MPI RESEARCH
54943 North Main Street
Mattawan, MI 49071-8353 USA
Telephone: +1 269.668.3336
Fax: +1 269.668.4151

September 8, 2014

Ms. Sara Forster
Materials Licensing Branch
U.S. Nuclear Regulatory Commission, Region III
2443 Warrenville Road, Suite 210
Lisle, IL 60532-4352

RE: Materials License 21-11315-02
Request to amend license for synthesis/manufacture of radioactive compounds utilizing radiochemicals produced by the MPI Research cyclotron and transferred from the MPI Research production license, as described in the amendment application dated February 17, 2014 and subsequent communications

Dear Ms. Forster,

MPI Research is requesting an amendment to Materials License 21-11315-02 to authorize the remaining items requested in the amendment request of February 17, 2014, as modified by subsequent communications and requests for additional information. The addition of an authorized quantity of actinium-225 for research was included as part of Amendment 34.

The primary purpose of this amendment request is to allow MPI Research to process into end products the radioactive materials produced by the MPI Research cyclotron, upon approval of the pending application for a production license. The materials would be internally transferred upon production from the production license to the broad scope license. The various radioactive compounds needed for research would then be synthesized or processed under the broad scope license, utilizing the facilities and equipment in the cyclotron center, as described in the attached materials. Permission for commercial distribution is not being requested.

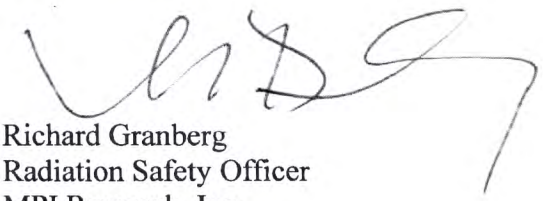
Enclosed with this letter are responses to the questions posed by you during our conversation on September 5, 2014. I believe we have fully addressed each question. Please let me know if you need any follow-up information.

This amendment request does not change the prescribed amount of financial assurance for the broad scope license (currently $225,000.00). As discussed with Mr. Kevin Null, upon receipt of the production license (at which time we will have the license number available) MPI Research will submit a revision to our financial assurance plan that will include both the financial assurance for the broad scope license and the updated decommissioning funding plan financial assurance required for the cyclotron production license into one financial instrument. When the final financial assurance documentation is submitted, MPI Research will request that the original financial instrument covering the

broad scope license (letter of credit) and the previous request covering financial assurance for cyclotron possession only, be cancelled and returned.

Please contact me at 269-668-3336 extension 2050, if there are any questions, or if further information is required.

Best regards,



Richard Granberg
Radiation Safety Officer
MPI Research, Inc.

