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Mémoire de Anna Tilman

In the Matter of

À l'égard de

Application to allow the production of lutetium-177(Lu-177) at the Bruce Nuclear Generating Station (NGS)

Demande de modification de permis visant à permettre la production de lutécium 177 à la centrale nucléaire de Bruce

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Public Hearing - Hearing in writing based on written submissions

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Canada

Submission to the CNSC re:

Bruce Power's Licence Amendment Request re: Production of Lutetium-177

Background - Overview[1]

In November 2020, Bruce Power submitted a request to the CNSC to amend its Operating Licence in order to produce Lutetium-177 (Lu-177), a medical radioisotope, in Unit 7 of the Bruce B station.

The production of medical isotopes is not novel to Bruce Power in that its current operating licence only allows for the production of Cobalt-60 (Co-60). For more than 30 years, the four reactors at the Bruce B generating station have been producing Co-60, an isotope used widely around the world for the sterilization of single-use medical equipment, such as sutures, syringes, masks, gloves, food irradiation, and to combat deadly diseases like the Zika virus through insect sterilizations. Since 2019, Bruce Power has been producing medical-grade Co-60 for use for brain cancer treatments.

The scenario of the development of medical isotopes, also referred to as radiopharmaceuticals (RPhs) is continuously evolving worldwide. Of particular note, Lutetium-177 (Lu-177), a short-lived isotope of half-life of 6.65 days, is gaining recognition and popularity worldwide as a treatment for advance stages of cancer in particular, prostate cancer, neuroendocrine tumours, as well as other cancers. Lu-177 specifically targets a cancer cell by breaking down its DNA.

To date, Bruce Power's reactors have not been used to produce short-lived medical isotopes, as this would require targets to be introduced and removed while the reactor is on power. However, since the design and operating characteristics of the CANDU reactor enable access to high neutron zones of the reactor, this feature may lend itself to the possibility of target loading and unloading specialized equipment while the reactor is producing power. This feature makes it feasible for Bruce Power to produce Lu-177, given specific requirements and various other arrangements that would have to be made.

Therefore, as required by the regulator (CNSC), Bruce Power is applying for an amendment to its Power Reactor Operating Licence (PROL) to expand its isotope production business line to produce Lu-177, and thereby contribute to providing a constant and reliable source of Lu-177 to meet the growing world-wide demand for radiotherapy treatment.

Bruce Power and its Partners

A number of companies in Canada and abroad are involved in various stages of the production and marketing of this radioisotope. Bruce Power has partnered with the company IsoGen (a joint venture between two companies, Framatome and Kinectrics), situated in the local area of Bruce Power, on developing a specific tool, an Isotope Production System (IPS), which would be used to deliver a specific isotope (referred to as a target) into the core of the reactor unit, that would be irradiated and then result in the production of Lu-177. Framatome holds the patented design for the delivery and retrieval of targets from the reactor core, while Kinectrics is responsible for project management, design, and safety analysis.

[1] Bruce Power CMD 100-1 p. 13-14

Bruce Power is responsible for operation of the IPS and packaging of the irradiated targets for shipment.

Because IsoGen is a contractor, it does not require a CNSC licence to produce Lu-177. Bruce Power will have the ultimate responsibility to ensure the safe production of Lu-177. As such, it would be responsible for the irradiation of the targets from receipt of the source material, Ytterbium-176 (Yb-177), through to the packaging and shipment of the irradiated targets, Lu-177. (The shipping itself is to be handled by an "authorized" commercial shipper typically used for the shipment of nuclear substances.)

The form of Lu-177 (referred to as non-carrier free) that would be produced at Bruce Power is not the highly purified form required for use in treatment.[2] All other components involved to produce the highly pure form of Lu-177 required for treatment, including radioisotope enrichment, processing and drug manufacturing, and including disposal of radioactive wastes associated with the production of this form of Lu-177, would be handled by a third party company that is a licensed entity outside of Canada. This company would also be responsible for the disposal of radioactive wastes associated with the production of the pure form.

As stated in CNSC's CMD 21-H100, the name of this third party is being withheld due to commercial confidentiality.[3] However, there is some confusion as to the "third party". The issuer of confidentiality, i.e., the third party, does not appear in Bruce Power's submission. In fact, its submission clearly notes that "Bruce Power and IsoGen have entered into a supply agreement with Isotopen Technologien Munchen (ITM) as the company that guarantees a customer for the product and sustainable demand for Lutetium-177 production once the IPS is installed."[4]

This matter of confidentiality is confusing, moreso as a background search into the relationship of Bruce Power and this "third party" clearly indicates the involvement of the company ITM. As an example, as stated in "Nuclear Engineering International 2 November 2020":

> **"**Germany's ITM Medical Isotopes and Canada-based Isogen have signed a formal supply arrangement to provide a reliable supply of lutetium-177 to the world's health care system using Canada's Bruce Power reactors as a key supply source." ITM Medical Isotopes is a subsidiary of the biotechnology and radiopharmaceutical group of companies Isotopen Technologien München (ITM), and Isogen is a joint venture between France's Framatome and Canada-based Kinectrics."

