Radiological Risk Assessment and Safety Evaluation For:

Advanced Accelerator Applications, 57-59 East Willow Street, Millburn, NJ, 07041

Executive Summary:

Advanced Accelerator Applications (AAA) is currently fitting out an existing facility located within the Township of Millburn that will contain light medical manufacturing and ancillary office space on the recently subdivided lot 87 which is situated within an office/light manufacturing zone. The Township's Planning Board approved the AAA site plan application related to this facility on Wednesday, April 1, 2015.

AAA has submitted a license application to the New Jersey Department of Environmental Protection's Bureau of Environmental Radiation (BER). The purpose of the license application is to obtain approval from the BER to incorporate radioactive material into an anti-cancer drug product that is intended for distribution to properly licensed medical providers. The radioactive substance in question is an isotope of Lutetium [loo-**tee**-shee-*uh*m], specifically Lutetium-177 (Lu-177). The drug that AAA intends to produce at the Millburn facility is called Lutathera. You may find more information about Lutathera at http://www.adacap.com/company/about-us/.

Over the past several months, some members of the community have expressed concerns regarding the safety of this facility. Hearing the terms "manufacturing" and "radioactive materials" associated with a business in town understandably tends to create heightened trepidation particularly for those residents living in the immediate vicinity of the subject site. As a result of the concerns raised by local residents, the Township of Millburn has hired me to: review AAA's license application to the BER; engage in fact finding investigative activities with AAA and the BER on the Township's behalf; evaluate the proposed processes and safety procedures at AAA's site; and, most importantly, to utilize my expertise as a Certified Health Physicist to determine if there is risk to the citizens of Millburn in the event that AAA is granted a license to utilize Lutetium-177 at the Millburn facility. In addition, I have responded to resident questions regarding the AAA facility on the Millburn Township website. I have also held preliminary discussions with Township personnel regarding emergency response operations and planning.

The summarized findings of my safety evaluation are as follows:

- AAA's license application is "in process" with the BER. In my professional opinion, AAA is very open and transparent with the BER and they are committed to following or exceeding industry standards with respect to radiation safety.

- The Food and Drug Administration (FDA) also regulates the manufacture of Lutathera. Anyone who manufactures a drug must do so under strict FDA protocols that preserve the sterility and cleanliness of the product. The manufacturer (in this case AAA) must constantly perform quality assurance and quality control testing to prove their products are manufactured in a clean environment and contain exactly what they are said to contain. These requirements insure that operations are standardized, well documented and supervised by qualified individuals.

- The physical characteristics of Lu-177 make it very good at killing cancer cells once it is incorporated into a drug product, but generally poor at providing a radiation dose to the public. (It is a beta emitter with a weak gamma component. As a general rule, one must either inhale or ingest Lu-177 to receive a substantial dose.)

- AAA (and any licensee in New Jersey) must operate such that no member of the general public is likely to receive more than 100 mrem over and above his or her normal background radiation dose as a result of the licensee's operations. A rem is a unit used to quantify radiation dose in people and a milli-rem (mrem) is 1/1000th of a rem. With respect to background radiation dose, the average U.S. resident receives approximately 620 mrem/year from all sources. These sources include cosmic radiation, terrestrial radiation, radiation from medical procedures and the foods we eat. From my review of the license application and discussions with both the BER and AAA staff, I am confident that AAA operations are designed in such a way that there will be ZERO radiation dose to the public as a result of normal operations.

- Transportation hazards: It was clear from the public comments and questions that the potential hazards of transporting the radioactive materials to AAA (typically via FedEx or other common carrier) were a concern. I trust that my answer to the public question was satisfactory. I refer you to http://www.twp.millburn.nj.us/310/Professional-Consultant-Questions-and-Re to read more on this.