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

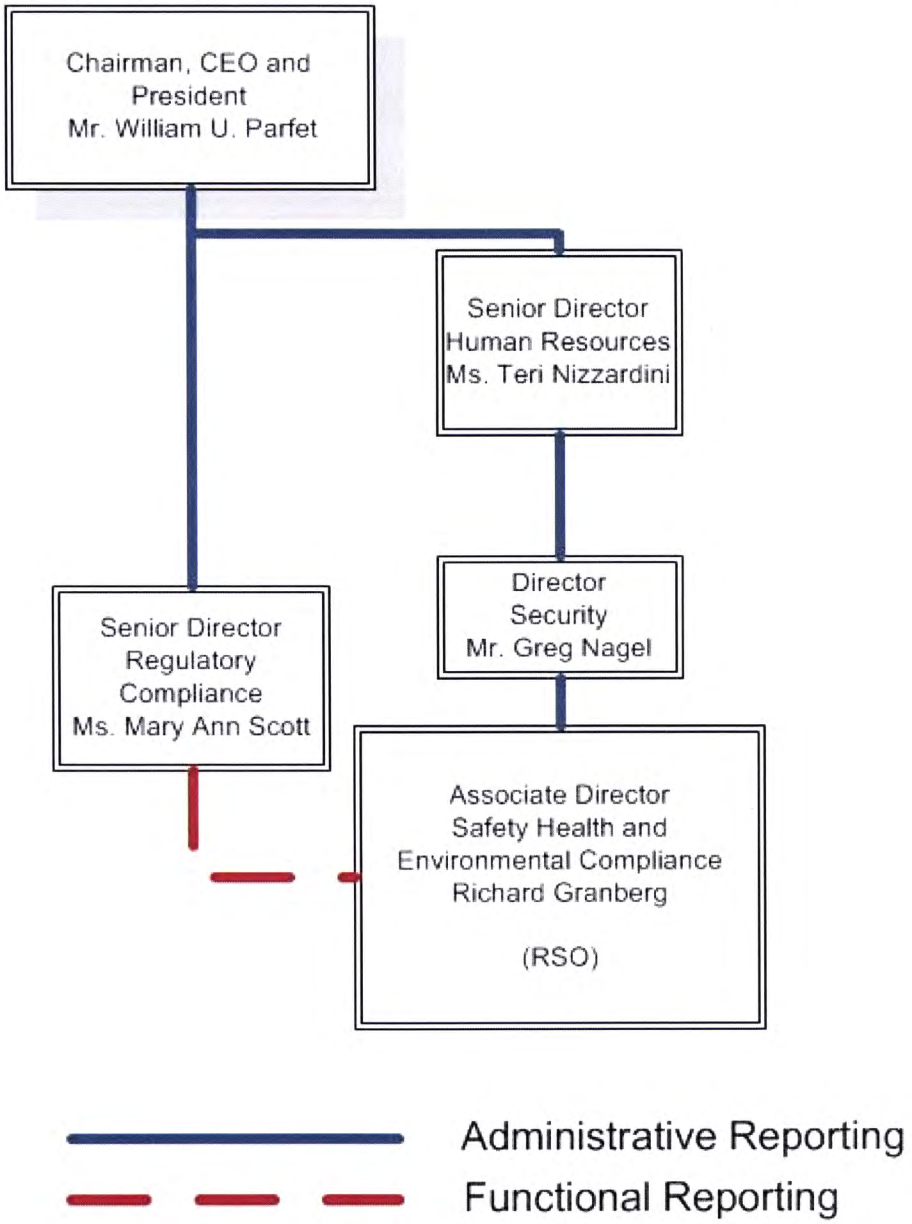
Table of Contents

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

Question 1:

The management structure (and RSO functional reporting structure) has changed since the broad scope license renewal application and the request for additional information on 06/06/2014. The current management structure is as follows:



Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

The open health physicist position previously mentioned has not yet been filled, but interviews for the position continue and a current preferred candidate has been identified. If a more qualified candidate is not identified from upcoming interviews in approximately the next two weeks, an offer will be made to the current preferred candidate. MPI Research still expects at this point to have an applicant confirmed for the position by approximately end of third quarter. In any case, as committed to previously, Dr. Berridge will remain available to assist the RSO as required until the position is filled.

