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TIJDSCHRIFT VOOR NUCLEAIRE GENEESKUNDE

Molybdenum production: crisis and opportunities

High Flux Reactor Petten resumes vital role

Alternative methods for producing ^{99}Mo

Economics of the ^{99}Mo/^{99m}Tc supply chain

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The good news or the bad news first?

Well, we had many crises the past years and some of them are still continuing. Dear reader, we decided to analyse in-depth the latest crisis on molybdenum production. Because of its importance and world-wide impact, we invited both national and international professionals to make their contribution. Consequently, this issue is published in English.

We have got good news and bad news for you. To start with the good: Molybdenum-99, the raw material generally used for the production of our beloved Technetium-99m, is now once again widely available for nuclear medicine purposes. The bad news is, however, that without structural changes, the current and future supply chain of this essential isotope is far from guaranteed.

For this Special Issue ten outstanding professionals were asked to describe the causes of the shortages and how they were dealt with, to analyse the underlying economics, and to suggest improvements and alternatives that may help prevent or alleviate future crises.

De Widt, as manager of Irradiation Services, was directly involved in the repair project and restart of the High Flux Reactor (HFR) in Petten. HFR is a key supplier of medical isotopes, covering about 70% of the European demand. It is the world's second largest supplier of Molybdenum-99, right after National Research Universal Chalk River in Canada. De Widt provides us with a very personal eye-witness and project manager's report of the recent outage of the HFR and the unique repair project that finally returned it to full production last September.

De Lange, site director at Covidien's Petten plant, describes the short-term shortage impact and the way the Molybdenum-99 processing industry has dealt with it. He even successfully called in Maria's help, Maria being the Polish research reactor Covidien recently contracted into the supply chain.

During the latest crisis, Verzijlbergen, as president and spokesman of the Dutch Society of Nuclear Medicine, was closely involved in communication about the Molybdenum-99 shortages. He discusses alternatives to the use of Technetium-99m labeled tracers. Although conversion towards PET-techniques might reduce our dependency on Technetium-99m to some extent, Technetium-99m labeled agents will still remain the workhorse of Nuclear Medicine for many years, he reveals.

In his article Seeverens presents a summary of the recent report of the High-level Group on the security of supply of Medical Radioisotopes. This international group of 20 experts analysed the economics of the current Molybdenum-99 supply chain and came up with a number of highly relevant conclusions and suggestions. As former medical specialist and current policy advisor within the Dutch government, Seeverens gives his personal opinion on the report.

Three separate contributions, by Lewis of CERN, Zimmermann and Geets of IBA and Wolterbeek of Delft University of Technology, discuss several

alternative methods for producing Molybdenum-99. A variety of methods, in various states of maturity and feasibility, is summarized. Recently Delft has offered to make its research reactor available for back-up Molybdenum-99 production, using conventional fission of Uranium-235 targets. A novel production method Delft is investigating might eliminate the need for Uranium-235 targets in the future.

This in-depth analysis is concluded by Van der Schaaf and De Jong who present PALLAS, the projected successor of the aged High Flux Reactor in Petten. They report on the progress made towards its realisation.

We hope this Special Issue will illuminate the way forward to a stable long term supply of all medical isotopes.

Editors-in-Chief of this Special Issue

Bertjan Arends
Nuclear medicine physicist
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Filiz Celik
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Front page
Characteristic "blue glow" of Cherenkov light, emitted by a reactor core submersed in water. It is generated when charged particles (as those released in nuclear reactions) pass through an insulator at a speed greater than that of light in this medium (0.75c for water). Pavel Cherenkov, the 1958 Nobel Prize winner, was the first to describe it. Original image: courtesy Gudron Vis, NRG, Petten, The Netherlands.

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From Atom to Image

The High Flux Reactor in Petten resumes the vital roles of production of medical radioisotopes and nuclear research

E.J. de Widt, MSc *Irradiation Services, Nuclear Research and consultancy Group, Petten, The Netherlands*

Abstract

De Widt EJ. The High Flux Reactor in Petten resumes the vital roles of production of medical radioisotopes and nuclear research

On August 20, 2008 a bubble jet was discovered in the primary cooling water system of the High Flux Reactor (HFR) at Petten. As the possible impact on safety of this phenomenon was unknown, Nuclear Research and consultancy Group (NRG) - the operator of the nuclear reactor - decided not to restart the HFR.

As part of an HFR return-to-services programme NRG generated a plan to restart the HFR and - in parallel - to prepare for a full final repair of the cooling water system. The time needed to prepare the repair was estimated at one year. Additional technical and organisational measures were added to maintain safety and after internal, national and international review, the plan was approved. In February 2009 the HFR was back in operation for one year on a temporary license and NRG prepared for the final repair. During these preparations the National Research Universal (NRU) reactor at Chalk River unexpectedly went out of service for major repairs. Alternative supply options were developed for the period the HFR would be out of service for the repair and NRU would remain out of operation.

The approach for the final repair project was to involve specialists from day one and to develop and test each step of the project at work bench scale and then in 1:1 scale models. Accurate engineering and thorough testing proved its value: the project proceeded well and according to plan.

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NRG and the High Flux Reactor

Since the early sixties, the High Flux Reactor (HFR) in Petten has been a vital link in the chain of nuclear facilities in the Petten dunes. Nuclear Research and consultancy Group (NRG) operates these facilities and employs 360 people. NRG develops and supplies sustainable nuclear technology, with applications in power generation, the environment and healthcare. Utilizing the HFR, NRG has grown into a key supplier of medical radioisotopes with about 70 % of European demand produced in the HFR at Petten. The HFR runs around the clock, with on average 10 cycles of 28 full power days per year. After safety, NRG's first priority is to provide reliability of supply in order to contribute to optimal patient care. The physical properties of medical radioisotopes prevent the stock-piling of isotopes. As only 5 nuclear research reactors together provide over 90% of the world demand for medical radioisotopes, the production programmes of these 5 reactors are accurately tuned, in order to maintain continuity of supply.

Deformations in the cooling water system

Each summer the HFR is shut down for maintenance and inspection. In the summer of 2005, deformations were detected in two parts of the reactor's primary cooling water system, called "reducers". These consist of cone shaped pipe sections which on their large diameter side are connected to the reactor. Their small diameter side is attached to the cooling water pipes. The reactor is located in a concrete pool with floor and walls some meters thick, lined with aluminium. For cooling and radiation protection purposes the pool is filled with water 9 meters deep and the top of the pool is open to enable reactor loading and unloading during operation. The reducers and connecting cooling water pipes are embedded in the concrete at the bottom of the reactor pool.

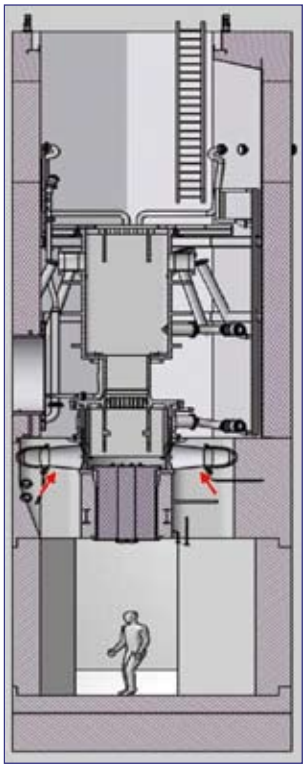

Figure 1.
Cross section of the HFR. Arrows (in red) indicate the position of the reducers which had to be exposed by removal of concrete from below.

Figure 2. The reducer prior to repair.

Investigations to find the cause

Investigations were started to find the cause of the deformations in order to determine their possible impact on the safety or reliability of the HFR. We also decided to increase the frequency of the periodic inspections of both the reducers and the deformations.
The hypothesis was developed, that on the outside of the reducers, a combination of carbon steel, moisture and aluminium initiated a galvanic corrosion process causing a decrease of the reducer's aluminium wall thickness. The corrosion product has a volume 2 to 3 times greater than the volume of the aluminium. As the concrete was unlikely to deform, it was likely that the reducer wall would be pushed inwards, thus causing the observed deformations. From 2005 onwards additional investigations were executed and we involved experts from many different fields in order to avoid "tunnel vision".

Sustainable supply of radioisotopes

The very first question we raised after detection of the deformations was: "What is the impact on safety?" Only when safety is ensured, the reactor can be operated. To ensure sustainable supply of medical isotopes, the next very important question was the reliability of the reactor, both on short and long term.
To answer these questions we frequently updated our safety analysis with new data from our investigations. From this we learned that the risks from the deformations were well within safety limits; however, the risk for unscheduled downtime was increased. We decided to set-up a project to look for solutions. At first we considered repair to be very difficult or even impossible and wanted to investigate options other than total repair. We hired a British engineering company with broad experience in the nuclear industry. One of the first steps in the project was to define a decision matrix and decision criteria.
The position of the isotope customers also played a crucial role. Both minimum down time of HFR for repair and speed of availability of solutions were high on the priority list. The latter was important, because early availability of a repair solution could prevent a long down time in the case of an unexpected failure of the reducers. With these criteria at hand, we reviewed many repair options. A few, potentially successful solutions were engineered further in order to substantiate the decision making process. By this time it was already the summer of 2008.

A gas bubble jet and a decision with major impact

In agreement with the coordinated operating schedules of the main medical isotope production reactors, July 28, in the year 2008 was the first day of the HFR summer maintenance stop. The planned date for the restart was August 24 and inspection of the reducers was scheduled. At this time we were still working on repair options for the reducers.
The inspection progressed according to plan; the results confirmed again our view of the situation. The deformations had grown slightly; but wall thickness had decreased very little. We were glad that we had already started to prepare for repair of the reducer.
On August 20, 2008 at lunchtime, with a flushed face, the inspection team leader interrupted a project progress meeting. The inspection team was performing final measurements when unexpectedly they saw a gas bubble jet released from one of the deformations. With some disbelief their first action was to keep the camera focussed on the spot

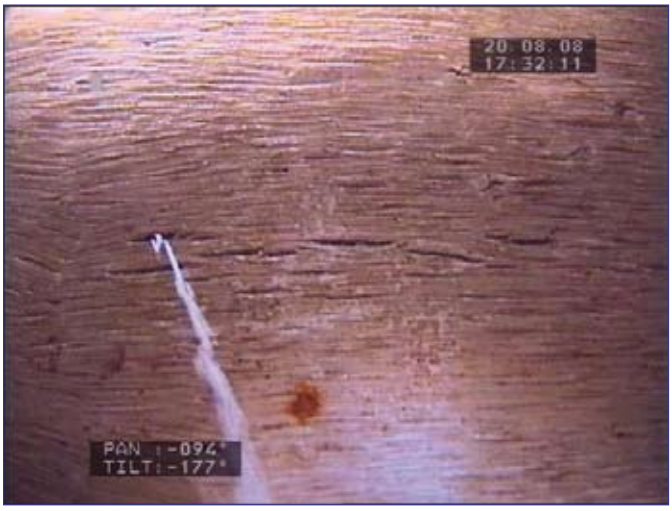

Figure 3. Bubble jet on the inside of the cooling circuit, at the reducer position.

and start the video recorder.
By the next day we had learned that the gas bubble jet emerged at a frequency of once every 10 – 20 minutes and lasted 10 to 30 seconds each time. What followed was a discussion about these observations, a first exchange of ideas about the origin and cause of the gas bubbles, decisions about possible extra investigations, preliminary considerations about the possible consequences and finally decision making within the management team about "go" or "no-go" for the planned HFR restart.
We were fully aware of the impact a "no-go" decision would have on all the customers and on the patients who are dependant on the radioisotopes from Petten. At that point in time, the cause, extent and possible safety impact of the observed phenomena on the reactor were unknown; so we decided not to restart HFR.