It is important that the CNSC clarify this issue of "confidentiality" and the roles and responsibilities of each party involved in the whole process of producing this isotope. After all, Bruce Power and Canada have a shared responsibility in ensuring the safe production of the Lu-177 for treatment.

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[2] Carrier-Free (CF) or No-Carrier-Added (NCA): A radionuclide is referred to as carrier-free (CF) if it has isotopic purity - that is, all atoms contain one isotope of the element, and it is free from any stable isotope. It is an idealistic situation. An NCA does not mean 100% isotopic abundance or purity as in that adding another isotope (usually a stable isotope) is to prevent the agent from adhere to container wall.

[3] CMD 21-H100 Executive Summary p.1

[4] Bruce Power's submission – CMD21-H100, p. 3

Furthermore, regarding the waste disposal issue resulting from the processes entailed in purifying this isotope, indeed it is a recognition that waste (radioactive and presumable non-radioactive) would result. But the question is – where or how is the waste being disposed of? That this is not being disclosed, whether it is a confidential matter, or for some other reason, means that people are not being given the information that is needed for them to know of a potential threat to the environment and to their health, and/or to fulfill their right to make input into this matter.

While expectations are to have the production of Lu-177 in place in 2022, pending regulatory approvals, this may not be doable in that timeframe for a number of reasons, in particular, whether the equipment to be manufactured (IPS) and/or the process itself in the reactor may or may not be ready or trouble-free. Added to this, the pandemic could well result in supply, production and labour issues, at any or all of the stages of final production and distribution issues.

Production of Lu-177

Lutetium-177 (Lu-177) is produced by irradiating the isotope Ytterbium-176 (Yb-176). The process involves placing Y-176 source material in special sealed containers which are then conveyed into Unit 7 using the Isotope Production System (IPS). The Yb-176 is then irradiated for about one week. This results in the production of an intermediate Lu-177 isotope which is then sent to ITM for further processing into highly pure pharmaceutical grade of Lu-177 and for subsequent distribution to health care facilities worldwide.

The safety of the IPS is the critical piece of the whole operation. It could take time beyond what may have been expected to ensure that there are no problems. It is not clear how it would be tested prior to being utilized. Nor is it clear what responsibility Bruce Power would have, if any, as to the production and safety of the IPS or the timing as to when the IPS would be functional.

Based on its review of Bruce Power's licence amendment application, the CNSC staff has indicated that Bruce Power has adequate provision to ensure safe production of Lu-177 and that the installation of the equipment to be manufactured (i.e., IPS) would not result in significant doses to the public or the workers or in releases to the environment.

However, CNSC's indication is not based on any supporting evidence or even on precautionary concerns. As noted, the development of the IPS itself does not require a CNSC licence. Other components involved beyond the developing the isotope at Bruce such as shipping, the further processing needed, and the disposal of wastes ensued by this work would be handled by a company or companies licensed to carry out such activities, but not in Canada and thus are beyond the role and responsibility of Bruce Power and the CNSC.

Operation of the IPS - Design and Safety [5]

The target material to produce Lu-177 is ytterbium oxide (Yb_2O_3) powder that contains Ytterbium-176 (Yb-176). This powder is contained in sealed, leak-tested ampules designed to withstand temperature and radiation fields in the reactor. The IPS, which is effectively a

[5] CMD 21-H100 p. 14-16

pneumatic delivery system, delivers the target material into the reactor vessel (or reactor core) for irradiation via neutron capture. Following irradiation, the ampules are sent pneumatically to a radiation shielded (decay zone) to undergo further decay and dose reduction, before being sent to a shielded transport container.

The IPS operation for inserting and withdrawing target carriers will occur only during normal operation of the reactor, and would be restricted during other states (e.g., outages, unplanned shutdowns and unit start-up). The targets spend about 7 days in the reactor core.

As stated in CNSC's CMD p.16, "In the event that the targets are stuck, the design of the carrier tubes is such that they are able to remain in the reactor until the unit's next outage, typically two to three years. Once the unit is safely shutdown, an operator will be able to use a manual tool to extract the stuck targets."

Apparently, the stuck targets will not impact normal operations. Can this be demonstrated or validated in some way? However, inserting and withdrawing target carriers would be restricted, but to what degree? Is it even safe to continue inserting and withdrawing carriers in a reactor unit that is not fully functional?

Does this infer that the reactor can continue to function with stuck targets?? How does CNSC, Bruce, etc., know whether this is even possible?

Bruce Power has built a mock-up of the IPS to validate its design. However, while the mock-up was expected to be completed May 2021, which is the present time, there is no indication that this has been done. Unless Bruce Power can test the IPS mechanism to ensure its' safety, it is premature for CNSC to grant Bruce Power its licence request at this time.

Furthermore, Unit 7 will be shut down in about 6 years (year ~ 2028) to undergo Major Component replacement (MCR). How does that affect Bruce Power's isotope production plans? Why was Unit 7 chosen in the first place for isotope production over other units? Is it based on overall performance, timing? No information has been provided on this matter.