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

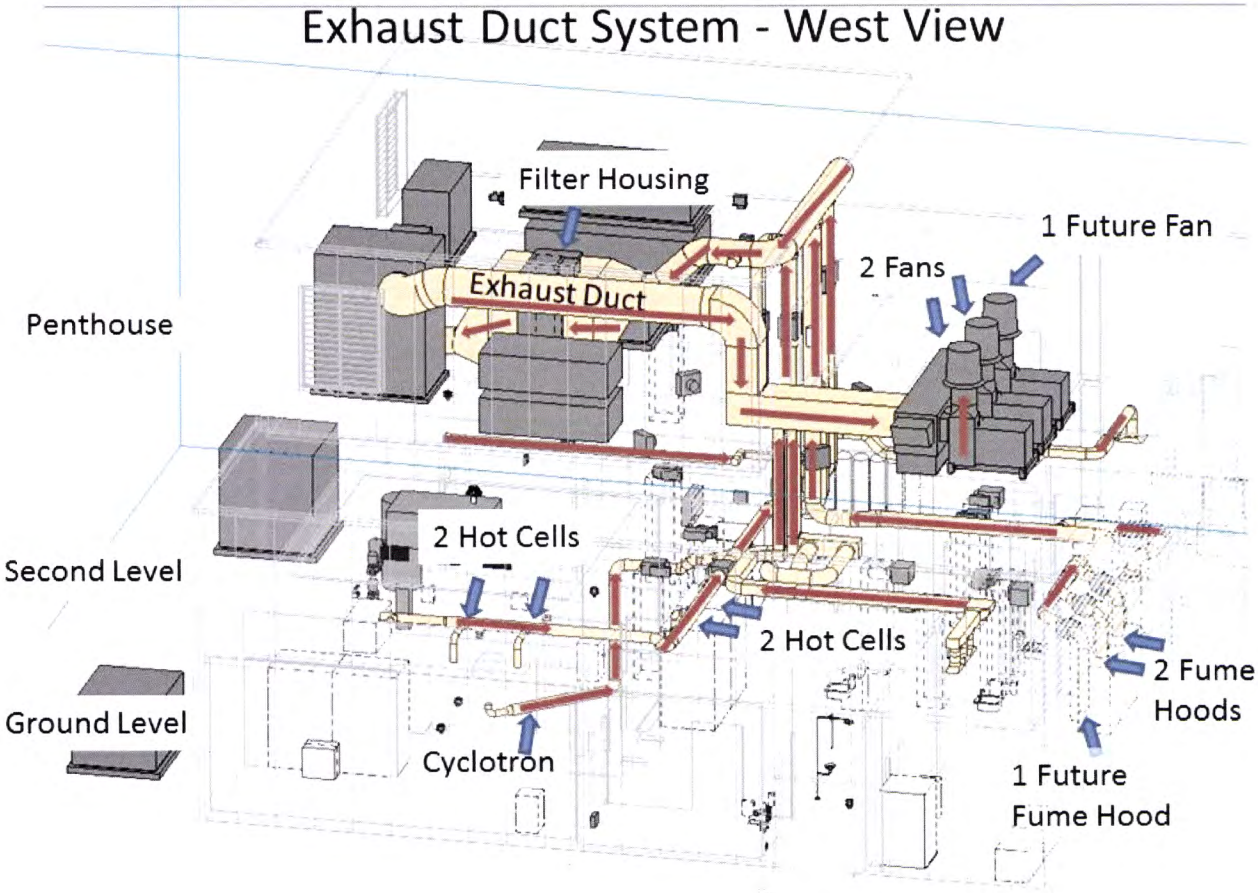
Responses

Question 2:

MPI Research confirms that any loss of air handlers for the T-Building will require immediate shutdown of cyclotron-related radiochemistry operations.

Requested diagrams of the T Building exhaust ventilation system are shown below:

This view of the T Building exhaust system shows the locations of the exhaust points for the four hot cells, two fume hoods, and the cyclotron (which exhausts from under the cyclotron). Air flow direction is shown with red arrows. Vertical ductwork is shown rising through second floor to penthouse. Penthouse exhaust is shown passing through carbon filter housing and out to exhaust fans. Note that capacity for an additional fume hood and an additional exhaust fan has been provided.

