee identified four potential cause(s) including: (1) use of a piece of equipment (Equipment 1) during the manufacturing process that had different dimensions than the one it replaced; (2) increased chemical (Chemical 1) content in a component (Component 1) of the generators; (3) use of a technique during the manufacturing process that resulted in problems with a generator component (Component 2); and (4) different molybdenum-99 breakthrough testing methods used by the industry.

The inspectors identified a violation of Condition 20 of NRC License No. 24-04206-01 involving failure to develop, implement, and maintain adequate Corrective Action Program (CAP) procedures. Specifically, the licensee's Product Quality CAP procedures did not include provisions for: 1) defining conditions that are adverse to radiation safety; 2) identifying conditions that are adverse to radiation safety; 3) reporting the conditions to appropriate management levels; 4) investigating adverse conditions, in sufficient detail to identify root

causes; and 5) establishing time tables (milestones) for each provision, commensurate with the significance of the adverse condition.

In addition to the violation, the inspectors identified a concern relative to the licensee's safety culture as it pertains to its response to the increased number of customer complaints.

There is one inspection item that remains open regarding reportability. The NRC is reviewing the applicability of 10 CFR Part 21 and Part 30 notification requirements as they pertain to the molybdenum-99 breakthrough problem.

The licensee's corrective actions to prevent the molybdenum-99 breakthrough problem included: (1) revising its automated inventory system to ensure that it has Equipment 1 with the proper dimensions in stock at all times; (2) revising a manufacturing process procedure to ensure that Equipment 1 with the proper dimensions is used; (3) initiating quality control testing of incoming Equipment 1 to verify that it has the correct dimensions; (4) developing training for applicable staff to prevent use of a technique during the manufacturing process that resulted in problems with Component 2; (5) recording and trending the rejection rate of Component 2 and documenting the reasons for the rejections as a means of identifying and reducing the number of rejected components; (6) revising its quality control procedure for molybdenum-99 breakthrough tests prior to product distribution; (7) developing and performing experiments to identify a correlation between the content of Chemical 1 in Component 1 and molybdenum-99 breakthrough as a means of establishing a Component 1 specification for acceptable Chemical 1 content; (8) establishing a standard test method and validation protocol to test Component 1 for Chemical 1 content prior to use in production; (9) identifying an alternate Component 1 vendor; (10) working with the Component 1 vendor to see if it can provide the component with low levels of Chemical 1; (11) conducting tests to determine if Component 1 lots with certain test results correspond with increased molybdenum-99 breakthrough; (12) investigating in-house methods of reducing the content of Chemical 1 in Component 1; and (13) investigating the differences between molybdenum-99 breakthrough testing methods used by the licensee and the industry as part of its investigation of the cause of the molybdenum-99 breakthrough problem.

On March 10, 2008, the licensee completed all of the actions described in Item 3 of Confirmatory Action Letter (CAL) 3-08-001 dated February 1, 2008, regarding its evaluation of 10 CFR Part 21 reportability of the molybdenum-99 breakthrough problem. The licensee has initiated but not completed the actions described in Items 1, 2, and 4 of the CAL regarding investigation of the molybdenum-99 breakthrough problem, corrective actions to prevent the problem, and Important Product Notification distribution, respectively. The licensee estimated that it would complete all of the actions described in Items 1 and 2 of the CAL by September 2008; and it would complete Item 4 of the CAL by October 2008.

Report Details¹

1 Molybdenum-99 Breakthrough Problem Chronology and Licensee Response Actions

a. Molybdenum-99 Breakthrough Complaint History

The licensee manufactures and distributes molybdenum-99/technetium-99m generators. The product of the generators, commonly referred to as the eluate, contains technetium-99m, which is used by medical licensees to prepare radiopharmaceuticals for diagnostic imaging. Licensees that use generators are required to measure the ratio of molybdenum-99 to technetium-99m in the first elution of each generator in order to ensure that the concentration of molybdenum-99 in the eluate does not exceed the regulatory limit of 0.15 microcurie of molybdenum-99 per millicurie of technetium-99m specified in Title 10 Code of Federal Regulations (CFR) Part 35.204, "Permissible Molybdenum-99 Concentration." The regulation also specifies that radiopharmaceuticals cannot be administered to patients if the concentration limit is exceeded. Based on operational experience, generators infrequently produce concentrations of molybdenum-99 that exceed the regulatory limit. From 2003 through 2007, the licensee received infrequent reports of molybdenum-99 breakthrough from customers.

The licensee defined molybdenum-99 breakthrough as an eluate of technetium-99m that failed to meet the molybdenum-99 concentration limit up to 12 hours post elution, the time at which the useful period for the eluate expires. The licensee established separate criteria for defining molybdenum-99 complaints. The "molybdenum-99 breakthrough" complaints pertained to molybdenum-99 breakthrough test results that exceeded the limit in 10 CFR 35.204 between 0 and 12 hours post elution. The licensee defined "molybdenum-99 feedback" complaints as molybdenum-99 breakthrough test results that exceeded the limit in 10 CFR 35.204 between 12 and 24 hours post elution. The licensee did not instruct its customers to report molybdenum-99 breakthrough or molybdenum-99 feedback complaints.

b. Identification of Increased Complaints about Molybdenum-99 Breakthrough

Sometime between September 15 and October 8, 2006, a piece of equipment (Equipment 1) used in the generator manufacturing process was damaged and replaced. In addition, on October 8, 2006, the licensee began using a new lot of a generator component (Component 1) to produce generators.

In October 2006, Corporate Product Monitoring (CPM) staff received several customer complaints about molybdenum-99 breakthrough. CPM staff e-mailed the customer complaints to the Customer Complaint Coordinator (CCC). For each customer complaint, the CCC completed part of a customer complaint evaluation form that was specific to generator complaints and sent it to the Manufacturing Engineer for investigation. In addition, the CCC was responsible for analyzing incoming customer complaints and identifying trends.