Mitigation of consequences

During the days after this decision, all possible powers within and outside NRG were mobilised to try to mitigate the consequences. The highest priorities were communication with customers and colleague reactors in order to minimise impact and to immediately set up an HFR return-to-services project.
The Association of Imaging Producers & Equipment Suppliers (AIPES), representing the international isotopes users community, took action with the objective to minimise the short to medium term disruption of supply for medical radioisotopes. Following an initiative of the Canadian government, the Organisation for Economic Co-operation and Development (OECD) / the Nuclear Energy Agency (NEA), convened a meeting in Paris in January 2009 to discuss the security of supply of medical isotopes. Several national governments participated and it was agreed to establish a 2 year OECD High Level Group programme (covered by Seeverens, see elsewhere in this journal issue) to address medium and long term supply issues. These processes resulted in further improvement in coordination of available resources and increased international political awareness.
The HFR return-to-service project consisted of 3 main elements:
1) Investigation and analysis of the condition of the reducers.
2) Find a solution where the HFR could re-start on the shortest possible time path.
3) Find a long term solution ensuring a reliable HFR.
It was clear, that whatever the solution, there would be no compromise on safety. For a short term solution we were prepared to compromise on operational reliability, if necessary.

HFR return to services

Prior to the discovery of the gas bubble jet, we had been developing potential repair methods. At this point we changed our approach based on the experience we had gained; our new strategy was now to find a company with extensive experience in this kind of repair and to quickly develop a temporary repair solution. In parallel they should also develop the final repair method. We selected a Swedish company who specialized in repair projects in the nuclear industry.
Quite quickly we decided to start detailed engineering on the so-called "sleeve option" for the temporary repair; an option already considered earlier that year. The idea was to install a specially designed pipe inside each reducer. However, during detailed design we encountered insurmountable technical problems.
In the mean time, it became clear that for the final repair, it would be necessary to either locally repair the corroded parts of the reducers or to replace both reducers completely. The only way this could be done successfully, would be to make the reducers accessible by cutting two large cavities in the concrete in which the reducers were embedded. Initial analysis showed that two cavities in the concrete could be accommodated from a constructional point of view. Preliminary calculations indicated that radiation levels at the repair sites could be reduced to an acceptable level by installing extra shielding material in the reactor to compensate for the radiation shielding effects of the primary water, which would need to be drained.
Confidence in the "concrete route", as it was called by that time was growing, while confidence in the "sleeve option" had decreased rapidly. Most importantly, our understanding of the actual status of the reducers and their impact on safety and operational reliability had increased a great deal since the first discovery of the gas bubbles. An important new fact was the clear confirmation that there was no water leakage at the reducers.
We estimated that we needed about one year to fully prepare for the "concrete route". We also judged that with additional detection systems for the possible but unlikely leakage of water from the reducers, safety could be maintained. This would allow the HFR to return to services temporarily while we prepared for the full repair. Comprehensive safety analysis

confirmed our assessments.
Our plans and supporting analysis were reviewed by national and international experts and the International Atomic Energy Agency (IAEA) sent an expert mission to assess in great detail all the safety aspects of the project.
On February 12, 2009, we received a temporary license to start and operate the HFR. Three important conditions were connected to the license. The HFR would only operate when necessary for medical needs; if any water leakage from a reducer was detected, then the HFR would be immediately shut down and execution of the project of final repair of the reducers had to be started by March 1, 2010.
As all preparations for start-up were already in place and we were able to start the HFR that same evening. Before midnight the HFR was running at full power and had resumed production of radio-isotopes.

Prepare for final repair

The first step towards the repair was setting up a dedicated project organisation. The author of this article acted as the project executive and appointed an experienced project manager to create and lead the project team. Specific expertise and strong teamwork characteristics were the main selection criteria.
People both from within NRG and from outside companies were appointed project team members. The project objective was to safely repair or replace the two reducers by gaining access through the concrete ceiling of the sub pile room, the space directly under the reactor vessel.
The repair should start no later than March 1, 2010 and in order to minimise the negative impact on the isotopes market, the reactor outage time for the repair project should be as short as possible without jeopardizing safety or quality of work. The quality of our planning and ability to accurately forecast the date of return to service of the HFR at the end of the project was also of utmost importance.
A major decision early in the project was to drain the reactor pool at an early stage of the work and this concerned the safety of the workers. Calculations had indicated that the pool bottom would be strong enough after removal of the concrete from the cavities, but to be absolutely sure there was no risk of flooding by the pool water, we decided to drain the pool. This decision had far reaching consequences, as we needed to install alternative radiation shielding material on the pool bottom. We selected a tungsten alloy with a density of 18,000 kg/m^3. Prior to draining the pool, we also needed to cover the open top of the pool with a concrete cover in order to reduce overall radiation levels within the reactor building.
Our approach during the design and engineering phase was to involve sub contractors from day one and to develop and test, preferably several times, each step of the project with 1:1 scale mock-ups.
For the concrete removal and restoration we built a replica of the section with one of the reducers. We found a Swedish mine which was able to supply the same high density concrete filler (magnetite) that was used 50 years ago. By practising concrete removal on the replica, we learned which tools and work processes were the best and staff doing the work gained experience in working in a limited space like the sub pile room.
For the actual repair of the reducers, several techniques were investigated and tested at both work bench scale and on 1:1 models. We tested a relatively new technique for increasing material wall thickness by means of "cold spraying", however this method could not be qualified for application in a nuclear facility, because there were no relevant standards. Welding was selected as the repair method and criteria were developed for the decision process to either repair locally or totally replace one or both reducers. The qualified welders practiced both repair options in models of the narrow cavities.

Chalk River NRU reactor outage

In May 2009 the Atomic Energy of Canada Limited (AECL) announced that a small leak of heavy water had been detected at the National Research Universal (NRU) facility at Chalk River. As a result, NRU went out of service until completion of repairs in August 2010.
The NRU is the world's largest supplier of medical radioisotopes and their outage had a major impact on the medical isotopes community. At first nobody knew that it would be mid August 2010 before NRU would return to services.
AECL and NRG have kept each other fully informed about the status of the NRU return to service project and the HFR repair project and the world wide medical radioisotopes community and national governments were involved in discussions to find the best possible solutions for maximising supply and maintaining patient care. NRG was very involved in the successful development of alternative supply options for customers during the critical period when the HFR would be out of service for repair.
It was concluded that the timing of the HFR repair project should not be changed.

Internal and external reviews

Our repair plan, the safety plan, the radiation protection plan and the detailed plans of the sub projects were modified and reviewed several times as part of the engineering process.
To ensure the quality of all aspects of the project, internal and external reviews were a continuous part of the process. To mention a few: at Petten there are two permanent committees, the HFR Safety Committee and the Petten Reactor Safety Committee. Specifically for this project we also installed a Technical Expert Advisory Group. In December 2009, an international Peer Review Team was invited to Petten for in depth discussions and project review. In early 2010, an IAEA mission was in Petten again for thorough discussions and project review. During the whole process, the Dutch national authority - the Kern Fysische Dienst (KFD) - supervised each project phase and all the reviews.

By mid January 2010 all documents were approved and the project was ready for execution.

The repair

The repair started February 19, 2010 and the reactor internals, like fuel elements, control rods, isotope production rigs and experimental facilities were removed. The first major test for the project team was the installation of the radiation protection equipment inside the reactor and shielding blocks at the bottom of the reactor pool. Accurate engineering and thorough testing proved its value and the installation went according to plan. After covering the pool top with the concrete slabs and draining the water, the radiation levels were measured. It showed that the shielding had reduced the radiation levels by the required order of magnitude, but at some locations the levels were still too high. With these measurements in hand, additional shielding was designed, constructed and applied. This proved to be adequate and after draining the reactor and pool, we started removing the concrete.

Using a hollow-drill-technique holes were cut of various lengths depending on the position of the reducer inside the concrete. The total length of the holes was more than the height of the Eifel Tower. For this type of drilling, practise and "touch-and-feel" are the key to success, as we had learned by training on the mock-up. On one occasion during drilling, a flange on the outside of the reducer was hit. The flange position was slightly different from the 50 year old drawings. We had already planned to replace the flange and we were happy to have real evidence of the exact location and condition of the reducer and flange. The last 'bit' of concrete was removed by cutting with hand tools, to avoid damaging the reducers.

After cleaning, the next step was thorough inspection and measurement of the reducers. Until this point in the project, we had been forced to rely on the afore mentioned hypothesis of the cause of the deformations and had to be alert that it could prove to be incorrect. We were able to confirm that the cause of all the deformations was galvanic corrosion, initiated by the combination of steel, aluminium and moisture. The reactor pool has an aluminium liner which is designed in such a way, that when small amounts of pool water are released due to thermal movement, they are transported to a drain system through small channels in the concrete. Some of this moisture migrated through the concrete and reached the reducers.

A very important point was that we found that the rest of the reducer material was in perfect condition and the criteria for local repair were met. In both reducers we cut a larger hole at the bottom and a smaller hole at the top. All four holes were closed with new pre-fabricated aluminium plates. The top plates were welded from within the reducers through the larger holes and then the bottom plates were welded from outside.

Despite many trials, the welding in situ proved to be more difficult than expected. After several improvement actions we succeeded in producing welds that passed the tests in accordance with the relevant standards.

After welding was completed, the cavities were filled with reinforcement bars and concrete. To prevent air being trapped during the pouring of the concrete, we installed four vents in each cavity and a camera was inserted through a vent pipe to enable monitoring the concrete filling process.

At the time of writing this article we are in the process of recommissioning the HFR equipment and controls. This will be followed by extensive testing of all systems prior to reloading the core and starting up the HFR. September 9, 2010 is the target date for full power operation and the resumption of isotopes production.

Figure 4. The welder at work.

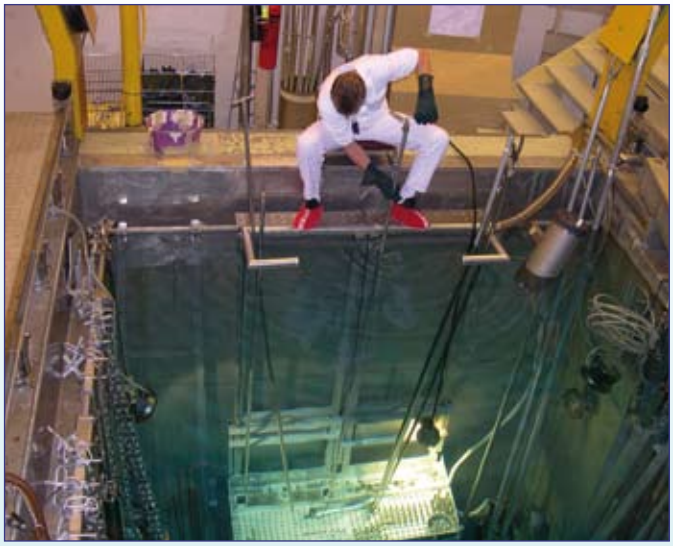

Figure 5. Loading of isotopes in the core.

Evaluation and outlook

The repair project proceeded well and according to plan. Until today we have had no safety incidents. The individual and collective radiation dose has been about half of the quite stringent limit we had set at the start of the project. We created a learning attitude within all teams involved and during execution, several safety improvement proposals were made and implemented. Our project planning involved all parties in interactive sessions leading to a project plan and detailed work plans of high quality. During project execution, at the times when reality deviated from planning, we were able to maintain the same attitude. We solved the problems with focus on safety, quality and proper decision making processes.

