

November 26, 2008

Mr. Steven Reynolds
U.S. Nuclear Regulatory Commission, Region III
2443 Warrenville Road, Suite 210
Lisle, Illinois 60532-4352

**RE: NRC License 24-04206-01
Docket Number 030-00001
CAL 03-08-001
Letter from NRC to Mallinckrodt dated October 28, 2008**

Dear Mr. Reynolds:

Mallinckrodt is providing this letter in response Items 1 and 2 of the U.S. Nuclear Regulatory Commission (NRC) Confirmatory Action Letter (CAL) issued on February 1, 2008 and the subsequent NRC letter dated October 28, 2008. Also included are updates the Corrective and Preventative Action Plan submitted to you by letter dated March 28, 2008.

As reported in our letter dated August 18, 2008, Mallinckrodt has completed the majority of corrective actions associated with the investigation into elevated reports of molybdenum-99 (Mo-99) breakthrough. Since Mallinckrodt has completed most of the corrective actions as noted above, updates are only provided for those items that remained open on August 18, 2008. Please note the item numbers in the paragraphs below correspond to the item numbers in our March 28, 2008 and August 18, 2008 letters.

3. Design, write, and perform a Design of Experiment (DOE) to establish and understand the role of Chemical 1 in Component 1 and its relationship to Mo breakthrough.

The final report for a Design of Experiment (DOE) to establish the role of Chemical 1 in Component 1 and its relationship to Mo-99 breakthrough was approved June 6, 2008. This initial study examined the role of Chemical 1 content from 350 ppm to 1500 ppm and confirmed higher Chemical 1 content in Component 1 results in higher levels of Mo-99 in the elution of the generators.

The above study was repeated at a larger scale to more accurately reproduce the current manufacturing procedures for Component 2 preparation and assembly. That study has been completed and confirmed the results of the initial study. That final report was approved July 23, 2008.

Mallinckrodt secured a different type of Component 1 from our current vendor with low Chemical 1 content (<100 ppm) and repeated the above studies at the low end of Chemical 1 content in order to gather enough data to set an appropriate specification for Chemical 1. The final report was approved August 5, 2008.

In support of a planned submittal to FDA, Mallinckrodt is currently conducting process validation runs for use of this different type of Component 1 in our generator manufacturing process. Three process validation runs utilizing this new component were completed on August 26, 2008. All testing was completed by September 25, 2008 and the final report was signed-off on October 3, 2008. Based on further review of the validation runs and associated test results, it was determined that additional process validation runs were necessary. Due to a worldwide shortage of Molybdenum, insufficient Mo-99 activity was available on the world market to immediately perform the additional manufacturing runs. During this time period, domestic suppliers were unable to secure enough Mo-99 to meet patient needs. As a result Mallinckrodt utilized our limited supply of Mo-99 to manufacture generators to minimize adverse impact to patients.

Mallinckrodt was able to secure enough Mo-99 to support the additional process validation runs in late October and early November. Three additional runs were completed on October 28, 2008, November 4, 2008 and November 6, 2008. All generator testing is expected to be completed and the results finalized by December 12, 2008. The results will be analyzed and compiled into a final report. We anticipate submitting this report to the FDA by January 19, 2008. Pending approval, we anticipate being able to utilize the new component in manufacturing on February 19, 2008.

6. Investigate whether Component 1 from our vendor needs to be treated with Chemical 2 and inquire into the manufacturing process of this component in order to minimize the Chemical 1 content of the received product.

As previously noted, we have identified an alternate type of Component 1 that has a low Chemical 1 content. We are in the process of performing validation runs to ensure the use of this component will not adversely impact generator performance. We anticipate making a formal submittal to the FDA by January 19, 2008 seeking concurrence that we can utilize this new component in routine generator manufacturing.

7. Attempt to identify and qualify a secondary supplier for Component 1.

We have been unsuccessful in our attempts to identify a secondary supplier. All viable secondary suppliers that we have identified source their Component 1 material through our current vendor.

13. Create label for top of generator reminding users to perform a Moly breakthrough test on each elution of the generator.