¹ A list of acronyms used in the report is included at the end of the Report Details.

The Radiation Safety Officer (RSO) became aware of the molybdenum-99 breakthrough complaints sometime in October 2006 at either weekly staff meetings that included discussions of open quality issues or by routine receipt of e-mails from Mallinckrodt Pharmacy customers that included various issues, including molybdenum-99 breakthrough complaints. At that time, a Health Physics staff member was stationed with the generator manufacturing group as a means of enhancing communication between manufacturing staff and health physics staff such that health physics staff could quickly learn about opportunities for improvement and take actions to address them. The RSO tasked the Health Physics staff member to follow up on the molybdenum-99 breakthrough problem. The Health Physics staff member met biweekly with the RSO to discuss the status of response actions taken, including possible causes of the problem and results of generator component reviews.

c. Phase I of Molybdenum-99 Breakthrough Cause Investigation

From approximately October 2006 to December 2006, licensee manufacturing staff investigated the cause of the customer complaints. The staff investigated whether or not the complaints were associated with generators that initially did not meet quality specifications and were subsequently re-worked to meet product specifications prior to distribution. In addition, the staff reviewed the generator production schedules, looked for product deviations, reviewed batch records, and autoclave cycles, among other things, in search of the cause of the problem. However, the cause was not identified.

Environmental Health & Safety (EH&S) staff, Quality staff, and the Site Director attended biweekly meetings to review customer complaints. The CCC provided a Quality Engineer with a table of the number and types of customer complaints that were received for presentation at the Steering Committee meetings. During the Steering Committee meeting in October 2006, the attendees discussed the increasing customer complaints regarding molybdenum-99 breakthrough test results.

Based on the increased number of customer complaints received in October 2006, the CPM staff requested that 94 percent of the generators that failed the molybdenum-99 breakthrough test be returned to the licensee's facility in November 2006. The generators were returned and held for about 90 days to allow the residual molybdenum-99 to decay to a low level of radioactivity so that they could be disassembled safely.

On or about November 29, 2006, the licensee identified that the new Equipment 1 that was used during the generator manufacturing process had different dimensions than the damaged one it replaced. On January 9, 2007, the licensee identified the correct vendor name and part number for Equipment 1 that was replaced; and used that information to order the correct Equipment 1 with the proper dimensions.

Equipment 1 (with the wrong dimensions) was used to produce generators from approximately October 8, 2006, through February 27, 2007. The licensee ceased generator production between approximately February 28 and March 30, 2007, due to sterility problems.

The Site Director, Quality Site Manager, and RSO assumed that customers followed the generator package insert, which instructed the user to perform molybdenum-99 breakthrough tests on each generator elution, and not administer material that exceeded

the molybdenum-99 concentration limit. Based on this un-validated assumption, on or about March 8, 2007, the licensee staff concluded that the molybdenum-99 breakthrough problem did not impact generator safety.

On March 9, 2007, the licensee received new Equipment 1 with the proper dimensions, which were verified, before it was used during generator production. To prevent recurrence of the problem identified with using Equipment 1 with the wrong dimensions, the licensee revised its automated inventory system to ensure that it had at least one extra correct size of Equipment 1 in stock at all times. In addition, the licensee initiated quality control testing of incoming Equipment 1 to verify the correct dimensions.

d. Phase II of Molybdenum-99 Breakthrough Cause Investigation

Since the manufacturing staff could not confirm the cause of the molybdenum-99 breakthrough problem, the licensee initiated a "Deviation Investigation" on March 22, 2007, comprised of a team that included the Manufacturing Supervisor, Manufacturing Manager, and Quality organization representatives. The Deviation Investigation was broader than Phase I of the investigation. The Deviation Investigation Team (DIT) analyzed the generator manufacturing process; analyzed chemical and hardware lot changes that coincided with the start of molybdenum-99 breakthrough events in October 2006; reviewed changes in applicable personnel, facilities, and applicable records; analyzed generator component production; analyzed generator reprocessing to see if it correlated with molybdenum-99 breakthrough complaints; and reviewed all aspects of training for individuals involved with generator production, with a focus on generator product processing.

From approximately February through May 2007, the licensee disassembled the returned generators to, in part, attempt to identify causes of the molybdenum-99 breakthrough failures; however, the cause of the molybdenum-99 breakthrough failures was not identified during this process.

In May 2007, the licensee began elemental testing of Component 1 and noted that the concentration of Chemical 1 differed between the various lots of Component 1. Tests were conducted on the lots of Component 1 that were used in October 2006 and all subsequent lots of Component 1 to determine the concentration of Chemical 1. The DIT suspected that the cause of the molybdenum-99 breakthrough complaints was due to increased concentrations of Chemical 1 in Component 1. However, they could not confirm it because a Component 1 lot that was used in October 2006 was associated with several molybdenum-99 breakthrough complaints, and a Component 1 lot that was initially used on March 30, 2007, with similar Chemical 1 concentration was not associated with molybdenum-99 breakthrough complaints.

Another generator manufacturer (Manufacturer X), produced generators with less radioactive molybdenum-99 than that used by the licensee. Although Manufacturer X obtained Component 1 from the same vendor as the licensee, its production equipment and processes were substantially different than the licensee's. Based on communications between the licensee and Manufacturer X regarding molybdenum-99 breakthrough issues, the licensee learned that Manufacturer X had also identified increased molybdenum-99 breakthrough during quality control testing that it conducted prior to generator distribution.