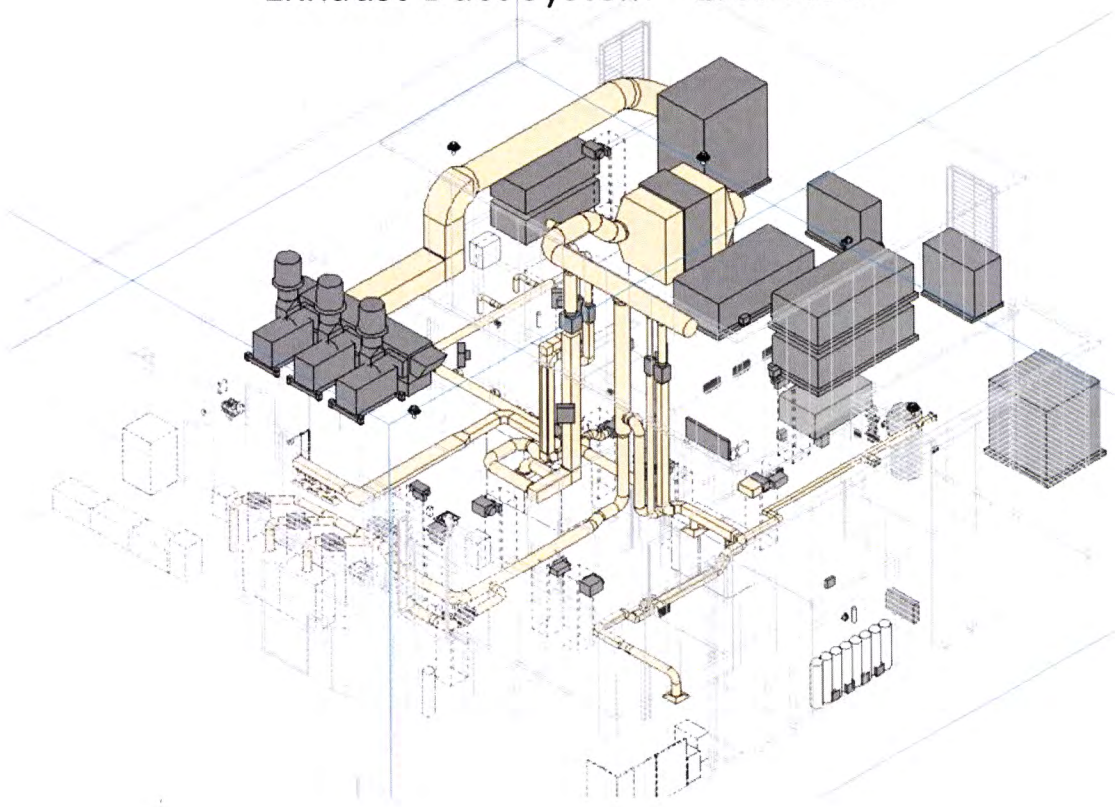


Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

This is an additional view (unlabeled) from the other side of the T-Building showing a better view of the vertical ductwork and of the exhaust duct arrangement in the penthouse.

Exhaust Duct System - East View



Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

Question 3a:

The overall facility boundaries (i.e. the boundaries of the controlled area) for the production license are at the boundaries of the fenced area of the site and are contiguous with the facility boundary for the broad scope license, in terms of adjacency to unrestricted areas.

Within the T Building, the boundary between the production license and the broad scope license is the hot cells, in that material produced by the cyclotron remains under the production license until it is delivered to the hot cells, either remotely via transfer lines or hand-carried (as in solid targets, for example). It then is transferred to the broad scope license. The only exception is that residual radioactive material vented in the hot cell into the waste gas management system remains under the production license, as described in the production license application.

Other radioactive materials produced by cyclotron operation (activated materials) remain under the production license, including any waste materials produced by operations such as target body cleaning or repair.

Radioactive materials flowpath – Cyclotron to hot cell:

The raw material from the target is either F-18 fluoride in water solution or is C-11 carbon dioxide. That material flows under target pressure through the transfer tubing, which as discussed previously is 1/8 inch OD stainless (C-11) or PEEK (F-18) tubing to arrive in the hot cell. The tubing path goes from the target through the under-floor penetrations to the transfer pit and then through additional under-floor penetrations and then rising through a shielded conduit from the floor into the hot cell. At this point the materials transfer from the production license to the broad scope license, except for the residual waste radioactive material which will be vented into the waste gas decay system as described below. The waste gas decay system and its contents fall under the production license, as described in the production license application.

Solid targets are manually removed from the cyclotron target holders, using appropriate shielding and remote handling tools to maintain doses ALARA, and transported in a shielded container on a cart, or hand-carried using secondary containment to the hot cell, where the shielded target material is either transferred into the hot cell or manually placed in the hot cell. At this point these materials are transferred from the production license to the broad scope license.