- Emergency Situations: It was clear that some citizens were interested in understanding the risks, if any, associated with the "worst case" scenario. The two most likely "worst case" scenarios are a fire and a flood. Even in the event of a fire in which a conservative portion (i.e., more than would be expected in an actual fire event) of the potential radioactive material inventory were consumed by the fire and released, the likely highest potential doses are still WELL BELOW the public dose limits allowed during normal operations. In the event of a flood in which a conservative portion of the potential radioactive material inventory mixed in with the flood waters, a

person would need to drink hundreds of gallons of flood water to approach the public dose limits allowed during normal operations.

In conclusion, it is my professional opinion that the proposed operations at AAA are safe and pose no hazard to the citizens of Millburn. Please feel free to read some of my supporting statements and explanations found on the following pages.

Respectfully,

Patrick J. McDermott, CHP
President, RyCon Solutions

Supporting Information for the AAA Safety Evaluation:

What is a health physicist, who is my client, and what role did AAA play?

A health physicist is someone who applies scientific principles to the protection of people from the hazards of radiation. A health physicist who is certified to practice by the American Board of Health Physics is known as a Certified Health Physicist (CHP) and is bound by a code of ethical behavior. The CHP code of conduct may be found here: http://www.hps1.org/aahp/members/wp_ethics.htm.

It should be noted that my client for this Safety Evaluation was the Township of Millburn, not AAA. I was charged with evaluating the AAA application and providing my professional opinion as to the potential risks to the Township's residents.

It should also be noted that AAA was cooperative with the Township and with my investigation. They met with me on more than one occasion for interviews; shared their records and building plans; shared their application materials to the BER; and provided me access to internal standard operating procedures (SOP's). This information was shared with me so that I might provide an informed opinion as to the safety of their operating procedures and evaluate the potential for impacts in the event of "worst case" scenarios. The majority of the documents shared with me would not normally be made public and many contained proprietary information. I have agreed to maintain their confidentiality in exchange for the total access that was granted.

What is Lutetium-177?

Lutetium is a rare earth metal. It is not reactive and has low toxicity. It is a solid, pliable metal at room temperature and has a very high melting point of > 3,000 ^{o}F. It does not turn into a gas or vapor easily and is not soluble in water. These characteristics, by definition, make it more difficult for lutetium to become airborne and be inhaled or mix with water and be ingested. The specific radioactive isotope of lutetium that is relevant to the operations proposed at the AAA facility is Lu-177. Lu-177 is a beta emitter, with a relatively weak gamma component. [I would expect many are not certain what the differences are between alpha, beta and gamma radiation. The following site has a good overview should you care to learn more. http://www.physics.isu.edu/radinf/cover.htm.] In general, beta emitters like Lu-177 are considered hazardous only when they are taken into the body, typically via inhalation, injection or ingestion. Lu-177 has a relatively short half-life of 6.6 days. In simple terms, if you have "X" amount of Lu-177 today and you leave it alone, in one week there will be about "0.5 X" remaining, and so on until there is a negligible amount of radioactive particles remaining.

In "bulk" quantities (i.e., in amounts similar to the vials proposed to be used at AAA), Lu-177 can be a hazard to the skin if handled directly. We do use the term "bulk", but please realize each vial contains only 3-5 milliliters* (less than 1/5th of an ounce). This is only a potential hazard to the employees handling the material and simple safe handling techniques minimize these potential doses. Also in "bulk" quantities, the weak gamma component can be a source of an external radiation dose to those in close proximity to the vials. For this reason, they are shipped and stored in lead (Pb) containers, sometimes called "pigs". This is standard practice at other similar facilities and hospitals that require the use of this type of material. In accident or release scenarios, like a fire or flood, the dispersion of the material effectively eliminates the small hazards from the gamma component and inhalation or ingestion becomes the only pathway for measurable doses. (More on this later.) For information on the chemistry of Lutetium, you may refer to the Royal Society of Chemistry's website, http://www.rsc.org/periodic-table/element/71/lutetium. For information on the radioactive properties of Lu-177, you may refer to the chart of the nuclides website hosted by Brookhaven National Lab, http://www.nndc.bnl.gov/chart/reCenter.jsp?z=71&n=106.