On June 2, 2007, the DIT noted that: (1) on or about October 8, 2006, the licensee began manufacturing generators with Equipment 1 that had different dimensions than the one it replaced; (2) on October 8, 2006, the licensee began using a new lot of Component 1 to produce generators; and (3) in October 2006, CPM staff received several customer complaints about generators failing the molybdenum-99 breakthrough tests. The DIT hypothesized that use of new Equipment 1 that had different dimensions was a cause of the molybdenum-99 breakthrough problem. In addition, the DIT noted that, since application of certain chemicals to Component 1 correlated with increased molybdenum-99 breakthrough complaints, those activities could also be a cause of the complaints.

From about June 2, 2007, when the licensee identified that wrong sized Equipment 1 was a potential cause of the molybdenum-99 breakthrough complaints, until February 27, 2008, the licensee initiated actions to ensure that its Quality Control staff had equipment and procedures to conduct quality control testing and assign lot numbers for incoming Equipment 1.

In August 2007, the licensee was aware that Manufacturer X visited the Component 1 vendor and learned that the vendor used Chemical 1 on Component 1. Manufacturer X noted that increased concentrations of Chemical 1 could result in molybdenum-99 breakthrough. The vendor informed Manufacturer X that Chemical 1 concentration is only analyzed qualitatively and there is no extra rinsing step after Chemical 1 is used on Component 1. Manufacturer X determined that the final Chemical 1 concentration in Component 1 should be reviewed further. Manufacturer X and the Component 1 vendor agreed on follow-up actions that included: (1) the vendor providing Manufacturer X with Component 1 samples for Chemical 1 concentration assessment; (2) Manufacturer X providing the vendor with the results of the assessment; and (3) Manufacturer X informing the vendor about how to quantify Chemical 1 concentration in Component 1 if Manufacturer X determines that Chemical 1 is causing molybdenum-99 breakthrough.

Based on preliminary laboratory tests, Manufacturer X identified that the concentration of Chemical 1 from samples of different batches of Component 1 and samples within a particular batch of the same lot of Component 1 were different; therefore, Manufacturer X concluded that Chemical 1 concentration is a source of variation in the quality of Component 1. In addition, Manufacturer X noted that there was correlation between increased Chemical 1 concentration in Component 1 and increased molybdenum-99 breakthrough.

The licensee reviewed quality control processes and records for the generator lots that were produced between August 16, 2006, and June 13, 2007. All of these lots passed the licensee's molybdenum-99 concentration quality control limit. The DIT could not confirm the cause of the molybdenum-99 breakthrough complaints.

e. Phase III of Molybdenum-99 Breakthrough Cause Investigation

Based on their investigation from March 22, 2007, through late August 2007, the DIT could not confirm the cause of the molybdenum-99 breakthrough complaints. Therefore, the licensee initiated a "Corrective and Preventative Action" (CAPA) investigation on August 24, 2007, to identify the cause of the molybdenum-99 breakthrough complaints.

The CAPA Team met monthly from August 2007 through December 2007 and included the Site Director and representatives of Operations, Quality, Procurement, Operational Excellence, Research and Development, Health Physics, and CPM. The CAPA Team maintained a draft report of their activities and findings. The CAPA Team investigated possible causes, including the chemical concentration of Component 1, Component 2, and other generator components; personnel involved with the addition of molybdenum-99 into Component 2; and the manufacturing process and associated hardware. The CAPA Team noted that most of the generator components changed lots so frequently that the combined effect of all of them did not correlate with increased molybdenum-99 breakthrough complaints.

In mid-October 2007, the licensee identified opportunities to improve its pre-distribution molybdenum-99 breakthrough quality control test procedure. The licensee identified that generator lots that were produced between August 16, 2006, and June 13, 2007, passed the licensee's molybdenum-99 breakthrough quality control test based on sampling; however, some generators that passed the quality control test were associated with molybdenum-99 breakthrough complaints.

As part of the CAPA Team's investigation, it had an outside lab test the concentration of Chemical 1 on a lot of Component 1 that had not been used to produce generators. On or about October 23, 2007, a member of the CAPA Team received the lab results indicating that the lot of Component 1 contained a significantly elevated concentration of Chemical 1. On October 24, 2007, the CAPA Team member sent an e-mail to some of the other CAPA Team members warning that the Component 1 lot that had not yet been used to produce generators had an elevated concentration of Chemical 1 similar to that used to produce generators associated with molybdenum-99 complaints that were received in October 2006.

The licensee continued to produce generators because it received very few molybdenum-99 breakthrough complaints between July 2007 and December 2007. Additionally, the licensee assumed that its customers would reject eluates that failed the molybdenum-99 breakthrough test.

In January 2008, the licensee conducted an experiment to determine if increasing the concentration of Chemical 1 in Component 1 would result in increased molybdenum-99 breakthrough. The licensee rinsed Component 1 with Chemical 1 to increase the Chemical 1 concentration. Afterward, the licensee tested for molybdenum-99 breakthrough and noted increased breakthrough associated with Component 1 that contained high concentrations of Chemical 1.

A new lot of Component 1 (i.e., the one that was previously identified as containing a significantly elevated concentration of Chemical 1) was first used to produce generators on January 9, 2008. Although the licensee suspected elevated concentrations of Chemical 1 in Component 1 as a potential cause for the molybdenum-99 breakthrough problem since May 2007, it used the new lot of Component 1 to produce generators despite knowing that it contained elevated concentrations of Chemical 1. The licensee used the new lot of Component 1 to produce generators because it determined that more testing was required to eliminate uncertainty about the suspected cause.

f. Significant Increase in Molybdenum-99 Breakthrough Complaints

The licensee received a high number of molybdenum-99 breakthrough customer complaints in January 2008. On January 11, 2008, CPM staff received its first complaint of molybdenum-99 breakthrough that month. On January 14, 2008, the CCC was notified of the complaint. On January 15, 2008, the CAPA Team met and decided to meet three times per week instead of monthly. From January 15 to 25, 2008, the CAPA Team reviewed generator batches that were produced during that time, including the Component 2 preparation process and batch records with a focus on Component 1.

