Molybdenum-99 Isotope Production Preparation At Sandia National Laboratory

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Abstract

Molybdenum-99 (^{99}Mo) is the precursor to Technicium-99m (^{99m}Tc) and used in the production of ^{99m}Tc generators. ^{99m}Tc has become the most widely used radioisotope in medical industry for diagnostic applications. Sandia National Laboratories (SNL) is in the preparation phase for the production of ^{99}Mo. The preparatory work includes: reproduction and verification of the Cintichem ^{99}Mo production process; development of production hardware; modification of the Hot Cell Facility (HCF), reconfiguration of the Annular Core Research Reactor (ACRR) core; and preparation of the documentation to meet the Good Manufacturing Practices (GMP) requirements of the Food and Drug Administration (FDA) process. In addition, radiation effect tests were performed at the Gamma Irradiation Facility (GIF) on processing chemicals and hardware used in the processing to evaluate the degradation due to the high radiation field experienced during the chemical separation.

Background

For more than forty years, the United States (US) Department of Energy (DOE) and its predecessor agencies have produced and distributed isotopes through the national laboratories. In 1989, Congress established the Isotope Production and Distribution Program (IPDP) to bring together under one program all DOE isotope production activities. Among other activities, the

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DISCLAIMER

IPDP has taken on the responsibility to establish a domestic capability to produce a stable supply of ^{99}Mo for the US medical community. Prior to 1989, ^{99}Mo was produced in the US by a single supplier, Cintichem Inc., Tuxedo, NY. Because of problems associated with the operation of their reactor, Cintichem elected to decommission the facility in 1990 rather than incur the costs for repair. The demise of the ^{99}Mo capability at Cintichem left the US totally reliant upon a single foreign source, MDS Nordion, located in Ontario Canada. At the present time, they supply approximately 90% of the ^{99}Mo used worldwide.

In 1991, the DOE purchased the Cintichem technology and processing hardware. DOE elected to establish production capability at Los Alamos National laboratory (LANL), but in 1992 the LANL reactor was shut down after the discovery of an underground leak from the primary coolant. DOE decided not to restart the reactor and looked to SNL as a potential source for production. In 1996, the National Environmental Policy Act (NEPA) process was completed and the Record of Decision was signed to select SNL as the production site for ^{99}Mo, with LANL manufacturing the targets.

The ^{99}Mo production preparation activities are focused in four areas: verification and reproduction of the Cintichem process, modification of the HCF, reconfiguration of the ACRR, and completion of regulatory requirements of the FDA's Current Good Manufacturing Practices.

Process Description

^{99}Mo is produced as a fission product from uranium fission in a target. The target is a sealed stainless steel tube, 18" x 1.25" OD, in which ~ 20 gr. of enriched uranium oxide, UO_2, has been electroplated. The uranium is enriched in U-235 to >90%. After irradiation, the target is cooled for six hours to allow short-lived fission products to decay prior to processing. The uranium matrix is dissolved from the surface of the target with heat and an acid mixture of H_2SO_4 and

concentrated HNO_3. ^{99}Mo is chemically separated from the unwanted fission products by the addition of hold back carriers, the precipitation of the iodine as a chloride, and the precipitation of ^{99}Mo as an organic compound with alpha benzoin oxime. The precipitate is then dissolved in sodium hydroxide and purified by column chromatography, (silver coated charcoal, zirconium oxide, and activated charcoal) which removes the remaining fission product impurities, primarily iodine and ruthenium. The final product form is sodium molybdate in 2 N (normal) sodium hydroxide.

Reproduction of the Cintichem Production Process

Cold and low irradiation tests, chemical separation

Although the Cintichem Drug Master File, Manufacturing Manual and Quality Control Manual were available, the process information was not sufficiently detailed to allow SNL to accurately replicate the Cintichem process. To thoroughly understand and identify critical steps in the chemical separation process, a series of tests was designed to reproduce the results described in the manufacturing manual.

The first series of tests used 20-gram samples of unirradiated or low irradiated depleted uranium dioxide (UO_2) powder samples. A 20-gram sample was chosen because this was the typical loading on the Cintichem targets. These tests were designed to gain process knowledge prior to processing an irradiated target. The chemical separation tests were performed in a fume hood using a pressure vessel to simulate the volume and conditions of the target dissolution vessel and an open beaker for chemical separation. This provided an opportunity to become familiar with the critical chemical and associated color changes that take place during the process, and to simulate the target conditions during the heating/dissolution steps. The use of a 0.19 MBq (5μCi)

^{99}Mo spike added to the uranium powder provided a diagnostic mechanism to evaluate the efficiency of the separation process.