Does Bruce Power intend to use the IPS to produce other isotopes? Is this even feasible? Does it plan to produce Lu-177 in any other units of Bruce B?

The CNSC has proposed to use "regulatory hold points" to track the completion of actions required to confirm operational readiness of the Lu-177 IPS for the staged progress to the initial operation for the production of Lu-177. This is a standard administrative operational practice due to the various stages and iterative processes that would need to be carried out.[6] However, it is not clear that "hold points' would necessarily address or speak to any issues that could or may occur throughout this process.

In fact, CNSC have concluded that "the installation and operation of the IPS will not result in significant doses to workers or members of the public and not result in releases to the environment".[7] There is no way to know this beforehand, and hence the "conclusion" is premature.

[6] CNSC CMD 21-H -100 p.30
[7] Ibid p. 29

While Bruce Power is bound to fill out a number of actions, there are unanswered questions regarding this project.

- What does Bruce Power propose in the long run with respect to the production of this isotope?
- Will Lu-177 be the one and only isotope or will there be others as time goes by? What units would be used for producing these isotopes?
- What other units are deemed feasible to carry this process out?
- What checks and balances will be carried out to ensure safety in production and for the workers, the local residents and the environment?

So much is unknown, from the technique itself to the employment of reactors to the production of the end product.

Commentary

The field of medical isotopes and radiopharmaceuticals (RPhs) is ever changing worldwide, not only in the particular isotopes being explored, but also in methodology, such as cyclotrons, e-beams, that do not endure the issue of reactors, and the waste and other issues they present. Curing cancer – also means preventing cancer. While some of these RPhs provide valuable treatment, there are also so-called side-effects that need consideration.

While so much emphasis is being placed on Lu-177 for cancer therapy, specifically but not limited to prostate cancer especially in advance stages, a lot of research is being carried out worldwide in the field of medical isotopes and treatment. While some of the medical isotopes can address cancers specifically, there are other lasting effects that could occur from these drugs, especially if they remain in the body for a length of time.

The enticement of the use of nuclear technology is not a panacea.

By the time that Bruce Power's isotope production system is proven to be working and safe, other, novel radiopharmaceuticals could well emerge. So why build a system now, the IPS, that may or may not be adaptable or flexible, for companies to get a share of a potentially very profitable market in pharmaceuticals, have the final production and resulting waste produced in other countries, unlikely with public consent, and only to present an image of corporate responsibility and concern, to win over people to the benefit of producing Lu-177?

Just as nuclear energy is complicated, isotope production in reactors is also complicated.

Concluding Remarks

The international scope of this work may not be unique at these times, but it is overwhelming, to say the least. Ultimately, it rests on the shoulders of Bruce Power, to ensure that all the mechanisms involved, from the IPS, to operations within the reactor, can proceed trouble-free.

Any project that is unique, as this one is, and that relies on new as well as old technology (i.e. the IPS development and Reactor # 7) would have to weather potential mechanical issues, breakdowns, delays, etc., and potential accidents.

- What plans do Bruce Power and the CNSC have to contend with unpredictable but potential issues or emergencies that may arise at various stages of the process, from the IPS development to the neutron activation in the core of the reactor to produce Lu-177?
- If there is a problem within the reactor, then with whom does the responsibility lie? The CNSC? Bruce Power? The Canadian Government?
- What, if any, other units (of Bruce B) are considered for the application of the IPS technique for this isotope Lu-177, or other medical isotopes?
- Why is Isogen, the very company responsible for the design and construction of this IPS not answerable to the CNSC? If there is a problem with the IPS, then who is held responsible?
- To whom is the final company (partner), be it ITM or another undisclosed firm, responsible?

As CNSC is not in a habit of denying licences, I would expect that it would approve Bruce Power's request, possible with conditions (more than just hold points).

However, before CNSC is to give or not give approval of Bruce Power's request to produce Lu-177 in Unit 7, more testing and evidence would be needed to support this initiative.

Timing is also an issue, especially during a pandemic whose effects are widespread in so many ways, including production, labour, and the supply chain as well as the final refining stages overseas. As it presently stands, one needs to be prepared for delays. It is not clear how the CNSC and/or Bruce Power plan to address this very potential matter, but it must be considered.

Are the procedures and methodologies safe? What are the downsides, aftereffects?
What can be done to prevent these diseases? What considerations are being given to use means other than nuclear reactors to develop radiopharmaceuticals?

This topic is extremely complicated. So many factors are in play, not only in Canada but worldwide. Should this project be undertaken now or delayed? That is a question for both the CNSC and Bruce Power. Much more effort should be placed in that direction. After all, at some time, the reactors will have to be retired. As mentioned in this submission, there are other means of producing such isotopes that do not depend on nuclear reactors.

In summary, while I am not opposed to work being done on developing radiopharmaceuticals for the treatment of diseases that affect so many directly and indirectly in the world, there must also be caution in the means of production in producing these drugs and potential longterm adverse aftereffects.

This topic as a whole is far more complicated than simply adding a technical device (IPS) to produce this one isotope.