To secure the long term medical radioisotopes supply, we have intensified our maintenance and reliability program for all nuclear facilities at Petten. When all medical isotopes producing reactors are in service, supply and demand for these isotopes are in balance. For securing supply on the longer term however, surplus reactor capacity is necessary. Well coordinated schedules for production and maintenance continue to be of utmost importance. But replacement of the current generation of reactors and increasing the capacity for the production of radioisotopes is essential.

The end-of-lifetime of the HFR is expected to be around 2020. To secure the strength of the existing chain of the nuclear facilities at Petten for the long term, we are developing the replacement of the HFR by a new reactor, PALLAS.

About the author

Eric Jan de Widt (1948) is manager Irradiation Services at The Nuclear Research & consultancy Group (NRG) in Petten. His responsibility comprises NRG's nuclear facilities, including the High Flux Reactor (HFR). For the HFR repair project that was recently finished successfully he served as the project executive.

In the past he has served in various management positions in the chemical industry.

Eric Jan de Widt studied Mechanical Engineering at Delft University of Technology.

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Covidien's role in the supply chain of Molybdenum-99 and Technetium-99m generators

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Abstract

De Lange F. Covidien's role in the supply chain of Molybdenum-99 and Technetium-99m generators

This paper covers the immediate consequences of the recent reactor capacity reductions in Petten (Netherlands) and Chalk River (Canada) for the worldwide availability of Technetium-99m (^{99m}Tc). Covidien, one of the Molybdenum-99 (^{99}Mo) processors and ^{99m}Tc generator manufacturers, helped alleviate the isotope shortages by contracting the Institute of Atomic Energy in Poland (IAE Polatom) for use of the Maria research reactor in Poland. Communications with hospitals and radiopharmacies worldwide on ^{99}Mo availability have been intensified to enable the end users to align their procedure schedules and prioritization.

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Introduction

Covidien is a leading global healthcare products company that manufactures, distributes and services product lines including surgical and energy-based devices, respiratory and vascular therapy products, diagnostic imaging agents, pharmaceuticals and medical supplies. The company has 42,000 employees in more than 60 countries and 58 manufacturing plants in 16 countries. Its products are sold in over 140 countries. The facility in Petten, also known as "Mallinckrodt Medical B.V.", employs about 300 people. Medical isotope products are manufactured, processed and distributed, including ^{99}Mo, the key material for ^{99m}Tc generators. Covidien is one of three ^{99}Mo/^{99m}Tc manufacturers in Europe together with General Electric (GE) Healthcare and the Ion Beam Applications (IBA) Molecular group.

Supply chain

Covidien's role in the ^{99}Mo /^{99m}Tc generator supply chain is to hire irradiation capacity in research reactors, to process purified ^{99}Mo and supply to its own ^{99m}Tc generator production facilities in Petten and the United States of America (USA) as well as to ^{99}Mo customers, and to manufacture and distribute ^{99m}Tc generators. The main players and roles in the supply chain are visualized in figure 1.

Impact of recent High Flux Reactor and Canadian National Research Universal reactor shut-down periods

For many years, the Dutch HFR and Canadian National Research Universal (NRU) reactor have provided around 70% of the worldwide capacity of medical isotope capable research reactors in the world (1-3). Normally these reactors operate 75% annually. The unplanned 15-month shutdown of NRU had a major impact on global ^{99}Mo availability. The overlapping HFR planned shutdown further increased the crisis. Covidien's facility in Petten experienced a related reduction in ^{99}Mo production runs, leading to shortages in the supply of ^{99m}Tc generators to hospitals. Although the company added extra irradiation capacity to the supply chain (see 'Short-term shortage impact mitigation'), there have been instances of significant shortages.

Short-term shortage impact mitigation

Different strategies were followed simultaneously to mitigate the shortages. Research reactor schedules were aligned as much as possible through the reactor working group Association of Imaging Producers & Equipment Suppliers (AIPES). AIPES' purpose is to reach agreement on which reactor operates when, preventing primary reactors from simultaneous shutdown for scheduled maintenance. The French Osiris reactor, for example, was originally scheduled for a five-month shutdown starting April, 2010.

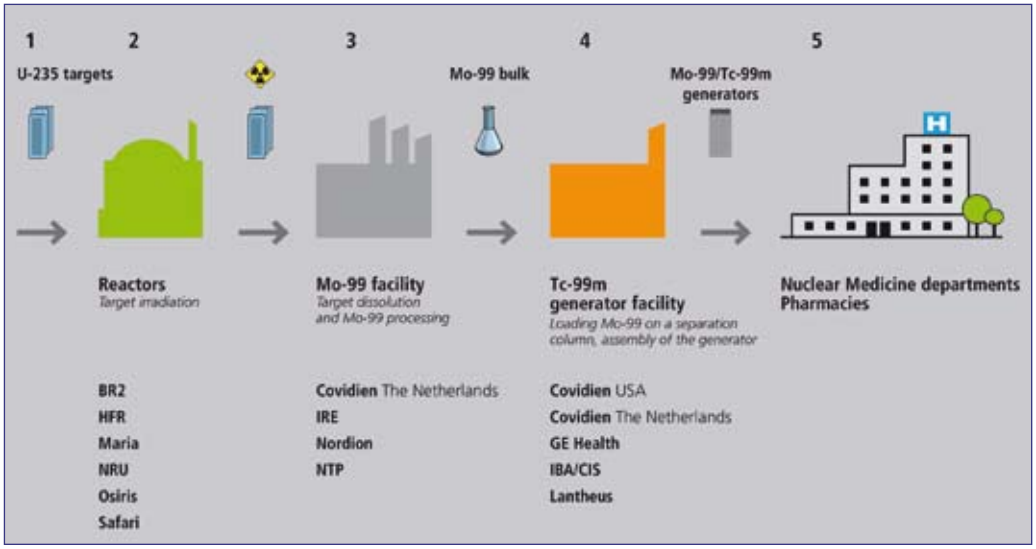

Figure 1.
Players and roles in the global supply chain of ^{99}Mo/^{99m}Tc generators. Source: Covidien, Europe, the Middle East and Africa (EMEA).

Molybdenum-99 production in Petten

The ^{99}Mo production process in Petten starts with the irradiation in a reactor of aluminium target plates holding Highly-Enriched Uranium (HEU). Three reactors being used for this purpose are the Belgian Reactor 2 (BR2), the High Flux Reactor (HFR) in Petten and the Maria Reactor in Poland (figure 1). Uranium-235 (^{235}U) is bombarded by neutrons, forming a cocktail of fission products, one of them being ^{99}Mo. A routine irradiation cycle takes 150-165 hours. After one day of radioactive decay, in order to get rid of short half-life products the uranium targets are ready to be trucked in heavily shielded transport containers from the reactor to Covidien's ^{99}Mo production facility, with the fission products still locked in the plates. During the first processing step, the target plates are dissolved in sodium hydroxide (NaOH) and then filtrated. During filtration, ^{99}Mo is separated from ^{235}U and many of the other unwanted fission products that do not dissolve. In subsequent process steps like column purification, evaporation, sublimation and final filtration, ^{99}Mo is separated from remaining isotopes like Iodine-131 (^{131}I) and purified to obtain the purest ^{99}Mo. The product is dispensed and the activity measured in an ionization chamber. A quality control sample is withdrawn for clearance testing. One production run normally takes around 12 hours, yielding enough ^{99}Mo for 40,000 to 50,000 patient doses of ^{99m}Tc. The product is packed in a container and inspected by means of leak-, dose rate and contamination tests, prior to shipment to the company's own ^{99m}Tc generator facilities in Petten and in the USA, or to external ^{99}Mo customers. Figure 2 shows ^{99}Mo production in hot cells.

Generator production in Petten

The company's facility in Petten produces the UltraTechneKow™ (UTK) ^{99m}Tc generator. The ^{99}Mo is the active pharmaceutical ingredient for the UTK generator. It is either supplied by Covidien's ^{99}Mo plant or by other ^{99}Mo suppliers like the consortium of the national Institute for Radio Elements (IRE) in Belgium and Nuclear Technology Products (NTP) in South Africa. The ^{99}Mo bulk is again measured in an ionization chamber. The activity is subdivided, diluted and formulated to achieve the right specific activity, pH and volume. Glass columns filled with aluminium oxide are placed on filling panels and thereafter the columns are loaded with ^{99}Mo. Each individual column is measured in an ionization chamber to check the activity per column. All columns are placed in boxes and steam sterilized. The sterilized generators are placed in an external lead shield and transport tin. The placement of the elution cap is the final step of the assembly. The assembled UTK generators are transported to the test-station. By pushing the elution ring, transport of saline through the column is started and ^{99m}Tc is eluted from the column, since ^{99m}Tc, the radioactive daughter of ^{99}Mo, is not adsorbed to the aluminium oxide. A set of generators from different production days, ranging from the smallest to the largest, are test- eluted daily for two weeks. Amongst others, ^{99m}Tc yield is being monitored. Finally, generators are shipped to the packing and staging department for shipment to more than 50 countries.

Figure 2.
^{99}Mo production in hot cells at the company's facility in Petten.

Since NRU was not expected to return until mid-2010 and the repair of HFR was scheduled to begin mid February 2010, Osiris maintenance was postponed until mid-June. Optimal reactor schedule alignment could not fully remove the irradiation capacity shortages. Covidien felt it to be imperative to investigate possibilities of adding irradiation capacity to the supply chain.

The company assessed Maria as the most efficient and favourable reactor to be made suitable for irradiations for ^{99}Mo production. The Maria reactor in Poland, a research nuclear reactor with high flux capacity, located approximately 30 km southeast of Warsaw, was first operated from 1975 until 1985, when it was taken off line for a complete redesign. It resumed normal operations in 1993. Maria is considered to be a relatively new reactor at a workable distance from Covidien's processing facility in Petten. After extensive pre-engineering, irradiation rigs were manufactured. HEU target storage was implemented. Handling equipment was designed and manufactured for rig loading/-unloading and transport container loading. An agreement was concluded with the IAE Polatom for several irradiation cycles. This allowed the company to meet the needs of more than one million additional patients in just the first six months after the reactor began supplying irradiation services for ^{99}Mo production. Over twenty licenses and permits from multiple regulatory agencies in five European nations were required and obtained. Extensive co-operation between IAE Polatom, Nuclear Research and consultancy Group (NRG) and Covidien made it possible to add a major resource to the medical isotope supply chain in only six months time.
Similarly, the IRE (Fleurus, Belgium) qualified and added the Czech reactor Rez (LVR-15) to the supply chain.
Covidien also invested in a dedicated additional irradiation cycle in one of the research reactors of the Nuclear Research centre in Belgium ("Studie Centrum voor Kernenergie"/"Centre d'Etude de l'Energie Nucleaire" (SCK/CEN)), Belgian Reactor 2 (BR2) (Mol, Belgium) to mitigate significant shortages in June, 2010.

Beyond increasing ^{99}Mo supply chain capacity, Thallous Chloride 201 (^{201}Tl) volumes were increased as an alternative for ^{99m}Tc, for those procedures where ^{201}Tl can be a clinically appropriate substitute.