The last test in the cold series processed a sample that contained low levels of fission product impurities, measured the efficiency of the separation process, and evaluated the performance of the purification columns. This was accomplished by irradiating a 20-gr sample of UO_2 powder in the Sandia Pulsed Reactor for six hours at 14 kW steady-state power, (302.4 MJ). The resultant yield of ^{99}Mo in the UO_2 was 18.5 MBq (500 μCi). At processing time, the activity of ^{99}Mo was 9.62 MBq (260 μCi) and the total radionuclide inventory was ~1.1 GBq (30 mCi), calculated using ORIGEN2®.

During cold testing, several tests were performed on individual components of the process to understand the processing variability and determine the parameters to be used when processing irradiated targets. Variables analyzed included the temperature and pressure during dissolution, the steps involving the addition of oxidizing reagents, and the performance of the purification columns.

Hot tests, chemical separation

Following cold tests and after the remote processing hardware design and construction were complete, a series of 'hot' tests was designed to process irradiated targets. These were designed to optimize the process, identify problems prior to processing higher inventory targets, and to refine the processing hardware developed for remote operations. The targets processed during these tests were below the fission product inventory expected for maximum production, [15kW target, 7-day irradiation, 22 TBq (600 Ci) of ^{99}Mo] to limit the potential for window damage to

the shielded containment box (SCB). Table 1 is a summary of the tests performed prior to the HCF modifications.

Table 1.

Test	Target Power (kW)/ Irradiation Time (hrs)	Post irradiation decay (hrs)	Total inventory (TBq*) /decay inventory (TBq)	^{99}Mo inventory (TBq)/decay inventory(TBq)
1	5.0 / 24	24	700 / 29	2.1 / 1.6
2	3.8 / 8	16	520 / 15	0.56 / 0.48
3	3.7 / 10	16	520 / 16	0.67 / 0.56
4	3.5 / 24	24	520 / 20	1.4 / 1.1
5	4.1 / 49	6	670 / 111	5.9 / 5.6

*27 TBq=1Ci

Dissolution problems were encountered during the first test when none of the uranium coating was removed during the dissolution process. As mentioned previously the typical Cintichem target had a mass loading of ~20 gr of UO_2; the uranium loading on the target processed was 27 gr. As a consequence, the dissolution cocktail was not sufficient to dissolve the heavier target. Cold target dissolution tests were performed varying the quantity and normality of each acid. Using the test data the optimum mixture of H_2SO_4 and HNO_3 was determined. (Talley and Bourcier, 1997)

Transfer of material into and out of the SCBs presented many challenges. Initially, many of the problems in processing were related to bottle-to-bottle transfer of liquid and the injection of reagents. These were resolved by pre-evacuation of the bottles, addition of vented charcoal columns and vacuum system assist. The color of the leaded glass windows used in the processing boxes made it difficult to identify color changes. This was resolved by using paint sample cards in the processing boxes as color comparisons.

Product quality control testing was conducted for all the tests and the results were compared to pharmaceutical purity specifications. The product from the final test was split and sent to pharmaceutical companies for cross-check evaluation. 2.7 TBq (72 Ci) was sent to Mallinckrodt Pharmaceutical Co., who produced several generators to evaluate compatibility with their production process. 2.2 TBq (60 Ci) was sent to MDS Noridon for evaluation as a backup to their product line. Both pharmaceutical companies verified that the purity specifications were met and the product was compatible with their production lines. With the shipment of product to pharmaceutical companies, SNL had met its commitment to the Secretary of Energy to produce and ship ^{99}Mo to a pharmaceutical company by December 1996.

Waste Handling

The production process generates a high activity acidic liquid waste. Several waste stabilization agents were tested in the GIF for long-term effects of high dose rates. Based on these results Portland cement was selected as the stabilization agent. A waste-handling container of stainless steel was developed which would facilitate the stabilization and neutralization of waste in the processing box. The cement, in addition to stabilizing the waste, neutralized the waste resulting in a mixture with a pH of ~ 6. The fission product waste was drained into a container preloaded with cement and tumbled on a rock tumbler for 20 minutes to mix the cement. The addition of sodium bisulfite to the acid waste solution prior to mixing with cement serves to keep the iodine remaining in the waste as elemental iodine and reduces the amount of iodine gas produced. (Longley, et al. 1997)

Processing hardware, fixtures, and tools

The processing hardware and fixtures were developed in parallel to the cold tests and tested in a mock-up facility. The process uses double-ended serum bottles to contain solutions and

hypodermic needles, syringes and needle assemblies for the transfer of solutions and reagent injection. Hardware, fixtures and tools were designed to easily transfer solutions, inject reagents, reconfigure processing equipment and make repairs.