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

Operations in hot cell:

Liquid/gas: Inside the hot cell the material flows through additional pathways of similar tubing and into glass septum-capped reaction vessels in the synthesis system. The components of the synthesis system will vary depending on the specific product to be made. The inlet tubing is often directed through the shielded dose-calibrator in the hot cell to permit measurement of the amount of radioactivity being delivered from the cyclotron. Controlled (flow-meter) flows of inert gas (Ar, N_2, He) through the sealed synthesis apparatus are used to move the material as necessary through the synthesis system. Vacuum provided by a vacuum pump which vents to the waste gas delay system may also be used to draw material, for example, through a filter into a glass vessel. Egress of the above-mentioned inert gas flow is also directed to the waste gas delay system from the sealed synthesis system. The gas, whether from the exhaust of the vacuum pump or flow from the synthesis system then exits the hot cell through 1/4 inch OD tubing following the same path to the transfer pit as was used for the incoming gas to reach the hot cell. The details of the waste gas delay system, which falls under the production license, are discussed in the production license application materials. Organic chemistry reactions are performed in the reaction vessels appropriate to the individual product to be made. Specific products being made will change frequently. The synthesis may be a single reaction step or up to four steps, all of which take place in the synthesis apparatus. At the end of the process, which takes place entirely within the hot cell and includes purification and formulation steps, the product is located in a septum vial or syringe.

Solid target material: The solid target material is handled in a similar fashion in the hot cell. It is placed in an appropriate reaction vessel to remove the radioactive material from the remainder of the target material. The removed material is then processed through one or more synthesis steps similar to the process described above.

Radioactive waste material (other than that vented into the waste gas decay system) is usually non-volatile material that may either be retained within the hot cell for decay if short-lived, or if longer-lived, may be removed from the hot cell. In this case the material is held for decay in storage after being logged into the waste inventory, and stored in a shielded waste container or storage area for decay. Longer-lived waste may be transported to the Radioactive Waste Storage Building for decay. A very small amount of volatile radioactive waste (radioiodine) may be produced at certain process steps. If any of this material escapes the process containers, it will pass through the carbon exhaust filter in the hot cell. Any material getting past the hot cell carbon exhaust filter

will travel through the T Building exhaust system to the main carbon exhaust filter bank, described previously.

The product at this point is similar to any material that would be purchased and received from a radiopharmaceutical or radiochemical supplier. The quantity of radioactivity in the product that is made is usually adjusted by varying the time of the cyclotron target irradiation to be commensurate with the quantity that is desired for imaging use. The amount of radioactive product transferred out of the hot cell is typically in the unit dose or multiple dose range for Imaging activities, so typical product activities would be in the single to tens of millicuries - much lower activity than the activity of the material originally produced by the cyclotron, or that could potentially be produced by the cyclotron.

The final vial may be pre-positioned in a lead pig for retrieval. In many cases the vial is ready to deliver for transfer to Imaging at that point. In some cases it is necessary to remove a portion of the batch for an individual scan. The vial may then be counted in the dose calibrator by transfer using the manipulators and delivered out of the cell using the transport mechanism of the cell, or it may be removed by opening the cell door sufficiently to retrieve it by hand, using shielding and remote handling tools appropriate for the material being handled. Using standard Nuclear Medicine dose dispensing techniques, and using appropriate shielding, a portion of the material may be removed from the vial using a syringe by hand and then placed in a shielded pig for transport. Alternatively the bulk vial itself may be transported for transfer to the Imaging area. The shielded pig is then hand-carried in secondary containment or on a cart from the hot cell rooms (either room T-1104 or T-1105) to the QC room (T-1101). A QC sample may have been obtained independently by sampling mechanisms in the hot cell, such as a rinse of the sterile filter or a remote side port on the delivery tube for sampling, or the QC sample may be obtained by hand from the vial using a microliter capacity syringe. Appropriate QC is performed which may include thin layer, gas, or liquid chromatography. Upon release of the product it may be transported in its shielded container to the Imaging area by transferring in the dumbwaiter or manually transferring on a cart, or hand-carrying in secondary containment. Throughout all operations radiation shielding, including lead pigs, L-block shielding, syringe shields, lead bricks, and specialized shielding items, as well as remote handling tools such as tongs, are used appropriate to the type and quantity of radioactive material, to maintain radiation doses ALARA.

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

Question 3b:

Most of the synthesis/processing operations for the cyclotron-produced radioactive materials into the specific compounds needed for research at MPI Research occur in the hot cells, as described in the previous response.