As expected, communication throughout the shortage was crucial. Covidien applied a "fair share policy", distributing available ^{99}Mo and thus the ^{99}Mo/ ^{99m}Tc generators fairly on a global basis to minimize patient impact. This distribution method often led to production of more ^{99}Mo/ ^{99m}Tc generators with lower activity. Through frequent communications with the hospitals and radiopharmacies worldwide, using monthly letters, availability projection calendars and a dedicated web page, the company aimed to enable physicians and radiopharmacies to align their procedure schedules and prioritization with availability. Examples of projection calendars for ^{99}Mo /^{99m}Tc generator deliveries in Europe are given in figure 3.

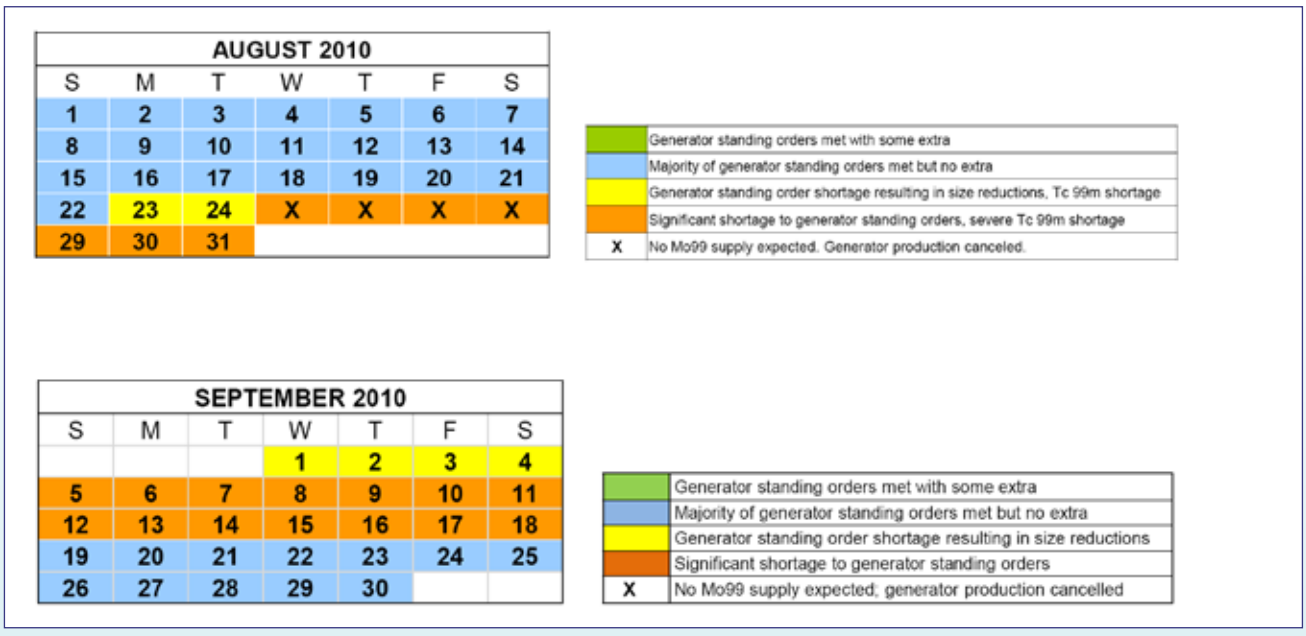

Figure 3. Projection calendars for ^{99}Mo /^{99m}Tc generator deliveries in Europe, the Middle East and Africa.

The company's Professional Services department in Petten played a key role in informing and supporting customers to help minimize patient impact, along with contact from sales representatives with expected production dates. In the continuous attempt to ensure the highest possible delivery levels, customers occasionally received their UTK orders on different shipment days than normal. Transport possibilities were taken into account: the company's distribution network by road and air had to be reorganized numerous times, because of the deviations on the regular shipment schedule. This was complicated by the fact that many flights are not available daily, and some airlines simply refuse to carry nuclear medicines.
This required effort and flexibility of all parties involved, including the physicians and nuclear medicine departments who maximized efficiency by minimizing the time between patient investigations and planning investigations during evenings and weekends.

Future supply chain improvements

With the HFR and NRU back in operation, shortages are no longer expected for now. Looking to the future, however, Covidien will focus on becoming less dependent on the aging research reactors. Multiple options are currently under investigation, including the development of a dedicated isotope production facility based on a Low-Enriched Uranium-(LEU-) fuelled Aqueous Homogeneous Reactor (as discussed by Lewis in this journal). To this end, Covidien has partnered with Babcock and Wilcox Technical Services (B&W) since January of 2009. The reactor's design will enable fuel to be recycled after ^{99}Mo is removed, minimizing radioactive waste and uranium usage. The company is also evaluating other mid- and long-term alternatives to current supply chain options.

About the author
After finishing his master degree in electronic engineering from Twente University at Enschede (the Netherlands) Frank de Lange joined Mallinckrodt in 1993 as a Cyclotron Development Specialist and was appointed head of the Cyclotron department in 2000. Preceding this appointment, he joined the Mallinckrodt Maryland Heights Cyclotron group in the US for three months. In 2005 Frank was promoted to the position of Manager Manufacturing and in 2008 he became Site Director at the Petten plant of Covidien. He is responsible for the operations and financial results of the Petten Nuclear Medicine facility and also acts as a managing director of the legal entity in Petten. Frank holds a level 3 degree in radiation safety, has been Six Sigma Black Belt trained and has led numerous Operational Excellence initiatives. One of his most recent significant project achievements was the addition of the Maria reactor in Poland to the global Molybdenum supply chain.

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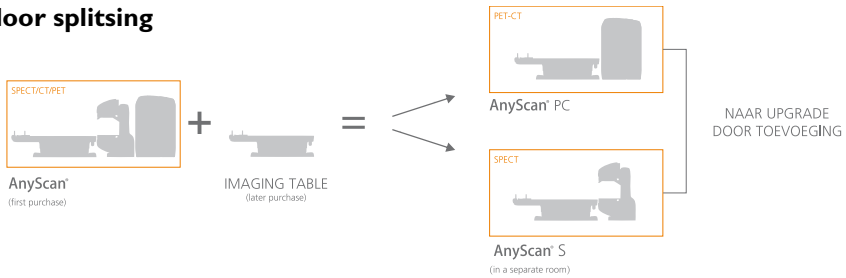

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How to make nuclear medicine a killer app for medical imaging?

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Introduction

Modern industrial companies would experience the 'molybdenum crisis' not as an ongoing nightmare, like we do, but as a challenge, as an opportunity to get rid of oldfashioned techniques, to enter modern workflows and to attract new indications and new patient categories.
In most hospitals the current Molybdenum-99 (^{99}Mo) shortage resulted in Technetium-99m (^{99m}Tc)-efficient workflows, which implicated that as many ^{99m}Tc studies as possible were carried out from the moment the generator arrived. Sometimes even weekend and evening shifts were necessary when ^{99m}Tc was plentiful available. Furthermore, it became apparent that ^{99m}Tc demand could be reduced by decreasing patient doses, which could be done without loss of diagnostic accuracy, especially with recently developed gamma cameras and state of the art SPECT algorithms.
To reduce the demand for ^{99m}Tc labeled with myocardial tracers many hospitals returned to myocardial perfusion SPECT protocols with Thallium-201 (^{201}Tl), despite less ideal imaging properties and a higher radiation dose. Although not accepted for registration yet, a few hospitals switched to Fluor-18 (^{18}F)-fluoride PET for bone imaging. Other 'tastes' to save ^{99m}Tc were not available, except for the few academic institutions in our country with cyclotrons.

From the ^{99}Mo-poor period we learned that the same amount of nuclear imaging studies can be performed with 60-75% of previous ^{99}Mo *standing orders*. This finding is not only important with regard to radiation protection, but also for budgettary reasons. The current price of a ^{99}Mo-^{99m}Tc generator is 3-4 times higher than 2 years ago and after both the National Research Universal (NRU) and the High Flux Reactor (HFR) resumed production the price of the generator certainly will not return to the level before the crisis.
One may assume that also in the future most hospitals will implement plans to cut back the use of ^{99m}Tc as much as possible. Hospitals who receive pre-filled syringes from the regionally working radiopharmacies were confronted with the same shortages and possible temporary solutions.

For almost 40 years ^{99m}Tc has been the workhorse of diagnostic nuclear medicine because of its attractive physical characteristics, convenience of on-site supply and the ability to image a variety of organ systems using chelates that can be prepared quickly, efficiently, reproducibly, and safely via kit procedures (1).

Demand for Molybdenum-99 and Technetium-99m

^{99m}Tc is the most widely used radioisotope in nuclear medicine. It accounts for 80% of all diagnostic nuclear medicine procedures.
This amounts to 7 million diagnoses per year in Europe and 8 million per year in the USA (2,4).
The present world wide demand for ^{99}Mo, the parent radioisotope of ^{99m}Tc, is estimated at 12,000 Curie (Ci) per week at '6 day curies' (the demand of the USA is 6,000 Ci, of Europe 2,000 Ci, Japan 1,000 Ci, Asia/Pacific 2,000 Ci and for the rest of the world 1,000 Ci). A '6-day curies' is meaning the number of Curies six days after the end of the production process, which is generally eight days after irradiation in the reactor is completed (2,3).
In the Netherlands 30,000 studies with ^{99m}Tc-labeled compounds are performed each month. In Europe a total of 8 million ^{99m}Tc imaging procedures in a year and worldwide around 30 million ^{99m}Tc imaging procedures per year are performed (3,4). The worldwide demand for some 600,000 doses of ^{99m}Tc per week requires 450 TeraBecquerel (TBq) of ^{99}Mo per week, which is produced by fission of Uranium-235 (^{235}U) in only five nuclear reactors: NRU at Chalk River, Canada; HFR at Petten, the Netherlands; 'Belgische reactor-2' (BR2) at Mol, Belgium; OSIRIS at Saclay, France; and SAFARI at Pelindaba, South Africa. The OPAL reactor at Lucas Heights, Australia, has recently come on line and is gradually increasing its yield (1). ^{99}Mo demands in emerging

markets like the BRIC countries (Brazil, Russia, India and China, which account for more than 40% of the world's population) are expected to grow rapidly but to what extent is difficult to predict. The major imaging equipment companies are investing heavily in these countries, future ^{99}Mo demands must be linked with installations of gamma cameras.

From the previous and current episodes with severe ^{99}Mo/^{99m}Tc shortage due to repairs of the NRU and HFR reactors it became painfully apparent that the old and vulnerable reactors represent a risc for ^{99}Mo diagnostic nuclear medicine with regard to uninterrupted clinical workflows. Despite the fact that the remaining reactors have struggled hard to ensure continuity of supply during the shutdown of the NRU- and HFR-reactors, major shortages occurred which could not be compensated by careful planning of production in the remaining 3 reactors and additional ^{99}Mo production in the Maria reactor in Poland and Rez reactor in the Czech republic.

It is quite clear that we are highly depending on ^{99m}Tc for most of our imaging procedures and that we have only very limited access to alternative radiopharmaceuticals to replace ^{99m}Tc at this moment.
In the Technopolis report 'The medical use of radiofarmaceuticals until 2025', which was written on behalf of the Dutch government before the molybdenum crisis, experts in the field of medical imaging and clinical specialists stated that the use of ^{99m}Tc labeled tracers will remain unchanged until 2015 and that probably a slow decrease may occur in the years 2015-2025 (5). Throughout these years a strong increase will occur of medical imaging in general and Positron Emission Tomography /Computed Tomography (PET/CT) and, maybe Positron Emission Tomography /Magnetic Resonance Imaging (PET/MRI), in particular. The amount of Single Photon Emission Computed Tomography (SPECT) studies will remain at the same level, but with a strong increase of hybrid studies, especially SPECT/CT. Additional to the Technopolis report, an increase of SPECT/CT scans is noted in the last few years with emerging indications in the fields of oncology, orthopedic medicine, but also in sports medicine.