Radiation Effects Testing, Processing Hardware

At full production, SNL expects to process targets with a higher inventory than Cintichem. The GIF was used to test the radiation effects on the hardware, chemicals, and the stability of the product from time of processing to use. A full-scale target would produce a dose rate of approximately 12 kGy hr^{-1}. Chemical separation takes about four hours and purification takes about 4 hours. Although all hardware exhibited radiation damage after the equivalent of one hour of processing time, none of the hardware experienced failure at a total dose of 0.11 MGy, twice that expected during processing. During processing, precautions will be taken to minimize the radiation damage with the use of time, distance and shielding.

Hot Cell Facility Modifications

Historically, the HCF had been used for Defense Program research, reactor fuel development studies, and Nuclear Regulatory Commission (NRC) fuel safety studies, following the Three Mile Island incident. The facility consisted of shielded glove boxes, unshielded glove box lines and the canyon, which had eight windows and eight sets of manipulators and three SCBs.

The original windows were dry windows of 100 density inches (thickness × specific density) and the canyon walls were reinforced concrete of approximately 100 density inches. The maximum source term expected during ^{99}Mo production is expected to be 741 TBq (15 kCi) of mixed fission products. This corresponds to a 20 kW target irradiated for 7 days and cooled for 6 hr. The existing windows and walls were insufficient to support this inventory on a continuous basis.

Major modifications were made to the facility to accept higher fission inventory and to configure the facility for production operations; the glove box lines and shielded glove boxes, all the windows, SCBs, and manipulators and associated plumbing and electrical were removed. The new configuration will have six windows, four extraction boxes and a waste packaging box on the one side of the canyon. The old windows will be up-graded with cerium oxide to withstand higher dose rates without darkening and will be used in the processing boxes. (Vernon, et al.1997). The canyon walls have had seven inches of additional steel plating added to increase the shielding. The walls and windows of the processing boxes will have the equivalent 150 density inches. The increased wall thickness will reduce the dose levels to <0.5 $\mu Sv\ hr^{-1}$(mrem hr^{-1}) at the surface of the wall.

Additionally, six smaller product purification and packaging SCBs will be installed on the opposite side of the canyon, together with five windows for waste barrel handling. The inventory of the purification box will be considerably less than the processing boxes with dose being from only ^{99}Mo. The increased wall thickness will reduce the dose levels to <0.5 $\mu Sv\ hr^{-1}$ (mrem hr^{-1}) at the surface of the wall. Both the extraction boxes and purification boxes will have under the box transport systems to move material into and out of the boxes. There will be a mechanism to pass the target and processing material in and two additional mechanisms to pass the product out through the canyon wall.

ACRR Modifications

Historically, the ACRR had been used to support Defense Program's weapons testing, fuels safety studies for the NRC, and a variety of other studies. The reactor originally utilized has 236 fuel rods, enriched uranium in a beryllium oxide (BeO) matrix, and was primarily used for pulse operations. The reactor had a central dry cavity, which allowed for insertion of experiments into

the center of the fuel core for irradiation. Modifications to the reactor consisted of removing the central cavity, removing all external irradiation cavities, disabling the pulse operations, and reconfiguration of the core. A target fixture was place in the central region , which will hold a maximum of 19 targets. The flooded central area increases the neutronic coupling for the target. Eventually, the BeO fuel will be replaced with a commercially available research reactor fuel to preserve the BeO fuel for any future Defense Program requirements. (Parma, 1997)

Process Validation Testing and FDA Requirements

Although ^{99}Mo is not a finished pharmaceutical, it falls under the FDA CFR210, 211 Current Good manufacturing practices. This involves a formal Process Validation Test Plan and Protocol, which will challenge the critical parameters of the process to demonstrate that the quality of the product is not affected by variability within the process and that an acceptable product can be consistently produced. Cintichem had been in production for several years, but ceased operation prior to FDA requiring process validation and, consequently, had not performed a process validation. After the facilities have resumed operation, process validation will begin. The test matrix will consist of a selected range of target powers and irradiation times. The product purity will be analyzed and compared to industry specifications. After the validation testing and with the concurrence of the pharmaceutical companies, call batch samples will be submitted to the pharmaceutical houses for their product validation testing, which would qualify SNL as a supplier of ^{99}Mo. All documentation to meet the requirements of the FDA Current Good Manufacturing Practices has to be completed and implemented prior to call batch submission.

Summary

SNL has accomplished the initial process verification and demonstrated to DOE and the Pharmaceutical Industry that it is capable, using the Cintichem ^{99}Mo Production Process, of

producing a product, which meets industry standards. Because of their prior mission, the facilities required major modification to accommodate routine ^{99}Mo production. The modification to the ACRR is complete and the modifications to the HCF will be complete in FY99. Once the facilities have gone through an Operation Readiness review, the final phase of process validation will begin, followed by review by the FDA and pharmaceutical companies, and finally the submission of call batches for supplier validation.

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