The remote manipulators have a long lifetime, are made of metals for the most part and are not in contact with radioactive material in such a way that they suffer radiolytic damage. Manipulators may occasionally suffer mechanical failures and need repair. If one fails, it is usually a gradual progression of failure that does not limit effective usage while needed parts are obtained. Repair is done after decay of any materials that had been in use in the cell. In the worst case, the cell can be shut down and usage can be shifted to a different cell if necessary. The same is true for other mechanical or pneumatic systems in the hot cell.

Tubing and fittings in the hot cell, including valves, are identical in nature to the tubing and fittings that were previously discussed in relation to the transfer of materials from the cyclotron. Since hot cell tubes and fitting receive much less radiation exposure than those associated with the cyclotron, potential for damage is much lower. The procedures, however, are the same. It is necessary during usage and cleaning to frequently handle the system components, following decay or removal of radioactive materials. Radiotracers being synthesized are constantly changing and the system is frequently being reconfigured to fit the usage at hand. Signs of radiation damage and wear are sought by manipulating or in some cases disassembling the materials when the opportunity is presented in the normal course of usage. If damage is found, the affected part is replaced.

Other equipment used in the synthesis/production process is primarily chromatography equipment. That equipment receives very little radiation dose, since the sample activities being analyzed are typically very small. The equipment suffers failures only commensurate with the same equipment used in a cold lab. We have not found routine inspection to be effective, as the required disassembly for inspection causes more degradation than use and is prone to creating new problems. Therefore when such equipment fails it may cause failure of a synthesis to deliver desired product, but it does not cause loss of radioactive material containment. The procedure used is to allow the radioactive material to decay, replace the unit, and then repair it.

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

Leak monitoring: Delivery lines are continuous from cyclotron to hot cell, and leak testing was described as part of the production license application. There are requirements as part of every synthesis that include pressurizing the system (not just delivery lines) and watching the pressure in the system using built in pressure sensors after the pressure source is disconnected. This is a routine check at every usage. Delivery lines are also protected in conduit. Leaks occur exclusively at the termini of the lines where they may be observed and easily repaired. Other parts of the system are tested by closing the system and opening a flow meter that delivers inert gas. The flow as read on the meter drops to zero in the leak test. If it does not, a leak is indicated in the system which is found and fixed either by replacing affected parts or securing fittings as appropriate.

Inspections: All permanent tubing and components of each hot cell will be visually inspected for damage or degradation at least annually, and will be observed for proper function each time they are operated. All fitting and ends of stainless steel or PEEK transfer tubing will be inspected for damage or degradation at least annually (stainless steel) or at least every six months (PEEK), respectively, as part of the transfer line inspection program under the production license. All temporary equipment (synthesis modules, vials, reaction vessels, tubing and fitting, other lines and connectors, etc.) will be visually inspected for damage or degradation each time it is reassembled or reconfigured, along with pressure or leak testing described above if applicable.