The RSO became aware of the first molybdenum-99 breakthrough complaint on January 11, 2008, based on receipt of an e-mail from a Mallinckrodt Pharmacy customer. The RSO forwarded the complaint to the Generator Process Engineer and the Health Physics Supervisor. As the RSO became aware of additional molybdenum-99 breakthrough complaints during the week of January 15, 2008, he met with the Site Director and her staff to discuss the issue on or about January 16, 2008.

On January 23, 2008, the licensee started to produce generators with a new lot of Component 1 that it received from Manufacturer X on January 21, 2008. The new lot of Component 1 contained a significantly lower concentration of Chemical 1 as compared to the previous Component 1 lot and had been used by Manufacturer X without molybdenum-99 breakthrough problems. On January 25, 2008, the licensee distributed generators produced with the new lot of Component 1.

On January 24, 2008, the NRC contacted the licensee regarding recent reports of elevated concentrations of molybdenum-99 in the eluates from Mallinckrodt technetium-99m generators. The licensee was aware of an increase in customer complaints and provided additional details of the complaints to the NRC during a teleconference on January 25, 2008. The NRC informed the Food and Drug Administration (FDA) about the increased number of molybdenum-99 breakthrough complaints the licensee received regarding their technetium-99m generators during a teleconference on January 25, 2008.

As a result of teleconferences with the FDA and the NRC on January 25, 2008, the licensee began distributing an "Important Product Notification" with all of its generators shipped on or after January 27, 2008. In addition, the licensee mailed the Important Product Notification to all customers who received generators from the affected lots. The Important Product Notification included a summary of the molybdenum-99 breakthrough problem, including the affected generator lot numbers; a reminder that the eluates expire 12 hours post elution, a reminder that each eluate should not contain more than the 0.15 microcurie of molybdenum-99 per millicurie of technetium-99m limit at the time of administration, and a recommendation to follow the generator package labeling.

By January 28, 2008, the licensee received a very high number of molybdenum-99 breakthrough complaints associated with nine generator lots. The molybdenum-99 breakthrough complaints included molybdenum-99 breakthrough test results ranging from 0.15 to 3.52 microcuries of molybdenum-99 per millicurie of technetium-99m at 12 hours post elution. The licensee noted that some of the complaints involved

generators that passed the molybdenum-99 breakthrough test on the first elution and failed the test on a subsequent elution.

In January 2008, the licensee requested that less than 3 percent of the generators associated with molybdenum-99 breakthrough complaints received that month be returned for investigation to determine the cause of the problem. The licensee decided to request that only less than 3 percent be returned because: (1) it did not identify any potential causes of the problem when it requested that 94 percent of the generators associated with molybdenum-99 breakthrough test failures be returned to the licensee's facility in the fall of 2006; and (2) it strongly suspected high concentrations of Chemical 1 in Component 1 as the probable cause. Therefore, it expected limited value associated with the impact of requesting that more than about 3 percent of the generators be returned.

The licensee did not notify its customers of the molybdenum-99 breakthrough complaints because it believed that its customers performed molybdenum-99 breakthrough tests on each elution of the generator and did not administer radiopharmaceuticals that exceeded the molybdenum-99 concentration limit in 10 CFR 35.204 to patients. The licensee did not notify the NRC about the molybdenum-99 breakthrough complaints because the licensee believed that: (1) since the generator product met all specifications prior to distribution, compliance with NRC regulatory requirements was achieved; (2) since the molybdenum-99 breakthrough problems occurred post distribution, the problems were an FDA issue (though it was not clear that the licensee was going to notify the FDA); and (3) there was no health and safety issue because the licensee assumed that the customers performed molybdenum-99 breakthrough tests as described in the package insert and did not administer radiopharmaceuticals that exceeded the molybdenum-99 concentration limit in 10 CFR 35.204 to patients.

From January 28 to February 4, 2008, the licensee conducted an assessment of the risk associated with possible administration of radiopharmaceuticals that exceed the limit in 10 CFR 35.204. The licensee determined that the safety significance of administration of radiopharmaceuticals with molybdenum-99 in excess of the 10 CFR 35.204 limit is very low. The licensee determined that a patient receives approximately 800 millirems TEDE from the most frequently administered technetium-99m radiopharmaceutical. The licensee calculated that the average increased molybdenum-99 concentration identified in early 2008 would result in an additional 15 millirems TEDE to the patient. In addition, the licensee calculated that the highest increased molybdenum-99 concentration identified in early 2008 would result in an additional 200 millirems TEDE to the patient. The licensee also determined that the chemical hazard associated with administration of radiopharmaceuticals with molybdenum-99 in excess of the 10 CFR 35.204 limit was very low.

In response to a telephone call between the licensee and the NRC on January 29, 2008, the licensee sent a letter to the NRC dated January 30, 2008, providing information about the molybdenum-99 breakthrough problem. The letter included actions already taken and future actions that would be taken in response to the molybdenum-99 breakthrough problem.

On February 1, 2008, the NRC issued Confirmatory Action Letter (CAL) 3-08-001 to the licensee confirming its understanding of the actions the licensee committed to take in response to the molybdenum-99 breakthrough problem based on telephone

conversations between members of the licensee's staff and the NRC's staff on February 1, 2008, and the licensee's letter to the NRC dated January 30, 2008.