Although the history of the past 50 years demonstrates that almost every 10 years a new imaging technique is introduced in the field of medical imaging, no new technology is within sight at this moment. Moreover, it takes about 18 years from the first presentations to clinical acceptance of a new imaging technique. This implies that at least past 2025 the currently available imaging techniques will dominate the imaging arena.

The Technopolis report stated that the use of ^{99m}Tc-labeled tracers remains unchanged after 2015, when several reactors approach their end of life and consequently the period that governments need to decide whether to build new reactors, but also the period that the actual construction needs to be accomplished. If the Dutch government takes the decision in 2011 to build the Pallas reactor, the first ^{99}Mo production may not be expected before 2018/2019. The timeframe for decisionmaking and construction is extremely tight. Meanwhile, recurrent shutdowns of the HFR must be feared. The French government decided to construct the Jules Horowitz reactor (JHR) which is expected to start production in 2016. The present French ^{99}Mo producing OSIRIS reactor will be closed after completion of the JHR. Multi-purpose hybrid research reactor for high-tech applications (MYRRHA), a proposed accelerator driven system is scheduled to be operated from 2022 in Mol, Belgium with an estimated capacity equivalent to the replaced BR2 capacity (6,7).
The Canadian government on one hand decided to repair the NRU, but on the other hand not to build a new reactor for production of medical isotopes. On behalf of the Canadian government a study will be performed which has to find an answer to the question if a chain of cyclotrons is able to produce enough ^{99}Mo for the country's own needs.

Future perspectives

Obviously, these are just a few cautious steps in the right direction towards uninterrupted ^{99}Mo supply. On a supra-national level decisions have to be taken to realise a chain of medical isotopes producing research reactors which are (in close collaboration) able to produce sufficient quantities of ^{99}Mo at any moment and for the whole world. Next to at least 5 research reactors dedicated to uninterrupted ^{99}Mo production a series of standby-reactors need to be available which are able to produce enough ^{99}Mo in times of serious defects in the 'main' facilities.
At this moment the contour of such a scenario becomes visible with the permission for Delft University to adapt their research reactor for ^{99}Mo production (as explained in more detail by professor Wolterbeek, also in this special journal issue).
Furthermore, MDS Nordion signed a contract with the Russian company Isotope for the production and marketing of ^{99}Mo. Under the deal, Isotope will supply MDS Nordion until 2020, starting late 2011. Finally, the 'Forschungsreaktor München II' (FRM II), a new research reactor in Munich is supposed to be able to produce 50% of European needs from 2014.

Not less important is the fact that Iodine-131 (^{131}I), Samarium-153 (^{153}Sm), Holmium-166 (^{166}Ho) and Lutetium-177 (^{177}Lu) are reactor products and can only theoretically be produced by accelerators. Amongst these are our most important therapeutic radionuclides.
Finally, it is important to realise that the production chain for radiopharmaceuticals involves companies and institutions like Nuclear Research and consultancy Group (NRG) in the Netherlands, Commissariat à l'énergie atomique (CEA) in

France and the "Studie Centrum voor Kernenergie"/"Centre d'Etude de l'Energie Nucleaire" (SCK/CEN) in Belgium, who manage the research reactors, as well as a processing industry with companies like Covidien, CIS/IBA and GE Healthcare who process the ^{99}Mo into generators ready to use.

Governments need to be aware of their responsibilities towards the huge numbers of patients who are depending on the diagnostic and therapeutic radiopharmaceuticals and need to work hard on solutions which guarantee uninterrupted disposal of these agents. It is obvious that with the realisation of a chain of research reactors and stand-by reactors the costs of nuclear medicine procedures will rise.

Several developments will determine what happens with the use of ^{99m}Tc in the period 2015-2025 (Table 1 and 2).

Roughly 75% of all non-PET studies in a general department of nuclear medicine currently are related to cardiac and bone imaging. The remaining 25% are a mixture of more than 15 different kinds of studies which, most probably, will remain ^{99m}Tc bound studies. These ^{99m}Tc radiopharmaceuticals cannot easily be replaced by different tracers. Moreover, the market for each of them is small and not economically feasible. The diagnostic strength of these studies will improve with new generations of fast solid-state gamma cameras with strongly improved sensitivities and spatial resolution (8).

It is difficult to predict what will happen with the huge amount of cardiac and bone studies. Currently, cardiac imaging is performed on a SPECT (/CT) camera, CT or cardiac MRI. Due to the recent introduction of impressive numbers of multislice CT scanners in the diagnostic armament of cardiologists many of them start to implement calcium scores and Computed Tomography Angiography (CTA) in the clinical work-up of patients with suspected coronary artery disease. The unacceptable low specificity of abnormal CTA's calls for additional functional studies. Myocardial perfusion SPECT and functional parameters from gated SPECT may be very valuable. In the next few years diagnostic accuracy of myocardial SPECT will strongly improve with the development of (absolute) quantitative SPECT techniques and improved gamma cameras (8).
In the meantime cardiac PET will become more and more accessible, first with traditional PET tracers, like Strontium-82 (^{82}Sr) generator based Rubidium-82 (^{82}Rb). In large centers with a high cardiac throughput dedicated cyclotrons will be introduced for the production of Nitrogen-13 ammonia and $H_2{}^{15}O$. In next few years many centers will work with the Lantheus agent Flurpiridaz-Fluor-18 (Flurpiridaz-^{18}F, formerly known as BMS-747158-02), which combines excellent imaging properties with a myocardial uptake strongly related to cardiac flow even at high flow rates, which makes this agent particularly interesting for absolute quantification. Depending on budgettary restrictions and available imaging time on the PET/CT scanner departments of nuclear medicine most probably will gradually shift from SPECT to PET studies. The diagnostic accuracy demands for hybrid PET/CTA studies. Future investments in new imaging equipment, training of professionals and negotiations about budgets should include discussions about the most proper technique in the local hospital.

Table 1.
Causes of decreasing use of ^{99m}Tc-labeled radiopharmaceuticals

- Competitive imaging techniques
- Awareness by clinicians
- Indications not proven
- Radiation protection issues
- Costs (radiopharmaceutical and equipment)
- Knowledge and training
- Service not 24/7 available
- Molybdenum supply
- Nuclear department too small

Table 2.
Which issues are important with regard to the future of nuclear medicine?

- Uninterrupted availability of the imaging technique
- (radiopharmaceuticals, camera´s, staff)
- Improved resolution and sensitivity of current techniques
- Rigid and internationally supported quality control programs
- Appealing new techniques/software/hardware
- Availability of staff members
- Highly trained staff
- Strong commitment of all specialists involved in Nuclear Medicine
- Clinical demonstrations and training of clinical staff
- Improved imaging technique
- Results of diagnostic imaging directly available for the clinician
- Much more specific tracers
- Nuclear Medicine specialists train and help collegues with new techniques
- Involvement in clinical trials
- Increased treatment options with radionuclides

Obviously, centers without dedicated budgets and PET (/CT) scanners will invest in ^{99m}Tc related cardiac imaging with new gamma cameras, probably in combination with cardiac CTA. At this moment more than 30% of all Dutch nuclear medicine departments have no PET (/CT) scanners at their disposal.

It is quite unclear in which way and magnitude ^{18}F-fluoride will replace the ^{99m}Tc bone imaging agents. Complex discussions about the amount of available imaging time on the PET/CT scanners, budgettary restrictions and unclear indications will hamper the rapid shift towards PET bone imaging.

Many new PET tracers are in different stages of development; they will not replace any of the current radiopharmaceuticals but will be introduced for new indications in the field of nuclear medicine. Most of these agents will be available for oncologic and neurodegenerative indications. These agents will broaden the field of nuclear medicine. Figure 1 shows the various indications for PET imaging.

Finally, a great potential lies with the Germanium-68/ Gallium-68 (^{68}Ge/^{68}Ga) generator (271 days, 68 minutes).

Most clinical experience has been gained with somatostatin receptor binding peptides for imaging of neuroendocrine tumours, but many different ^{68}Ga chelates may be produced in departments of nuclear medicine with GMP license.

Concluding remarks

^{99m}Tc labeled agents remain the workhorse of nuclear medicine for many years. Replacement of the old research reactors by new facilities is not enough; a chain of stand-by reactors throughout the world is needed to assure uninterrupted ^{99}Mo supply. It is the responsibility of governments to stimulate the construction of new reactors and to adjust smaller reactors (mainly university based) to fulfill its task as stand-by reactors.
In departments of nuclear medicine with PET (/CT) facilities gradually part of the current SPECT techniques will be replaced by PET imaging. Most new PET tracers are not commercially available currently and thus will introduce new imaging indications in the field of nuclear medicine. The exciting combination of sound traditional imaging techniques and a rapidly growing number of new indications makes nuclear medicine a potential killer app in the field of medical imaging!

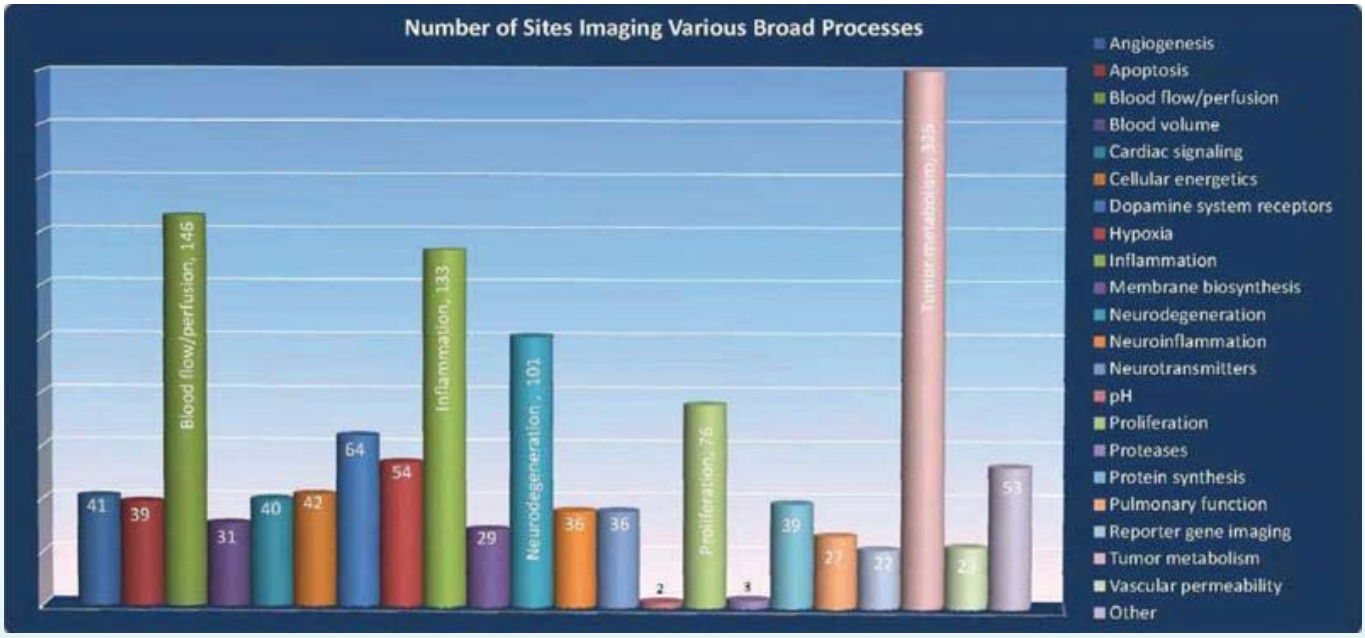

Figure 1.
Tumour metabolism was, by far the most widely-imaged metabolic process, followed by bloodflow/perfusion, inflammation, neurodegeneration and proliferation.