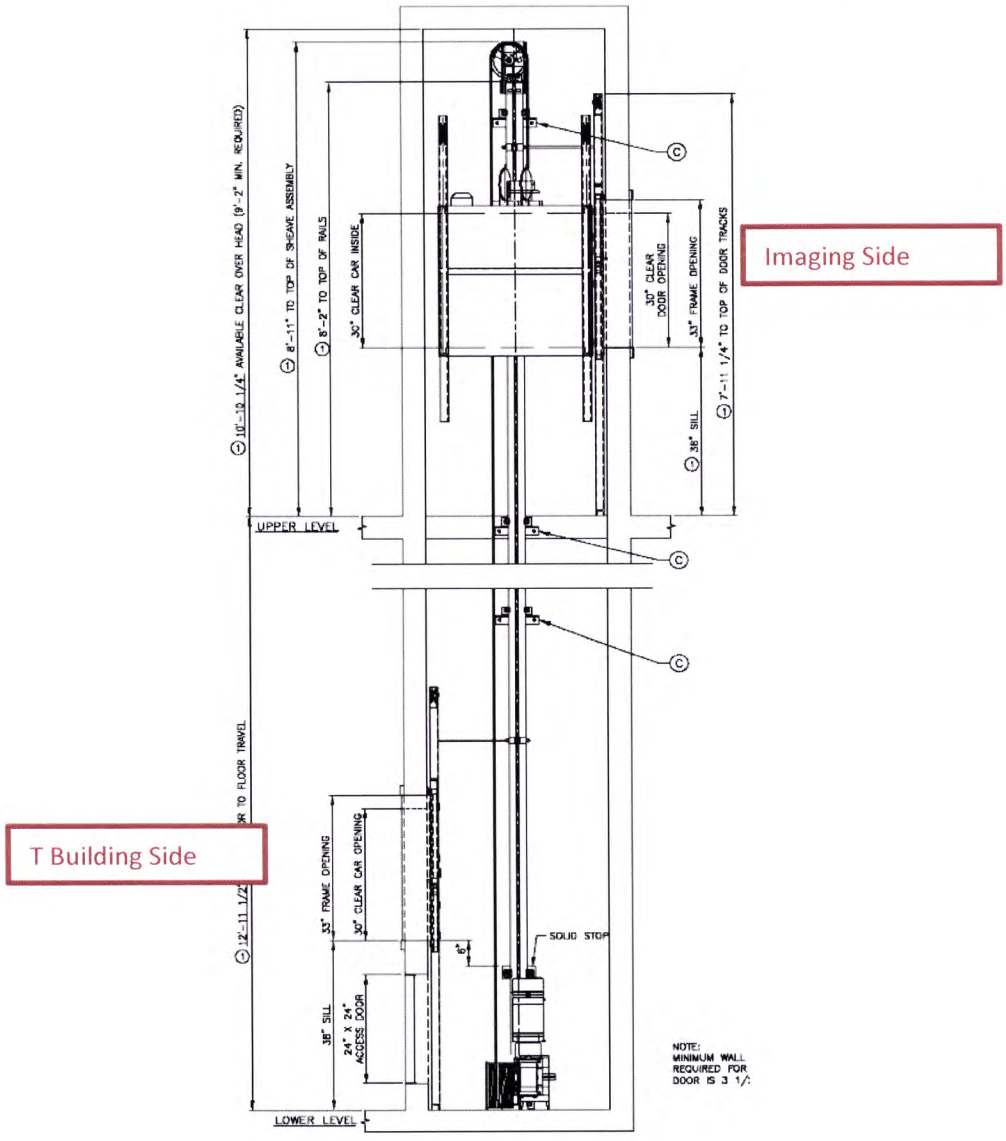
Synopsis of remote handling tools available:
Synthesis apparatus: The entire synthesis apparatus is remotely operated using switches located outside the hot cell. Additions of reagents are made from outside the hot cell through small bore tubing. Maintenance is specific to each component of the synthesis and is performed continuously during the periods when there are not radioactive materials present as the system is used and configured.
Manipulators: They serve to move materials as needed in the hot cell when radioactivity is present, but are not used for synthetic processes. They also serve to move sources behind secondary lead shielding that we put inside the hot cell and move needed items near the access doors for quick removal when necessary, to maintain doses ALARA.
Tongs: The laboratory possesses tongs of various configurations for remote manipulations of materials outside the hot cells.

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

Question 3c:

A cross-sectional diagram of the dumbwaiter system is shown below:



The dumbwaiter is dedicated to movement of research materials from the first floor of the T Building to the Imaging area in the adjacent H Building (second floor), and

possibly return of materials to the T Building. The materials moved will be primarily radioactive materials to be used in MPI Research studies, but may also include non-radioactive materials also required to be transferred as part of the research activities. All materials will be associated with licensed activities under the MPI Research broad scope license. The only groups allowed access to and use of the dumbwaiter are the cyclotron facility staff and the Imaging staff. No other groups will be allowed access to or use of the dumbwaiter.

The dumbwaiter has no built-in shielding, although the wall in which the dumbwaiter is installed is filled concrete block. Adequate shielding is provided by the shielded container in which the transferred material is transported. Although not anticipated to be necessary, the dumbwaiter has the capacity to support additional shielding (in the form of lead bricks) to further shield the lead transfer container. All sides of the dumbwaiter except the back (North) side on the first floor abut restricted areas. The room to the north of the dumbwaiter is an infrequently occupied research room, Radiation levels in this room (controlled area) from movement of materials in the dumbwaiter are expected to be very low, and will be verified using posted area monitors. This room could also be controlled as a restricted area if necessary.