On February 5, 2008, the NRC began a Special Inspection to follow up on the licensee's response to increased customer complaints that it received regarding the results of molybdenum-99 breakthrough tests conducted on technetium-99m generator eluates. The special inspection will continue until the NRC has verified that all of the actions described in CAL 3-08-001 have been completed.

Between January 28 and February 8, 2008, the licensee continued to receive several molybdenum-99 breakthrough complaints regarding generators from the affected lots.

g. Continued Phase III of Molybdenum-99 Breakthrough Cause Investigation

As of February 8, 2008, the CAPA Team suspected that increased Chemical 1 in Component 1 was a cause of the molybdenum-99 breakthrough complaints because: (1) there was a correlation between increased Chemical 1 in Component 1 and increased molybdenum-99 breakthrough complaints; and (2) preliminary laboratory studies indicated that increased Chemical 1 in Component 1 resulted in increased molybdenum-99 breakthrough.

In addition, the CAPA Team suspected that the use of a wrong sized Equipment 1 between approximately October 8, 2006, and February 27, 2007, caused increased molybdenum-99 breakthrough complaints during that time period. The CAPA Team also surmised that the use of a wrong sized Equipment 1 was the reason why the lot of Component 1 that was used to make generators between October 8, 2006, and February 27, 2007, had an increase in molybdenum-99 breakthrough complaints, and the lot of Component 1 that was used to make generators beginning on March 30, 2007, with similar Chemical 1 concentration did not have an increase in molybdenum-99 breakthrough complaints.

The licensee planned to update and implement the Component 1 specifications to include concentration limits for Chemical 1 before it uses a new lot of Component 1 for generator production. However, the licensee was unable to complete lab testing to identify the Chemical 1 concentration level that causes molybdenum-99 breakthrough before it ran out of the new lot of Component 1 that it received from another generator manufacturer. Therefore, in late March 2008, the licensee planned to use another Component 1 lot that contained about the same concentration of Chemical 1 as the previous lot of Component 1.

In late February 2008, the licensee received several molybdenum-99 feedback complaints associated with generators produced that month. The licensee identified that, during Component 2 production in February 2008, a high number of these components (Component 2) were rejected during quality control checks. The licensee also noted that new staff were involved with producing the Component 2 lots associated with the complaints. The licensee also identified that use of a technique during production of Component 2 could result in molybdenum-99 breakthrough. Therefore, as of March 10, 2008, the licensee instituted training for applicable staff to improve Component 2 production technique and reduce molybdenum-99 breakthrough. In addition, the licensee began recording and trending the Component 2 rejection rate and

the probable cause for the rejections as a means of identifying and reducing the number of rejected components.

On February 27, 2008, the licensee initiated changes to, in part, ensure that new Equipment 1 passes quality control testing, with reference to an Equipment 1 specification drawing; and that steps are taken to document processing for Equipment 1; and recording the lot number of Equipment 1 that is used.

As of March 10, 2008, the licensee was in the process of revising its quality control procedure for testing generator eluates for molybdenum-99 concentration prior to generator distribution. The revision involved increased accuracy in determining the molybdenum-99 concentration at 12 hours post elution.

The CAPA Team issued an interim report for the molybdenum-99 breakthrough investigation dated March 10, 2008. The report describes four potential causes for the molybdenum-99 breakthrough problem including: (1) use of the Equipment 1 with the wrong dimensions to process Component 1; (2) increased Chemical 1 concentration in Component 1; (3) use of an inadequate technique to produce Component 2; and (4) different molybdenum-99 breakthrough testing methods used by the industry.

The licensee planned to develop and perform experiments to identify a correlation between the concentration of Chemical 1 in Component 1 and molybdenum-99 breakthrough as a means of establishing a Component 1 specification for acceptable Chemical 1 concentration. In addition, the licensee planned to establish a standard test method and validation protocol to test Component 1 for Chemical 1 concentration prior to use in production. The licensee projected that these corrective actions would be completed on May 25, 2008.

If the licensee identifies a correlation between the concentration of Chemical 1 in Component 1 and molybdenum-99 breakthrough, it tentatively planned to identify chemical treatments that reduce the presence of Chemical 1 in Component 1. If it identifies a chemical treatment that effectively reduces the presence of Chemical 1 in Component 1, then the licensee may use the treatment during future Component 1 processing. The licensee projected that this tentative corrective action would be completed on July 25, 2008. In addition, the licensee planned to identify an alternate Component 1 vendor by May 16, 2008.

The licensee planned to visit the Component 1 vendor in late March 2008 to obtain more information about how the vendor processes the component. In addition, the licensee planned to work with the vendor to see if it can order Component 1 with low Chemical 1 concentration.

The licensee planned lab experiments to prove its hypothesis that use of Equipment 1 with the wrong dimensions resulted in molybdenum-99 breakthrough. In addition, the licensee planned tests to determine if Component 1 lots with certain test results correspond with increased molybdenum-99 breakthrough. The licensee projected that this corrective action would be completed on June 15, 2008.

The licensee planned to investigate the differences between molybdenum-99 breakthrough testing methods used by the licensee and the industry as part of its investigation of the cause of the molybdenum-99 breakthrough problem.

In late March 21, 2008, the licensee began using a new Component 1 lot that contained about the same concentration of Chemical 1 as the previous lot. Generators produced between January 25 and April 22, 2008, were associated with several molybdenum-99 breakthrough complaints. Therefore, the molybdenum-99 breakthrough problem remains unresolved.

As of April 24, 2008, the licensee had revised its quality control procedure for testing generator eluates for molybdenum-99 concentration prior to generator distribution.