With permission: MI Gateway 2010, SNM Molecular Imaging centre of excellence (9).

About the author
J. Fred Verzijlbergen finished his training as internal medicine specialist in 1982 and nuclear medicine specialist in 1985.
He is head of the Department of Nuclear Medicine in St. Antonius Hospital, Nieuwegein, the Netherlands and since 1989 with a special interest in cardiac-, endocrine and orthopaedic nuclear medicine. He is member of the Board of the Dutch Society of Nuclear Medicine and President since 2006. In this period molybdenum shortages and collaboration with radiologists, physicists, radiopharmacists and radiochemists were the main themes. From January 2011 he will become President-elect of the EANM.

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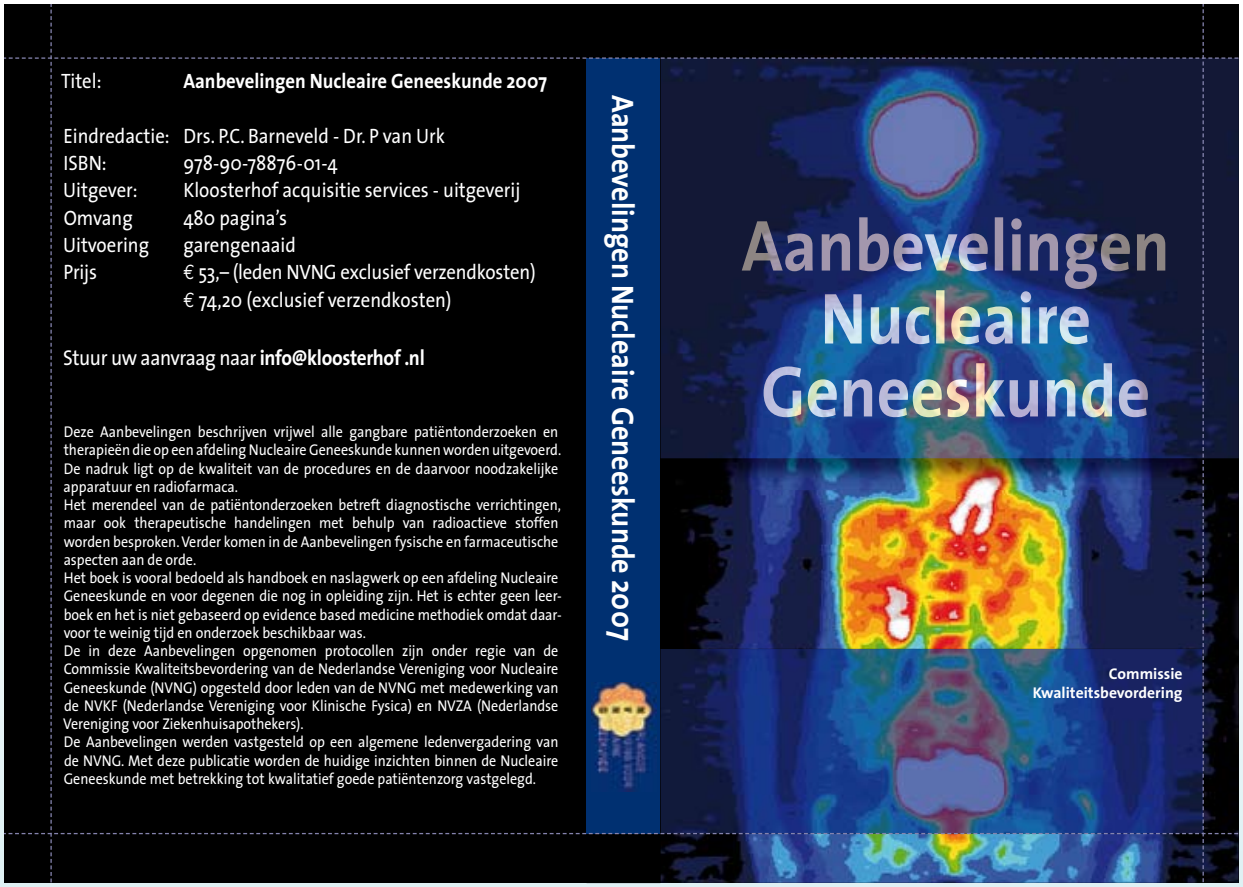

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The economics of the Molybdenum-99/ Technetium-99m supply chain

An increase in the sales price at the reactor level might be unavoidable

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Abstract

Seeverens HJJ. The economics of the Molybdenum-99/Technetium-99m supply chain

The short supply in radiopharmaceuticals during the past three years is mainly caused by technical problems in research reactors producing medical radioisotopes on an industrial scale. These reactors date from the 1950's and because of this it will be increasingly likely that more interruptions will follow. There appears, however, an underlying cause to these technical problems. The production of radioisotopes has been seen by the owners as a side-activity. As a result, over the years, the price of these isotopes has not been market conform. Necessary investments to secure the future supply of these isotopes (for example to build new reactors) appear to be very difficult. In a recent report from the OECD/NEA the economic aspects of the supply chain are studied in detail. An important conclusion is, that an increase in price of the isotopes at the reactor level would have very limited effects on the price of the end product at the radiopharmacy. The reimbursement rate, accounting for the price of the end product, the hospital facilities and the physicians fee, would also hardly be affected.

Tijdschr Nucl Geneesk 2010; 32(4):604-608

Introduction

The Nuclear Energy Agency (NEA) is a specialised agency within the Organisation for Economic Co-operation and Development (OECD), an intergovernmental organisation of industrialised countries, based in Paris, France. The mission of the NEA is to assist its member countries in maintaining and further developing, through international co-operation, the scientific, technological and legal bases required for the safe, environmentally friendly and economical use of nuclear energy for peaceful purposes. To achieve this, the NEA works as: a forum for sharing information and experience and promoting international co-operation; a centre of excellence which helps member countries to pool and maintain their technical expertise; a vehicle for facilitating policy analyses and developing consensus based on its technical work. The NEA's current membership consists of 28 countries, in Europe, North America and the Asia-Pacific region. The NEA works closely with the International Atomic Energy Agency (IAEA) in Vienna - a specialised agency of the United Nations - and with the European Commission in Brussels. Within the OECD, there is close co-ordination with the International Energy Agency and the Environment Directorate, as well as contacts with other directorates, as appropriate.

During the past three years, a few of the limited number of nuclear research reactors that also produce radioisotopes for medical purposes on an industrial scale, have been out-of-operation during a relatively long period of time. In most cases these outages were unforeseen. The High Flux Reactor (HFR) in the Netherlands, for example, was shut down from July 2008 until early February 2009 due to gas bubble formation in the aluminum wall of the cooling system and because of a significant decrease in thickness of the aluminum wall around this area. However the Dutch authorities allowed the HFR to restart its operations for a limited period of time. The operator scheduled in the

meantime an extensive repair of the cooling system lasting from February until September 2010 during which time all activities came to a standstill. In May 2009, the NRU reactor in Canada was shut down because of a leakage in the reactor vessel. The length of the period of repair was uncertain, but in the end lasted longer than at first foreseen, until 9th September 2010.
Both outages have repercussions world-wide because the HFR's estimated global market share of medical radioisotopes amounts to 30% and the NRU's share to 40%. Historically, there are only three other nuclear research reactors world-wide that are able to produce these isotopes on an industrial scale, which are the reactors in Belgium (Belgian Reactor 2 (BR2), France (OSIRIS reactor) and the Republic of South-Africa (SAFARI reactor). Furthermore there are some reactors, amongst others in Australia and Argentina, that produce for a regional market. It is therefore no surprise that these outages have caused very serious disruptions in the supply of medical radioisotopes in the years 2008-2010 (1).
Is it safe to assume that serious disruptions will not reoccur during the next years once the HFR and the NRU have undergone important repairs? Unfortunately, this assumption is very uncertain because all the above mentioned reactors (except the ones in Australia and Argentina) were built in the 1950's or early 1960's and are approaching the end of their 'life cycle'.
The Canadian government, therefore, took the initiative to convene a meeting with all stakeholders in the field of radioisotopes for medical use (i.e. from reactor operators to nuclear medicine specialists) to discuss the current situation and to explore future developments (2).
The meeting took place in Paris in January 2009 and was organised by the OECD/NEA. Following this meeting the NEA secretariat established a High-level Group on the security of supply of Medical Radioisotopes.

The High-level Group on the security of supply of Medical Radioisotopes

The High-level Group on the security of supply of Medical Radioisotopes (HLG-MR) undertook an initial review of the past, current and future situation of nuclear research reactors with regard to the production of medical isotopes and examined the supply chain (i.e. from reactor to end-user) as a whole. Based on this initial examination, it arrived at the tentative conclusion that the problems in recent years have not only been on a technical level, but might also have been on the level of a market failure in the Molybdenum-99 (^{99}Mo) supply chain. To further explore this important suggestion, the HLG-MR asked the NEA Secretariat to perform an economic study on the full supply chain. This report has recently been published under the auspices of the OECD/NEA (3). In this article I will discuss some important points from this report. With regard to the current situation it is important to be aware of the historical situation that all large scale producing reactors were built to do basic research and in particular applied nuclear technology research. This research has been the main focus of activities during the early years and in some reactors this is still the case. The production of medical radioisotopes started on a relatively small scale as a side activity. However, this production gradually increased in importance and it turned into an important – though not the most important – activity within the reactor. Especially from the late 1980's onward the production of isotopes continued to grow. However, research reactors were financed, built and owned by national governments (4). Operating and maintenance costs as well as major refurbishments or future decommissioning and replacement costs were also paid by governments. Isotope production, although as stated above an important activity within the reactor, was still not considered as a revenue source to support any share of these broader costs. Other factors that have contributed to this situation relate to the interaction between the processing units and the reactors. Generally, there are less processing units than reactors and this, combined with some excess production in the past and established contracts, has led to a certain negotiating power for the owners of the processing units over the reactor owners. The result of these combined factors is that the price paid for the isotopes from the reactor does not reflect a sustainable market price, namely a price via which a reactor can produce ^{99}Mo in an economically sound manner. It has become clear that the insufficient income for reactors has led to the current situation where capacity building with the aim to sustain a reliable supply now and in future has fallen behind. In other words, based on the current economic structure, there are insufficient financial incentives to develop additional infrastructure for the production of these isotopes. There is therefore currently a situation of market failure, the NEA report concludes. The report has arrived at this conclusion by studying not only the historical situation but also by analyzing data from all relevant stakeholders in the supply chain. The report suggests that changes are required and it offers several options. In fact, before considering these options, the report states unequivocally that the current situation is unsustainable and that to reach a sustainable situation, changes in the supply chain's economic structure need to be made. The supply chain is shown in figure 1.