Dumbwaiter security is accomplished by the MPI Research keycard access control system that limits access to the first floor of the T Building, and then further limits access to the restricted area of the first floor T Building (where the lower end of the dumbwaiter is located) only to authorized personnel. The upper end of the dumbwaiter is located in the Imaging area, where access is similarly controlled using the keycard access control system only to authorized personnel. All access logs on all doors are recorded and time stamped for investigation if required.

Transfer of radioactive material by dumbwaiter is tightly controlled by close coordination between the T Building staff and Imaging staff to ensure that materials are transferred only when the receiving party is expecting them and is ready for them. T Building and Imaging will be in voice communication when the material is placed in the dumbwaiter, and the Imaging end of the dumbwaiter will be continuously observed until the material is retrieved. Communication will be maintained until the material is retrieved in Imaging. The reverse process will be observed for any transfers from Imaging to T Building. The RSO will be contacted immediately if the dumbwaiter fails with radioactive material onboard. Hand-carried materials are continuously attended from point of origin to point of turnover.

Responses for questions posed during telephone conversation dated 09/05/2014 to complete amendment request

Responses

Inventory control and inventory transfers: Radioactive products for Imaging, produced using cyclotron produced radioactive materials, are already part of the MPI Research broad scope license radioactive material inventory. That occurred when the materials entered the hot cell, and transferred from the production license to the broad scope license. An inventory transfer does take place by moving inventory control of the material from the T building production inventory (inventory of materials produced/synthesized from cyclotron produced materials) to the Imaging inventory of materials being received, stored, and utilized for research purposes. Inventory control may be via paper record or by an electronic inventory system.

For materials that are transferred either via dumbwaiter or hand-carried from T Building to Imaging, T Building informs Imaging of the amount being transferred (either verbally or electronically). Imaging verifies the amount upon receipt and records it on the inventory sheet or system (that same sheet/system is also used to record usage and any residual). That amount is then deleted from the T Building inventory. The reverse process is followed for materials being transferred the other way, if necessary. Each inventory transfer is authorized by the RSO.

Forster, Sara

From: Richard Granberg <Richard.Granberg@mpiresearch.com>
Sent: Monday, September 08, 2014 3:26 PM
To: Forster, Sara
Subject: Amendment Request for MPI Research, Inc., NRC Lic. No. 21-11315-02
Attachments: Amendment Cover Letter.pdf; Responses for broad scope amendment.pdf

Hi Ms. Forster,

Please see the attached files for our request to amend our broad scope license to process materials produced under our cyclotron production license, and our responses to your request for additional information of September 5, 2014. Please let me know if there is any additional information you might need.

I also recapped our plan to revise our financial assurance for both licenses, as previously worked out with Mr. Null.

And let me again express our gratitude for your help and patience in guiding us through this process.

Best regards,

Dick Granberg

From: Forster, Sara [mailto:Sara.Forster@nrc.gov]
Sent: Friday, September 05, 2014 12:10 PM
To: Richard Granberg
Subject: Additional Information Request for MPI Research, Inc., NRC Lic. No. 21-11315-02

Dear Mr. Granberg,

See the attached file for additional information needed to complete an amendment to your NRC Lic. No. 21-11315-02, authorizing your previously requested use of accelerator-produced radionuclides. Note that the attached conversation record requests additional information on or before close of business on September 12, 2014.

Additional guidance may be found in NUREG 1556, Vol. 11, "Program Program-Specific Guidance About Licenses of Broad Scope," which may be found at:

http://www.nrc.gov/reading-rm/doc-collections/nuregs/staff/sr1556/v11/

Submission of your response as a pdf file attached to an email or via facsimile will allow for the quickest processing. Do not hesitate to call me with any questions you may have.

Sincerely,

Sara A. Forster, Health Physicist Licensing Reviewer
U.S. Nuclear Regulatory Commission - Region III
Division of Nuclear Materials Safety
2443 Warrenville Rd. - Ste. 210
Lisle, IL 60532-4352
sara.forster@nrc.gov
Direct: (630) 829-9892

U.S.NRC
United States Nuclear Regulatory Commission
Protecting People and the Environment