2 Implementation of the Corrective Action Program

2.1 Inspection Scope

The inspectors interviewed selected licensee management representatives and staff, and reviewed Standard Operating Procedures (SOPs) in order to evaluate the licensee's implementation of its Corrective Action Program (CAP) required by License Condition 20. The inspectors focused their review on the licensee's implementation of its CAP regarding customer complaints about molybdenum-99 breakthrough from the licensee's molybdenum-99/technetium-99m generators.

2.2 Observations and Findings

a. Development, Implementation, and Maintenance of CAP Procedures

Condition 20 of License No. 24-04206-01 required that the licensee maintain a CAP to identify and correct deficiencies associated with radiation safety, and that:

- (1) It develop, implement and maintain procedures to assure that conditions adverse to radiation safety, such as failures, malfunctions, deficiencies, deviations, defective material and equipment, and non-conformances that could reasonably affect exposures to workers or the public, or releases of radioactive material in effluents or to the sanitary sewer system, are promptly identified and corrected. In the case of significant conditions adverse to radiation safety, the measures shall assure that the cause of the condition is determined and corrective action taken to preclude repetition. The identification of the significant condition adverse to radiation safety, the cause of the condition, and the corrective action taken shall be documented and reported to appropriate levels of management. The procedures shall include appropriate quantitative or qualitative acceptance criteria for determining that the procedures have been satisfactorily accomplished; and
- (2) The procedure(s) shall include provisions for: 1) defining conditions that are adverse to radiation safety; 2) identifying conditions that are adverse to radiation safety; 3) reporting the conditions to appropriate management levels; 4) investigating adverse conditions in sufficient detail to identify root causes; 5) developing and implementing corrective actions to address the identified root cause(s) and to prevent recurrence; and 6) establishing time tables (milestones) for each provision, commensurate with the significance of the adverse condition.

The licensee developed an overall CAP that encompassed two program areas, EH&S and Product Quality. However, the licensee interpreted the requirements of License Condition 20 differently for product quality issues compared to EH&S issues. Issues related to product quality that occurred with products that met all NRC regulatory requirements prior to distribution were incorrectly assumed to be solely under the regulatory authority of the FDA not the NRC. Additionally, EH&S issues were not considered product quality issues and the licensee interpreted that the NRC had regulatory authority for those issues. The licensee developed EH&S procedures to include all of the requirements in Condition 20 of License No. 24-04206-01. The licensee developed Product Quality CAP procedures without including all of the requirements in Condition 20 of License No. 24-04206-01. As a result, the licensee developed separate CAP procedures for EH&S and Product Quality issues.

The licensee did not develop, implement, and maintain CAP procedures that included actions to assure that conditions adverse to radiation safety were promptly identified and corrected. In addition, the licensee's CAP procedures did not include measures to be taken to assure that the cause of significant conditions adverse to radiation safety were determined and corrective action was taken to preclude recurrence, and that the cause of the condition and the corrective action taken was documented and reported to appropriate levels of management. Specifically, the licensee's Product Quality CAP procedures did not include provisions for: 1) defining conditions that are adverse to radiation safety; 2) identifying conditions that are adverse to radiation safety; 3) reporting the conditions to appropriate management levels; 4) investigating adverse conditions, in sufficient detail to identify root causes; and 5) establishing time tables (milestones) for each provision, commensurate with the significance of the adverse condition. The licensee's failure to include those provisions in its Product Quality CAP procedures is a violation of Condition 20 of License No. 24-04206-01.

The inspectors noted the following examples of the licensee's failure to fully implement its Product Quality CAP procedures in response to the molybdenum-99 breakthrough problem: (1) the CPM staff did not inform the manufacturing site of the need to notify additional personnel (e.g., the RSO) about a regulatory issue regarding molybdenum-99 breakthrough complaints as stated in Item II. of the licensee's SOP 33-213, "Performing Complaint Investigations;" and (2) the deviation investigation of the molybdenum-99 breakthrough problem did not include a determination of the impact on product safety as stated in Item II.G. of SOP 33-23, "Exception and Deviation Reporting." In addition, the licensee is required to ensure that conditions adverse to radiation safety related to product quality, such as molybdenum-99 breakthrough complaints, are promptly corrected in accordance with Condition 20 of the license.

Although the licensee became aware of the molybdenum-99 breakthrough problem in October 2006, it had not corrected the problem as of April 24, 2008. The licensee has stated that, since the molybdenum-99 breakthrough problem is very complex, more time was needed to identify potential causes, conduct experiments to verify the causes, and implement appropriate corrective actions. Therefore, the licensee believed that efforts to correct the problem were prompt.

b. Safety Culture Concern

The inspectors identified a concern about the licensee's safety culture pertaining to its response to molybdenum-99 breakthrough complaints that it received between October 2006 and February 2008. Below is a discussion of examples to support the concern.

In October 2007, a member of the CAPA Team received the lab results indicating that a new lot of Component 1 that had not been used to produce generators, contained a high concentration of Chemical 1. The CAPA Team member promptly sent an e-mail to some of the other CAPA Team members warning that the lot of Component 1 that had not yet been used for generator production, had increased concentrations of Chemical 1 similar to that used to produce generators associated with molybdenum-99 breakthrough complaints that were received in October 2006. Although licensee staff suspected elevated concentrations of Chemical 1 in Component 1 as a potential cause for the molybdenum-99 breakthrough problem since May 2007 and they knew the new lot of Component 1 contained elevated concentrations of Chemical 1, the licensee used the new lot of Component 1 to produce generators in January 2008. The licensee subsequently received a very high number of molybdenum-99 breakthrough customer complaints in January 2008 associated with generators made with the new lot of Component 1.

Subsequent to the high number of molybdenum-99 breakthrough complaints that the licensee received in January 2008, the licensee did not request customers to return a representative sample of generators associated with those complaints as a means of investigating the cause(s) of the problem. Specifically, because the licensee expected limited value associated with the impact of requesting the return of affected generators, it requested that less than 3 percent of them be returned as a means of investigating the cause(s). As a result, the licensee missed opportunities to identify the cause(s) of the problem.