Mallinckrodt prepared a label and made a formal submission to the FDA on May 27, 2008 to allow use of this label. The label will be used to inform customers that every elution taken from the DTE generator should be tested for Mo-99 breakthrough. We received approval to utilize the label from the FDA on November 17, 2008. We are in the process of modifying our procedures and verifying that all necessary international approvals have been received. We anticipate using the new labels beginning December 17, 2008.

15. Write an engineering report to evaluate performing Mo-99 breakthrough testing in-line on each generator manufactured.

The engineering report was completed June 26, 2008. We have conducted Mo-99 breakthrough testing on each generator manufactured since September 17, 2008.

Your October 28, 2008 letter also requested information related to the potential root causes that we have eliminated. Our investigations ruled out a large number of potential root causes that can be broadly categorized into six areas: inadequate materials, inadequate equipment, inadequate methods, inadequate environment, inadequate measurements, inadequate machines, and inadequate process interface with personnel.

Numerous potential root causes were examined within each of these broad categories. As an example, under the broad category of materials, the following items were evaluated and eliminated as potential root causes: generator hoods, vials, glass wool, glass columns, silicar, stoppers, water, needles, saline, saline vials, molybdenum, hydrochloric acid, acetic acid and sodium hypochlorite. Similar lists exist for each of the other broad categories. Root causes have been eliminated by a number of means including change analysis and direct experimentation.

As stated in our August 18, 2008 letter there are three remaining focus areas for completion of our investigation and final corrective actions. We continue to make progress in these areas: 1) Chemical 1 content of Component 1, 2) Component 2 manufacturing and 3) measurement systems.

The status of our investigation into the Chemical 1 content of Component 1 has been addressed in item 3 of the update above.

We have completed all corrective actions associated with Component 2 manufacturing. These included standardizing critical aspects of Component 2 manufacturing and improving the inspection and defect tracking process. The majority of these actions were completed by April 30, 2008. Validation of the process improvements was completed September 9, 2008.

Regarding the measurement systems we have replaced all of the Mo-99 assay canisters at our internal Covidien pharmacies. This reduces variability introduced as a result of damaged canisters. As previously mentioned, we have also initiated testing 100% of the generators manufactured for Mo-99 breakthrough. This step ensures that each generator shipped meets the Mo-99 breakthrough specification at the time of shipment.

Implementation of the corrective actions identified in our March 28, 2008 and August 18, 2008 letters has already significantly reduced the frequency of Mo-99 breakthrough reports associated with our Tc-99m Generators. As you are aware, we have experienced a significant reduction in the number of Mo-99 breakthrough occurrences since July 1, 2008 as a result of the above described corrective actions. We continue to focus on completing the remaining corrective actions as quickly as possible.

If you have any questions related to this matter, please feel free to contact me at 314-654-7998 or Jim Schuh at 314-654-7981.

Sincerely,

A handwritten signature in cursive script that reads "Mitzi Pennington".

Mitzi Pennington
Manufacturing Site Director

cc: Patricia H. Duft – Mallinckrodt
Robert Gattone – US NRC Region III
Jim Schuh – Mallinckrodt
Kay Yoder – Mallinckrodt

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ROUTING		DEPARTMENT <u>HP</u>	SHIPPED FROM
DELIVERY INSTRUCTIONS		TELEPHONE EXT <u>314-654-7981</u>	MALLINCKRODT, INC. 2703 WAGNER PL. MARYLAND HTS., MO 63043
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Account: S 063001317

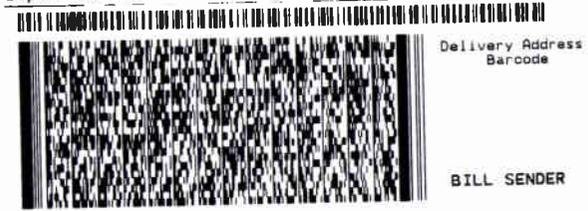
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UNITED STATES US

TO ATTN: STEVE REYNOLDS
US NRC REGION III
2443 WARRENVILLE RD. STE 210



LISLE, IL 605324352

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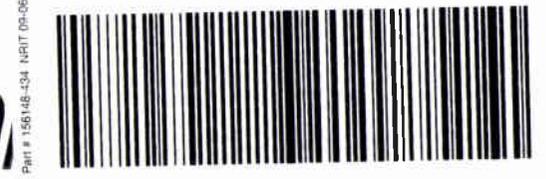
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