* - I have included the volumes of each of the bulk vials so that you may have a visual idea of the quantities involved. During my interaction with the Township Administrator's office and some of the Committee members, the volume or physical quantity of material was a question many had. In radiation safety, the amount of radiation (the activity) and the type and energy of the particles emitted are what determines hazard, not the volume.

<u>What is AAA doing with the Lu-177? Why do they need it?</u>

In simple terms, AAA is taking the Lu-177 and adding it to their drug compound to create an anti-cancer drug called Lutathera. The drug compound is designed to find specific cancer cells in the body and attach only to those cells. By "labeling" (or attaching) Lu-177 to this compound, they can deliver a dose of radiation (via the Lu-177 betas) that is given almost exclusively to the cancer cells, and not the healthy cells in the body.

The labeling process is achieved via a simple chemical reaction that takes place inside of a well-shielded fume hood. This specialized fume hood is called a "hot cell". The actual labeling and vial preparation of Lutathera is automated and the final product vials are placed into shielded containers before they are removed from the hot cells. These final product vials are what is shipped out to licensed medical facilities for use in patients. While this process is automated, there is an important skilled labor component. In order for the computer software to properly formulate and dispense the drug product, people must do the following:

- Remove the waste and consumables from the prior run.
- Decontaminate and disinfect the interior of the hot cell.

- Introduce the new raw materials (vials, tubes, reagents, etc.) into the hot cells.
- Measure the activity of the next Lu-177 vial.
- Prepare the final product vials and labels.
- Initiate and monitor the production via computer software.
- Perform QA/QC on the final product.

The list above is a simplified description, but suffice to say that without the skilled labor component to prepare and monitor the process, production is not possible.

The hot cells are designed with enough shielding so that there is essentially zero radiation dose outside of the containment unit. In addition to the shielding, the ventilation of the hot cells passes through filters prior to exiting the building. These filters are constantly monitored with a radiation detector. If there is any radioactive material detected on the filters, the ventilation system is immediately shut down to prevent any releases. This effluent control mechanism is standard operating procedure for facilities like AAA. In other radiopharmaceutical facilities, the isotopes handled in hot cells are potentially volatile and there is a higher potential for gaseous effluents to be released. With respect to the proposed AAA facility, Lutetium is not volatile and the reactions take place at temperatures below the boiling point of the drug compound. Based on the above data, the likelihood of a release of Lu-177 from these hot cells is remote. That said, AAA has still engineered these mitigating effluent control systems into the life safety design of the proposed facility.

<u>What about the radioactive waste?</u>

Whenever you utilize radioactive materials to label compounds or drugs, it is never a 100% efficient process. Some traces of the radioactive material are left in each container, in the lines used for transferring the material and in byproducts of the reaction. These are all considered radioactive waste.

Due to the short half-life of Lu-177, federal and state regulations would allow for AAA to "decay" much of their waste on-site and then dispose of it as non-radioactive. AAA would also be free to dispose of some of their radioactive liquids (but only if otherwise aqueous) via the sanitary sewer system. Both of these disposal methods are legal and safe, but AAA has committed to disposing of all of their radioactive waste (whether it has fully decayed or not) via a licensed radioactive waste vendor.

AAA will not take back "empty" but contaminated vials from its customers. Once the vial is shipped to the hospital or medical clinic, it will not return to the Millburn site. (Some radiopharmacies produce their doses in pre-loaded syringes. Many of these operations accept back the used syringes so they may be sterilized and re-used. This is not the case for AAA.)

How is AAA's European compliance record in regards to radiation safety?