The licensee missed an opportunity to obtain additional information regarding the extent of condition associated with the molybdenum-99 breakthrough problem. Specifically, it presumed that all of the molybdenum-99 breakthrough complaints that it received represented the extent of condition of the problem without independently verifying the information through other means, such as contacting other customers who received generators from the affected lots.

The licensee missed opportunities to identify the cause(s) of the molybdenum-99 breakthrough problem during its root cause evaluation. Specifically, as of March 10, 2008, the change analysis that was performed did not include a review of "like-for-like" changes that occurred on the generator production line. For example, if a piece of production line equipment was replaced with the same make and model number, the licensee did not evaluate the replacement part as a potential cause. "Like for like" replacement parts may have been modified by the manufacturer resulting in a change in operability, possibly contributing to the cause of the problem.

Despite receiving several complaints of molybdenum-99 breakthrough that occurred after the first generator elution, the licensee did not revise its customer complaint form to request information necessary to identify molybdenum-99 breakthrough test failures that occurred after the first elution. In addition, the licensee did not have a procedure to assist the responsible staff on how to identify customer complaint trends (e.g., definition of “trend,” etc.), even though they were responsible for identifying customer complaint trends.

2.3 Conclusions

The inspectors identified a violation of Condition 20 of License No. 24-04206-01 involving failure to develop, implement, and maintain adequate CAP procedures. Specifically, the licensee’s Product Quality CAP procedures did not include provisions for: 1) defining conditions that are adverse to radiation safety; 2) identifying conditions that are adverse to radiation safety; 3) reporting the conditions to appropriate management levels; 4) investigating adverse conditions, in sufficient detail to identify root causes; and 5) establishing time tables (milestones) for each provision, commensurate with the significance of the adverse condition. In addition, the inspectors also identified a concern about the licensee’s safety culture as it pertains to its response to increased customer complaints regarding molybdenum-99 breakthrough.

3 Reporting Requirements Relative to the Molybdenum-99 Breakthrough Problem

3.1 Inspection Scope

The inspectors reviewed the NRC reporting requirements relative to the molybdenum-99 breakthrough problem by interviewing selected licensee staff, including the RSO. In addition, the inspectors reviewed selected records regarding the licensee’s conclusions about the applicability of the NRC reporting requirements as they pertain to the molybdenum-99 breakthrough problem.

3.2 Observations and Findings

The NRC is reviewing the applicability of 10 CFR Part 21 and Part 30 notification requirements as they pertain to the molybdenum-99 breakthrough problem as an Open Item. The findings associated with the NRC’s review of the Open Item will be documented in a future inspection report.

3.3 Conclusions

The inspectors identified an Open Item regarding the applicability of NRC notification requirements as they pertain to the molybdenum-99 breakthrough problem.

4 Potential Generic Issues Relative to the Molybdenum-99 Breakthrough Problem

The inspectors interviewed selected licensee staff, including the RSO and licensee management; reviewed selected records, including SOPs and licensee correspondence with the NRC; and observed selected generator parts as means of identifying potential generic issues associated with the molybdenum-99 breakthrough problem. The

inspectors continue to review potential generic issues relative to the molybdenum-99 breakthrough problem. Identified generic issues relative to the problem, including actions taken to address the generic issues, will be documented in a future inspection report.

5 Implementation of Actions Described in CAL 3-08-001

5.1 Inspection Scope

The inspectors reviewed the licensee's implementation of actions described in CAL 3-08-001 by interviewing several members of the licensee's staff involved with those actions including, but not limited to, senior licensee managers, the RSO, chemists, health physicists, and product quality staff. In addition, the inspectors reviewed applicable licensee documents including, but not limited to, investigation reports, batch records, SOPs, correspondence from Manufacturer X, and procurement records. The inspectors also contacted selected licensee generator customers to verify the licensee's implementation of actions described in the CAL.

5.2 Observations and Findings

a. Investigation of the Molybdenum-99 Breakthrough Problem

As stated in Item 1 of the CAL, the licensee committed to provide the following information and take the following actions as soon as possible:

Conduct an investigation (which has already been initiated) into the problem of elevated concentrations of molybdenum-99 in elutions from technetium-99m generators. The investigation will include how and why the problem occurred, when the problem first occurred, the extent of condition of the problem, the root and supporting causes of the problem, and the safety significance of the elevated concentrations of molybdenum-99 in elutions from technetium-99m generators. The results of the investigation will be provided to the Nuclear Regulatory Commission (NRC), including any interim reports.

The licensee continues to conduct an investigation into the molybdenum-99 breakthrough problem. Details regarding the licensee's investigation to date are discussed in Sections 1 and 2 of this report. The ongoing investigation includes how and why the problem occurred, when the problem first occurred, the extent of condition of the problem, the root and supporting causes of the problem, and the safety significance of the elevated concentrations of molybdenum-99 in generator elutions.

The licensee provided an interim report for its molybdenum-99 breakthrough investigation dated March 10, 2008, to the NRC inspectors while they were at the licensee's facility from March 10 through 13, 2008. The report included preliminary results of the licensee's investigation. Details regarding the preliminary results of the licensee's investigation are discussed in Section 1.g of this inspection report. The licensee estimated that it will complete all of the actions in Item 1 of the CAL by September 2008.

b. Corrective Actions to Prevent the Molybdenum-99 Breakthrough Problem

As stated in Item 2 of the CAL, the licensee committed to provide the following information and take the following actions as soon as possible:

Identify and implement immediate, short-term, and long-term corrective actions to address the causes of the problem and prevent recurrence. Provide the NRC with the corrective actions that have and will be taken, including a timetable for completion.

