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Healthcare

Mallinckrodt

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January 30, 2008

Mr. Steven Reynolds
Director, Division of Nuclear Material Safety
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
Verbal Request for Information from Ms. Patty Pelke to Jim Schuh 01-29-08

Dear Mr. Reynolds:

Mallinckrodt Inc. is providing this information in response to the specific information requested by Ms. Patty Pelke of your staff to Mr. James Schuh of Mallinckrodt on January 29, 2008.

As we communicated to your staff via a series of telephone conversations on January 25th, 2007, Mallinckrodt learned through customer feedback reports that there was an apparent increased potential for elutions from the Technetium-99m (Tc) generators to exhibit elevated levels of Molybdenum-99 (Mo). These specific customer reports commenced in early January of this year. Upon initial investigation, the potential for elevated levels of Mo appear to be related specific lots of Technetium-99m generators. As we discussed with you, Mallinckrodt's generator labeling, which includes a package insert detailing instructions for use, requires that each elution from the generator be tested for Mo breakthrough and that the concentration of the Mo/Tc ratio not exceed 0.15 uCi/mCi at time of administration. Furthermore, the United States Pharmacopeia (USP) monograph associated with Sodium Pertechnetate Tc-99m Injection which establishes appropriate standards for use of this product also indicates this same practice. Based upon these documents, customers using Technetium-99m generators should be testing for Mo breakthrough prior to patient administration to meet the 0.15 uCi/mCi limit for administration.

It is Mallinckrodt's belief that the vast majority, if not all users of our Technetium generator, continue to perform Mo breakthrough tests on all elutions from our generators in accordance with the requirements of our package labeling and in order to assure compliance with the USP monograph. While the NRC regulations do not require a licensee to perform the Mo breakthrough test on each elution, Mallinckrodt product labeling, as well as that of the other generator manufacturer in the United States, continues to instruct users to test for Mo breakthrough on each elution.

Background Information

There have been periodic customer complaints regarding Mo breakthrough historically. These complaints are not common; however there have been rare periods of increased reports. The typical report describing Mo breakthrough seems to indicate that the breakthrough occurs during the first or second elution with subsequent elutions meeting acceptable levels. While the USP limit on Mo breakthrough is 0.15 uCi/mCi at time of administration, Mallinckrodt's release specification is 0.10 uCi/mCi.

There were more frequent customer reports documenting Mo breakthrough in late 2006 and 2007. Due to this apparent increase in customer complaints, Mallinckrodt opened an investigation in March, 2007 to identify the cause of these breakthrough reports. The investigation report was finalized in August, 2007 without a

definitive root cause being identified. A formal Corrective and Preventative Action investigation team was organized in August 2007 to continue the investigation.

The initial conclusions drawn from the investigation suggested that a process chemical that the alumina vendor used in the washing process may be a contributing factor. The relationship between Mo breakthrough and the alumina was suspected, but could not be confirmed since other lots of alumina with comparable levels of the chemical produced different levels of Mo breakthrough.

There had been no additional Mo breakthrough complaints from August, 2007 until the most recent series of complaints were received by Mallinckrodt on January 11, 2008.

The specific information requested by Ms. Pelke is listed below in the following paragraphs. Mallinckrodt's answers have been inserted directly below the questions that were posed.

1) **Provide actions taken in response to Mo breakthrough issue. Include means of problem identification and notifications made. Include specific timetable with who was notified and the timing of that notification.**

Corporate Product Monitoring began receiving customer complaints associated with the most recent Mo breakthrough events on January 11, 2008. These complaints were associated with generator lot 8005 manufactured and distributed January 9, 2008. Subsequent Generator lots 8006, 8007, 8008, 8009, 8010, 8011, 8012, and 8013 also had an elevated number of Mo breakthrough complaints. Beginning on January 27, 2008, a customer notification letter was included in all generator shipments. The same letter was also mailed on January 28, 2008 to all customers who received generators from these lots. On January 29, 2008, a field alert was issued to the FDA Kansas City District.

The Maryland Heights plant complaint coordinator was first notified of the issue January 14th (Monday) and the Corrective and Preventative Action (CAPA) Investigation Team was reconvened on January 15th (Tuesday). The investigation team consisted of personnel representing Health Physics, Quality, Operations, Procurement, Operational Excellence, Research and Development and Corporate Product Monitoring

The areas of investigation of the CAPA team included the following:

- Batch Record review
- Alumina elemental analysis reviewed
- Comparison of elemental analysis to past lots of Alumina
- Review of analytical test methods, results, and trends
- Review of column preparation process
- Review of column lots (alumina) used in process and timing
- Analysis of generator size and Mo breakthrough
- CAPA Team meets three (3) times per week

2) **Describe the extent of the condition including date problem was first identified, lot numbers affected, number of generators affected, max Mo-99 concentrations reported in generator elutions at 12 hours post elution. Include your safety assessment of the significance of the increased Mo concentration.**