A resident submitted this question via the on-line question portal and I promised to look into it during my investigation. I conducted an aggressive on-line search for any public record of a radiological safety violation by any AAA site. I could not find any. AAA itself was founded in 2002, and they operate in France, Germany, Italy, Portugal, Spain, Switzerland, Poland, Israel, UK, U.S. and Canada. I did ask the North American Operations Manager if any of the AAA sites had compliance issues with the European regulators and most importantly if they had been cited or fined for any public safety related issues. After double-checking with his European counterparts, the answer was a definitive no. Having uncovered no references to AAA safety violations as a result of my independent investigation, and based on the cross-checked responses I obtained from AAA interviews, I conclude that AAA has been fully complaint over its 13 year operating history.

What is the role of Millburn's first responders and are they prepared if something happens to the AAA site?

Ultimately this is a question for the Township. However, in my meeting with the Township Business Administrator, Mr. Timothy Gordon, we discussed emergency response operations and planning. At the time, it was premature to discuss details because I had yet to evaluate AAA's license application or develop a thorough understanding of their proposed operations. Provided the license to use radioactive materials is granted, and once the facility fit out is completed, it is my understanding that fire, police and other first responders will tour the facility and coordinate response operations with AAA.

I have offered my services to Millburn and am available to assist in training its first response community. Whether or not the township uses me or another health physicist, a subject matter expert (and AAA representatives) will train and help to coordinate response protocols with the township.

What was the basis for the worst case scenarios mentioned in the executive summary?

With respect to the fire scenario, I utilized conservative assumptions as inputs to the HotSpot modeling software. The HotSpot Health Physics codes were created by the Lawrence Livermore National Laboratory to provide emergency response personnel and emergency planners with a fast, field-portable set of software tools for evaluating incidents involving radioactive material. The software is also used for safety-analysis of facilities handling nuclear material. HotSpot codes are a first-order approximation of the radiation effects associated with the atmospheric release of radioactive materials.

Fire Event

In short, I assumed a fire that was capable of consuming and releasing 10% of the total maximum inventory of Lu-177 that would be allowed on-site under the proposed license for AAA. This is a very conservative assumption as Lu-177 is not volatile, the building will be equipped with a fire suppression system, and any large quantities of material will be stored and encased in lead "pigs" such that a release would be unlikely. Additionally, the model that I ran assumes that there is a single fire plume and calculates the potential dose to a person standing in the area within the plume that has the highest potential for delivering a dose. In addition, I assumed that this fictitious person would stand at this point for four straight days (96 consecutive hours). Even under these circumstances, the highest calculated dose is below the 100 mrem/year allowed under normal operating conditions. The driving factor behind the potential doses being so low is that you must inhale (or ingest) the Lu-177 in the plume. There is virtually no "external" radiation dose expected from the passage of the plume. If you would like to learn more about HotSpot, you may find it at the National Atmospheric Release Advisory Center's website at: https://narac.llnl.gov/HotSpot/HotSpot.html.

Flood Event

When evaluating the flooding scenario, I assumed first that the 15,000 sq. ft. building was flooded with 4 feet of water (60,000 cu. ft.). Assuming that 10% of the total maximum inventory was mixed in with the water in the building (using the same conservative assumption as referenced above for a fire event), you would have a concentration of Lu-177 in the building water that would require a person to drink over 1 gallon of this building water to reach the 100 mrem public dose threshold.

In reality, there would likely be thousands of times this volume of floodwater passing through the AAA facility and all throughout this area of Millburn. This is why one would need to drink hundreds (more likely thousands) of gallons of water to receive even a small dose. Considering the level of other pollutants and microbes that are found in urban floodwaters, the nearly non-existent hazard from Lu-177 pales in comparison.

<u>What about the office staff and non-scientists working in the building?</u>

Approximately 40% of the AAA facility in Millburn will be non-laboratory/manufacturing space. It will house office and administrative staff that have no part in the handling or manufacturing the drug product. These individuals, while AAA employees, are still considered "members of the public" with respect to the radioactive materials licensee. Therefore, AAA must conduct their operations in a manner such that even their employees working in the administrative spaces located in the same building are not likely to receive more than 100 mrem over and above their background doses. If the administrative employees who work inside the

building 50 weeks out of the year will receive essentially zero dose, those surrounding the building should expect the same.