In its letter to the NRC dated March 28, 2008, the licensee provided corrective actions taken and planned to prevent the molybdenum-99 breakthrough problem. The corrective actions were based on the probable causes of the problem that were identified by the licensee, with the realization that its investigation of the problem was ongoing. Most of the licensee's corrective actions are described in Section 1 above. The licensee estimated that it will complete all of the actions in Item 2 of the CAL by September 2008.

c. Evaluation of 10 CFR Part 21 Reportability

As stated in Item 3 of the CAL, the licensee committed to provide the following information and take the following actions as soon as possible:

Conduct an evaluation of the reportability of this problem pursuant to 10 CFR Part 21 and provide the NRC with the results of this evaluation.

The licensee conducted its evaluation and, in its letter to the NRC dated March 10, 2008, described why it determined that the molybdenum-99 breakthrough problem did not require notification pursuant to 10 CFR Part 21.21. Therefore, the licensee completed the actions described in Item 3 of the CAL on March 10, 2008. As stated in Section 3.2 of this report, the applicability of NRC notification requirements as they pertain to the molybdenum-99 breakthrough problem is an Open Item.

d. Important Product Notification Distribution

As stated in Item 4 of the CAL, the licensee committed to provide the following information and take the following actions as soon as possible:

Continue distribution of the "Important Product Notification" (Notification) dated January 26, 2008, to your customers. Prior to discontinuing the distribution of the Notification, you will contact the NRC to discuss: (1) why distribution of the Notification is no longer necessary; (2) your understanding of the Food and Drug Administration's perspective on whether or not distribution of the Notification is no longer necessary; and (3) whether or not you have completed all of the corrective actions necessary to prevent recurrence.

As discussed in Section 1.f above, the licensee began distributing the Important Product Notification with all of its generators on January 27, 2008. In addition, the licensee mailed the Important Product Notification to all customers who received generators from the affected lots. The licensee continued to distribute the Important Product Notification

with all of its generators. In addition, after the licensee completes the CAL actions described in Sections 5.2.a. and b. above, it planned to contact the NRC to discuss: (1) why distribution of the Notification is no longer necessary; (2) its understanding of the FDA's perspective on whether or not distribution of the Notification is no longer necessary; and (3) whether or not it completed all of the corrective actions necessary to prevent recurrence. The licensee estimated that all of the actions described in Item 4 of the CAL will be completed by October 2008.

5.3 Conclusions

On March 10, 2008, the licensee completed all of the actions described in Item 3 of the CAL regarding its evaluation of 10 CFR Part 21 reportability of the molybdenum-99 breakthrough problem. The licensee has initiated but not completed the actions described in Items 1, 2, and 4 of the CAL regarding investigation of the molybdenum-99 breakthrough problem, corrective actions to prevent the problem, and Important Product Notification distribution, respectively. The licensee estimated that it would complete all of the actions described in Items 1 and 2 of the CAL by September 2008; and it would complete Item 4 of the CAL by October 2008.

6 **Exit Meeting**

The inspectors discussed the preliminary conclusions described in this report with licensee management during exit meetings conducted at the licensee's facility on February 8 and March 13, 2008. An inspector discussed the preliminary conclusions described in this report with the RSO during a teleconference conducted on April 10, 2008. In addition, the final exit meeting to discuss the inspection findings was held at the Maryland Heights, Missouri facility on April 24, 2008. On May 23, 2008, the inspectors contacted the licensee to discuss the inspection findings.

PARTIAL LIST OF PERSONS CONTACTED

- # Julia Balliet, Manager of Quality Assurance Systems
Branda Breaden, Quality Engineer
Edna Burgess, Production Superintendent
- # Russ Cairns, Production Superintendent
April Chance, Manager of Radiological Affairs/Radiation Safety Committee Chair
- # Steven Duffy, Quality Site Manager
- # Patricia Duft, Vice President, Legal
Keith Edwards, Environmental Compliance Supervisor
Mike Engdale, Materials Manager
- # Russell Gall, Vice President of Manufacturing
- # Steven Hanley, President of Imaging solutions
Lauren Hartstein, Quality Assurance Engineer
- # Dan Hoffman, RSO Trainee, Environmental Health and Safety
- # Bryan Lowery, Health Physics Supervisor
Kevin McCarthy, Process Engineer
- # Craig Miller, Manager, Plant Engineering
- # Mitzi Pennington, Site Director
Sheree Pineda, Quality Engineer
David Pipes, Technical Fellow

- #* Jim Schuh, Radiation Safety Officer
- # Dirk Stevens, Vice President of Quality
Zach Vavra, Dry Top Eluting Supervisor
Sumit Verma, Production Superintendent
- # Kay Yoder, Director, Environmental Health and Safety
- # participated in onsite exit meeting on April 24, 2008
- * contacted by telephone on April 10, 2008, for final exit meeting

OTHER PERSONS PRESENT AT THE ONSITE EXIT MEETING ON APRIL 24, 2008

Cynthia Flannery, Team Leader, NRC, Headquarters Office
Michele Perry-Williams, Investigator, FDA, St. Louis Office

LIST OF ACRONYMS USED

CAL	Confirmatory Action Letter
CAP	Corrective Action Program
CAPA	Corrective and Preventative Action
CCC	Customer Complaint Coordinator
CFR	Code of Federal Regulations
CPM	Corporate Product Monitoring
EH&S	Environmental Health and Safety
FDA	Food and Drug Administration
DIT	Deviation Investigation Team
NRC	Nuclear Regulatory Commission
RSO	Radiation Safety Officer
SOPs	Standard Operating Procedures
TEDE	Total Effective Dose Equivalent