Reactors

Historically, there were five reactors producing ^{99}Mo on an industrial scale, providing 90 to 95% of the global supply. These reactors were originally built and operated with full government funding. Gradually isotope production developed, but the produced isotopes were - and in fact still are - considered as a by-product of the reactor activities, notwithstanding the fact that isotope production has become an increasingly important activity within the reactor. However, the sales price of the produced isotopes did

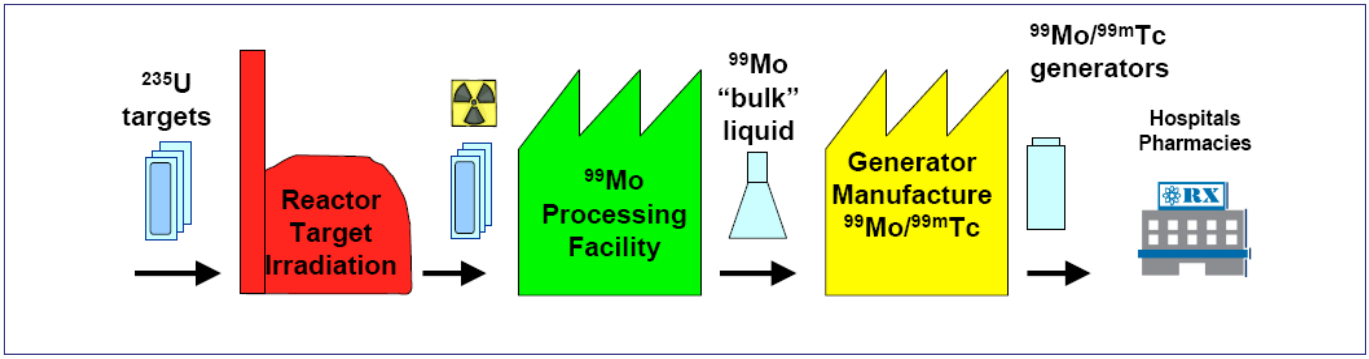


Figure 1. ^{99}Mo Supply Chain (with permission: Ponsard, 2010) (5)

not and still does not reflect the overall costs of operating and maintenance of the reactor, let alone other aspects such as nuclear waste management, refurbishment or decommissioning.

Processing

The processing component in the supply chain was originally also funded by governments, but in the 1980's and 1990's these activities were separated from the reactor activities and commercialised. However, this did not result in significant changes in price of the isotopes from the reactor; rather the historical situation with low prices continued and was built into long-lasting contracts between the reactors and processing units. This historical development, combined with the historical existence of excess reactor capacity, has led to a certain market power for the processors.

Generator manufacturers and hospital pharmacies

Further down the supply chain the manufacturers of generators continue to pay a low price for the isotopes, but increase their income through the coupling of the isotopes with the relatively high sales price of the cold kits. In radiopharmacies the isotope is made available as a radiopharmaceutical product for administration to the patient. The ^{99}Mo is undervalued in the price of the generators and the effect of this is that the upstream prices of ^{99}Mo will continue to be low as well.

It is evident that along the supply chain, during each step, an increasing value is added to the reactor product – otherwise it couldn't be administered as a radiopharmaceutical product – and that by consequence the sales price of the radiopharmaceutical at the end of the supply chain is much higher than the price of the reactor product. This difference in sales prices may be fully justified. Even so, the current sales price of ^{99}Mo at the reactor would appear to be too low to be considered in line with market requirements for economic sustainability.

Price development along the supply chain

Using data gathered on prices (pre-shortage) from stakeholders in the supply chain, the NEA secretariat calculated representative prices for each step in the supply chain (6). The sales price of ^{99}Mo 6-day curie end of production (EOP) at the reactor is €45, at the processor it is €315, at the generator manufacturer this is €375 and at the radiopharmacy the price is €1,810.

According to the report the marginal revenue from production was lower than the marginal costs, with reactors in fact losing approximately €26 per 6-day curie EOP. However, it is even more important to understand the percentage net revenue of each stage in the supply chain based on the final reimbursement rate.

The median value of a ^{99m}Tc dose is €11. This amount can be broken down as follows. The reactor receives €0.25, the processor €1.65, the generator manufacturer €0.35 and the radiopharmacy €8.60. The price of the total radiopharmaceutical (i.e. ^{99m}Tc and cold kit combined) is about €39. The median amount paid as reimbursement is €245.

Comparing these figures as percentages calculated against the full reimbursement we find that the reactor receives 0.11% (0.25 / 245), the processor receives 0.67%, the generator manufacturer 0.14% and the radiopharmacy 3.51%. These figures demonstrate a remarkable price difference between the molybdenum sold by the reactor operator and the molybdenum sold by pharmaceutical companies to end users.

The reimbursement rate is, understandably, even higher, because reimbursement also pays for hospital facilities, nuclear medicine specialists and technicians and the like.

It would appear to me – and the report makes the same comment – that raising the sales price of the isotope at the reactor level (even if one would multiply it several times) would only have a marginal influence on the price patients or health insurers would pay as reimbursement for the procedure. This would also make sense because an increase in the price of a commodity (in this case ^{99}Mo) does not imply that additional effort is required down the chain that

would justify a steep increase in price along the supply chain and certainly not a steep increase in reimbursement.
The sales price of the reactor product forms, as demonstrated, only a small fraction of the sales price at the hospital pharmacy. Even significant changes in sales price at the reactor level would only have a limited impact on the price at the hospital pharmacy level and even a smaller effect on the reimbursement level.

The question arises why reactors continue to produce these isotopes on an economically unsound basis? The answer is that governments continue to pay for the reactors, including its waste management. Recently however, governments have begun questioning this situation, one reason being an increased awareness of the level of subsidisation for the less-than-commercial production of medical radioisotopes that are the basic compound of pharmaceuticals commercially marketed by others world-wide, but also the awareness that this non-profitable production supports other countries' health-care systems. This realisation makes governments as owners of the research reactors reluctant to further invest in older reactors. The shortages during the last few years may therefore be a symptom of the current unsound economic situation. Furthermore, governments also hesitate to invest in the building of new reactors that have production of medical radioisotopes as an important activity. With regard to the above governments may reappraise their financial involvement in the currently existing reactors or the building of new reactors.
In fact, the NEA's report states as its first recommendation that governments should define their financial involvement in current and future reactors. Ideally, governments should harmonise their position regarding financing, with governments from other producing nations. Nevertheless, the NEA's report offers three options, namely a traditional model, a modified traditional model and a commercial model. In the traditional model a national government builds and finances a research reactor. The government would also finance maintenance, replacement and decommissioning. In the modified traditional model the government would only finance the construction of the reactor. The reactor would operate on a commercial basis and it is clear that sales price would reflect these operating costs, including maintenance, replacement, nuclear waste management and so on. In the commercial model the portion of the reactor facility attributable to the ^{99}Mo production (and other medical radioisotopes I suppose) will be funded on a completely commercial basis. Governments would be still involved in funding the other non-commercial uses of the reactor.

Conversion from highly enriched uranium to low enriched uranium targets

Another factor that will become increasingly important in the coming years is the conversion for nuclear non-proliferation reasons from highly enriched uranium (HEU) targets to low enriched uranium (LEU) targets. Before this conversion can take place technical adjustments need to be made inside the reactors and at processing facilities. Therefore it is important to note that if a processor is required to deliver the same yield of radioisotopes the nuclear waste evidently will increase. At the moment it is not known with certainty what the financial consequences will turn out to be for the major producing reactors. Recognising this uncertainty, the report undertakes a simplified scenario that assumes limited advances in target design and finds that, even under this restrictive scenario, such a conversion would have a limited effect on the price to be paid by the end users. The National Academies in the USA suggest in their recent report about this conversion that the influence on the price will be rather limited (7).

Reserve capacity

Historically, every reactor has some reserve capacity to produce medical radioisotopes. To date this capacity has been important in those situations where another reactor had been shut down for a – foreseen or unforeseen - prolonged period of time. Continuing this reserve capacity (and building it into new reactors) is therefore important. It is also important to find a mechanism to pay for the development, maintenance and not using reserve capacity. The NEA-report highlights that the current market price does not compensate reserve capacity and therefore reactor management could be tempted to use the reserve capacity in the regular process rather than leaving it idle. This could result in lower prices for irradiation as a result of increased competition with other reactors, ultimately resulting in a downward spiral and the sales price would again be less than necessary for sustainable pricing. To prevent this downward trend, coordination between reactors is necessary, along with the creation of a payment mechanism. The question is how far this coordination could go without trespassing antitrust regulations. The NEA report states that there are lessons to be learned about payment mechanisms in the liberalised electricity market, but that the experience is not directly transferable. The report suggests a few mechanisms, including charging security premiums or creating a reserve capacity credit system, noting that further examination of the options is required.

Conclusion

The NEA has written a report on the economics of the supply chain of ^{99}Mo/^{99m}Tc. This report demonstrates that the current and future supply chain of this isotope is unsustainable unless changes are made. These changes are particularly important with regard to the sales price of the isotopes at the reactor level. A substantial increase in price at this level would result, according to the report, in a limited increase in price of the end product (i.e. the radiopharmaceutical to be administered to the patient) and would have even less influence on the reimbursement rate.

There are some uncertainties regarding the future price. One of these is how the retain of a (necessary) reserve capacity should be reflected in the sales price of reactors. Another uncertainty is what the effect on the price will be of the future change of HEU-targets to LEU-targets in reactors. The report provides three main options for changes to be made in the funding and operation of research reactors, although it does not give a preference for one of these options. That remains in fact the remit of national governments.

Acknowledgements
Chad Westmacott and Ron Cameron, the secretariat of the Nuclear Energy Agency at the Organisation of Economic Cooperation and Development (OECD/NEA).

Disclaimers
The views expressed in this article are the author's personal view and do not express the views of the Ministry of Health, Welfare and Sport of the Netherlands nor the view of OECD/NEA.

About the author
Harrie J.J. Seeverens worked from 1977 until 2002 as an internal medicine specialist in the field of general internal medicine, oncology and nephrology. In 1994 he started working parttime as a policy advisor at the Department of Pharmaceutical Affairs and Medical Technology at the Ministry of Health, Welfare and Sport, in the Netherlands. Since 2002 he has a fulltime position at the Ministry. While there, he has gained experience on dossiers about Orphan Drugs and Rare Disorders, Medicines for Children and Radiopharmaceuticals.
He represented the Netherlands in the Committee for Orphan Medicinal Products (COMP) in the European Community (EMEA, London, UK) from April 2000 – April 2006 and he will be representing the Netherlands in a new European committee for Rare Disorders and Orphan Drugs, just started in December this year.
His work approaches the field of Nuclear Medicine as he became Vice-chair of the High-level Group on the security of supply of Medical Radioisotopes last June.