Generator lot numbers affected are 8005, 8006, 8007, 8008, 8009, 8010, 8011, 8012, and 8013. 1639 generators were distributed for the affected lots. As of January 29th, 2008 Mallinckrodt has received 116 reports of elutions with a Mo/Tc ratio exceeding 0.15 uCi/ml at 12 hours post elution from these lots. The single highest ratio that was reported for a generator was 3.52. This value was observed during the first elution of the generator. Distribution of the reported values are included in the table below

Mo/Tc Ratio Range	Number of Reports
0.15 – 0.25	50
0.25 – 0.50	27
0.50 – 1.00	22
1.00 – 2.00	11
2.00 – 3.00	5
3.52	1

As previously stated, it is Mallinckrodt's belief that the vast majority, if not all users of our Technetium generators, continue to perform Mo breakthrough tests on all elutions from our generators in accordance with the requirements of our package labeling and in order to assure compliance with the USP monograph. In the event that a clinician fails to perform the required Mo breakthrough test, the data above would indicate that patient doses would be very low. A normal (20 mCi Tc-99m) cardiac imaging dose using the worst case elution would result in a total effective dose equivalent to the patient of approximately 213 mrem due to Mo-99 assuming the dose was injected at the time of expiry. Dose calculations for a cardiac dose compounded using an elution with a Mo/Tc ratio of 0.25 and administered at the time of expiry would result in a dose of approximately 15.1 mrem.

3) **Provide results of investigation into the problem including a discussion of how and why the problem occurred. The information provided should be in sufficient detail to identify root causes and support conclusions.**

The investigation regarding this issue is on-going. Based upon our findings to date, we believe the most probable cause is the presence of sulphur thought to be from sulphuric acid that the alumina vendor uses in a wash process. This was identified during the investigation when we were performing an elemental analysis of the alumina. Sulphur content is not part of our material specification. An elevated level of sulphur was identified in the affected lot of alumina that was utilized in the generator lots listed above. Recent laboratory studies have confirmed that the addition of this chemical to columns will result in Mo breakthrough.

4) **Identify short-term and long-term corrective actions to address root causes and prevent recurrence. Include timetable for completion of all corrective actions.**

Short-term corrective action was to obtain a different lot of alumina that had a lower level of sulphur. Generator lot 8014 was the first lot of generators that incorporated the "new" lot of alumina. To date, three (3) lots of generators totaling 591 generators have been distributed with the new lot of alumina, with only one (1) report of Mo breakthrough. This is a significant reduction from the frequency

associated with generator lots 8005 – 8013. There is currently a two (2) month supply of this lot of Alumina on-site with more available.

Long term corrective actions identified to date (prior to use of the next lot of alumina):

- The Quality Control specification for alumina will be modified to include a specification for sulphur content.
- MI will investigate the use of additional vendors and qualify any that meet these new specifications through our normal procedure.
- We will evaluate the feasibility of adding a label to the generator itself reminding end users of our requirement to perform a Mo breakthrough test on each elution of the generator.

5) Provide your evaluation of the reportability evaluation conducted in accordance with 10 CFR 21

We have not yet completed our evaluation of reportability in accordance with 10 CFR 21; however initial indications are that there was no defect under the license as defined in 10 CFR 21.3. Specifically, there was no deviation or departure from the technical requirements included in the procurement document for the alumina used in the manufacture of subject generators. Similarly there was no failure to comply with either the Atomic Energy Act of 1954 as amended or any applicable rule, regulation, order or license of the Commission relating to substantial safety hazards. In accordance with these definitions initial indications are that there are no reporting requirements under Part 21 associated with this occurrence. Our evaluation is currently under internal review. However, the final determination will be made in accordance with the timelines identified in 10CFR21.

6) Provide assurance that you will notify the NRC prior to discontinuing distribution of the January 26, 2008 letter. Provide assurance that corrective actions to prevent recurrence will be taken prior to discontinuing distribution of the letter with generators.

It is our intent to continue to place the letter in each shipped box. We intend to distribute the letter to our customers until corrective actions are implemented to prevent recurrence. We further intend to evaluate the feasibility of a long-term label to replace this letter. Mallinckrodt will notify the NRC prior to discontinuing distribution of the January 26, 2008 letter to our customers. At that point in time we will convey to you the results of discussions we have had with the FDA regarding discontinuation of the letter.

7) An explanation of how you complied with your Broadscope license condition 20 as it applies to this problem.

Condition 20 of our NRC license requires us to maintain a corrective action program to identify and correct deficiencies associated with radiation safety. We have implemented a standard operation procedure to specifically capture the elements identified in the license condition. That operating procedure includes specific guidance for investigating feedback reports from customers. The investigations and corrective actions were initiated and documented in accordance with these operating procedures.

Mallinckrodt remains fully committed to complying with all NRC regulatory requirements. Mallinckrodt trusts that this letter addresses the questions that you posed in our conference calls. Mallinckrodt is continuing to investigate this issue; however, we believe the corrective actions we have identified and implemented will prevent recurrence of the issue identified in this letter. If you have any questions related to this matter, please feel free to contact me directly at 314-654-7981.

Sincerely,

James R. Schuh, CHP
Radiation Safety Officer
Manager, Environmental, Health and Safety

Endorsed by:

Mitzi Pennington
Site Director