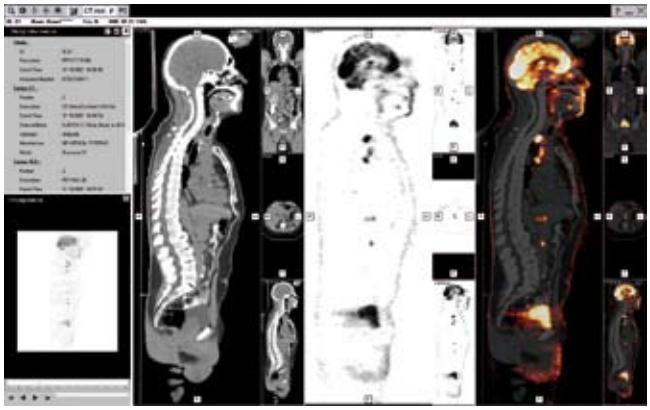
Notes and References

1. In the first half of 2010 two other research reactors (in Poland and in the Czech Republic) have started to produce ^{99}Mo
2. The reader should be aware that radioisotopes for medical use in this setting refer to Molybdenum-99 because this isotope and its daughter Technetium-99m are quantitatively by far the most important of all isotopes for medical uses
3. The Supply of Medical Isotopes: An Economic Study of the Molybdenum-99 Supply Chain. OECD-Nuclear Energy Agency, 15 September 2010. http://www.nea.fr/med-radio/reports/MO-99.pdf
4. The HFR started its activities in 1961. Shortly thereafter the reactor changed ownership from the Dutch government to the European Commission. The operator of the HFR is an independent Dutch company, the Nuclear Research & consultancy Group (NRG)
5. Ponsard, B. '^{99}Mo Supply Issues: Report and Lessons Learned'. Paper presented at the 14th International Topical Meeting on Research Reactor Fuel Management (RRFM 2010), Marrakech, Morocco, 21-25 March 2010. Published by the European Nuclear Society, ENS RRFM 2010 Transactions, ISBN 978-92-95064-10-2
6. The results of these calculations should be considered as approximations based on the data provided by the stakeholders.
7. National Research Council of the National Academies (2009). Medical Isotope Production Without Highly Enriched Uranium. The National Academies Press, Washington, DC

iSOFT Radiology:

Snelheid en Kwaliteit in Nucleaire Geneeskunde

De afgelopen jaren groeit het aantal radiologische verrichtingen sterk in Nederland. Stijgingen van meer dan 10% zijn geen uitzonderingen en in het aantal Sanderspunten zien we zelfs stijgingen van 150%. Ook het aantal te diagnosticeren beelden is de afgelopen jaren explosief gegroeid. Gelijkertijd verandert de complexiteit van de zorgvraag. De discipline ontwikkelt zich: nieuwe behandelmethoden dienen zich in een snel tempo aan hetgeen grote flexibiliteit van de clinicus en de radioloog verlangt.



iSOFT Radiology - de opvolger van RADI - speelt in op deze continue verandering in de radiologische discipline. Deze procesgeoriënteerde softwareoplossing is speciaal afgestemd op de eisen van de hedendaagse radiologie. De oplossingen voor nucleaire geneeskunde, radiotherapie en radiologie zijn dusdanig ontwikkeld dat deze direct bijdragen aan een efficiënte organisatie en communicatie op uw radiologieafdeling. Met iSOFT Radiology heeft u volledig controle over uw proces, waardoor de patiëntveiligheid binnen de zorgketen significant verbetert.

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Het belangrijkste doel van het Radiologisch Informatiesysteem (RIS) is een efficiënte en patiëntveilige ondersteuning van het radiologisch werkproces. De nieuwe QualityManager-module verhindert bijvoorbeeld dat er onderzoeksaanvragen zonder gerechtvaardigde indicatie worden uitgevoerd. Met iSOFT Radiology kunt u de structuur en het procesverloop binnen de radiologische afdeling – over meerdere locaties – precies weergeven en waar nodig optimaliseren. Bij deze optimalisatie wordt u geholpen door een speciaal ontwikkelde analyzer die uw managementinformatie in beeld brengt.

Door de uitgebreide configuratiemogelijkheden van de orderformulieren worden overbodige onderzoeken voorkomen en wachttijden verkort. Deze orderformulieren zijn zodanig ingericht dat uw medewerkers zich volledig op hun kerntaak kunnen concentreren. De werkdruk daalt, met name voor de ondersteunende functies. Samen met een goed geïntegreerd PACS, ongeacht van welke leverancier, kan de radioloog vanuit een werkstation onderzoeken beoordelen en verslaan. Het PACS wordt integraal met een digitaal dicteersysteem in de workflow van iSOFT Radiology opgenomen.

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Met de ordermodule kan het radiologisch onderzoek vanuit iedere aan het ZIS gekoppelde werkplek worden aangevraagd. Desgewenst zorgt iSOFT voor een naadloze integratie met applicaties op andere afdelingen, om een optimale interdisciplinaire data-uitwisseling te realiseren. Ook externe (huis)artsen kunnen radiologisch onderzoek aanvragen en uitslagen of beelden ontvangen. Alle betrokken partijen worden daarnaast direct geïnformeerd over gewijzigde of geannuleerde afspraken.

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Nieuw is de DemoNavigator, een speciaal ontwikkelde module om het interdisciplinair overleg voor te bereiden en te leiden. Met de DemoNavigator kunt u alle informatie van een patiënt (beelden, vorige onderzoeken, aantekeningen e.d.) aan een demonstratielijst toevoegen en deze overzichtelijk presenteren tijdens patiëntbesprekingen.

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Alternative methods for producing Molybdenum-99

Prof. D.M. Lewis *European Organisation for Nuclear Research (CERN), Geneva, Switzerland*

Abstract

Lewis DM. Alternative methods for producing Molybdenum-99 The use of nuclear medicine imaging, often referred to as molecular imaging, has increased substantially over the last two decades with Technetium-99m being the most commonly used radionuclide. It is supplied in the form of Technetium-99m/Molybdenum-99 generators and there exists a whole industry supply chain to provide the basic radioactive raw material Molybdenum-99. The production method is based on Uranium-235 fission in research reactors followed by fission radiochemistry and pharmaceutical finishing processing. Industry relies on Government owned research reactors for the irradiations and all the most suitable Molybdenum-99 producing reactors are ageing and prone to unscheduled maintenance and repair.
In 2009/2010, the two most prolific Molybdenum-99 producing reactors were shut down for extended periods for repairs with the result that the world's nuclear medicine community suffered numerous shortages of Technetium-99m. This production crisis has stimulated several organisations and laboratories to evaluate and to propose different methods of producing Molybdenum-99. This paper reviews conceptually many of these alternative methods and provides a commentary on the industrial infrastructure changes that would be necessary to implement some of these new methods. In addition to the cost of development and the capital costs of constructing new facilities, there may be additional expense in providing the starting materials, in disposing of the radioactive waste and in licensing with the nuclear and pharmaceutical regulatory authorities. Therefore the decision to initiate an alternative method of production becomes a major economic challenge.
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CERN

The European Organisation for Nuclear Research (CERN) operates the world's leading laboratory for particle physics finding out what the universe is made of and how it works. Founded in 1954, CERN has become a prime example of international collaboration, with 20 Member States. Additional nations, from around the globe also contribute to and participate in the research programme. The CERN site sits astride the Franco-Swiss border near Geneva. Its new flagship research facility, the Large Hadron Collider, is housed in a 27 kilometre tunnel under the plain between Lake Geneva and the Jura mountains. The technologies developed at CERN such as particle accelerators, detectors and software have direct applications in medical therapy and nuclear medicine.

Introduction

The radioisotope Technetium-99m (^{99m}Tc) is the most commonly used radionuclide in nuclear medicine imaging and accounts for around 80% of all such imaging procedures being performed. In 2009 it is estimated (1) that globally a total of almost 40 million procedures per year were performed in nuclear medicine and this equates to around 120,000 patient injections using ^{99m}Tc each day. The reasons for this extremely high dependence on just one radionuclide are essentially two-fold:

- Single photon emission scintigraphy is the predominant nuclear medicine imaging method and of all the possible radioactive nuclides, ^{99m}Tc is the most suitable for imaging with the present day Single Photon Emission Computed Tomography (SPECT) cameras, and
- For economic and customer convenience aspects, the delivery of ^{99m}Tc via the ^{99m}Tc/Molybdenum-99 (^{99}Mo) generator is superior to those for any other radionuclide.

The 3-day half-life radionuclide ^{99}Mo is the parent of ^{99m}Tc and its manufacturing is based on radiochemical extraction from highly radioactive fission Uranium-235 (^{235}U) targets which have been irradiated in nuclear research reactors. The central challenge to ^{99}Mo production in 2010 is that there are few research reactors in the world suitable for large-scale ^{99}Mo production and all these reactors are aged and require significant maintenance and expenditure to maintain their nuclear operating licence status. The enforced shutdown (2,3) of two of these major ^{99}Mo producing reactors in 2010 for the repair of ageing components has highlighted the precarious state of the global production environment.

The production of Molybdenum-99

The overall supply chain for ^{99}Mo manufacturing is complex, expensive and poses both chemical and radiological hazards and all the following steps are required:

- Mining of uranium ore
- Conversion to yellow cake
- Chemical conversion to gaseous uranium-hexafluoride (UF6)
- Isotope separation of ^{235}U from natural uranium
- Enrichment of ^{235}U to > 90% (i.e. highly enriched uranium (HEU)) for ^{99}Mo targets
- Fabrication of HEU targets
- Neutron irradiation of ^{235}U targets in high flux research reactors
- Radiation 'cooling' of irradiated targets
- Radiochemical extraction of ^{99}Mo
- Disposal of highly radioactive waste products
- Purification and preparation of radiopharmaceutical grade ^{99}Mo
- Delivery of ^{99}Mo to the factories of generator manufacturing companies
- Loading of ^{99}Mo onto alumina columns for insertion into generator units
- Delivery of generators to nuclear medicine and radiopharmacy customers

The whole manufacturing process must be carried in a 'just-in-time' manner because of the decay nature of the radioactive ^{99}Mo, whilst complying with all appropriate nuclear and pharmaceutical manufacturing regulatory requirements. The capital costs of these facilities are high but are in effect amortised by the nuclear power establishment whilst the operating expense and material costs are paid by the industrial companies involved in the business of supplying ^{99}Mo and manufacturing generators. Nevertheless the existing supply chain is technically mature and well adapted to supplying regular, reliable quantities of ^{99}Mo at economic levels provided that enough of these key research reactors keep operating. However the financial structure of this global supply chain depends on ongoing commitments by a few governments and nuclear research laboratories.

Alternative Methods of ^{99}Mo Production

The shutdown in 2009/2010 of two of the most important research reactors for ^{99}Mo production with a consequential reduction of world production capacity of 60 to 70% has stimulated a great amount of new proposals and indeed several new innovative methods for producing the much needed ^{99}Mo radionuclide. However implementing alternative methods of generating a radionuclide creates additional infrastructure demands:

- an alternative method invariably relies on a different nuclear reaction for the production e.g. by bombarding a nuclide by a proton (p) en producing a new nuclide and 2 neutrons (2n), denoted by (p,2n)
- a different reaction may involve a different source of radiation e.g. a superconducting linear particle accelerator (linac)
- new starting materials may be required, invariably necessitating different isotope enrichment e.g. > 95% Molybdenum-100 (^{100}Mo)
- new radiochemistry methods may be needed both for extraction of the radionuclide product and the recovery of the valuable starting materials
- any new production method will be subjected to the expense and the uncertain delay of radiopharmaceutical regulatory licensing
- a different method may force the manufacturer to establish new facilities and different logistics for the delivery of the product

Consequently the decision to set up an alternative method will be based not just on the technology or capacity criteria but on a full economic and comprehensive business evaluation. Of the numerous alternative production methods which have been proposed, eight are outlined below.

1. Neutron capture irradiation

Before fission production was used, the original method of producing ^{99}Mo was by the neutron capture reactions with thermal neutrons: Molybdenum-98 (^{98}Mo) (n, γ) ^{99}Mo, i.e. by bombarding ^{98}Mo with a neutron, ^{99}Mo and a photon (γ) are produced. The starting material may be natural molybdenum whose natural abundance of ^{98}Mo is only 25% or ^{98}Mo enriched to levels greater than 90%. However the reaction cross section is low: approximately 0.14 barns compared to the very high level of fission production of 586 barns with 6% efficiency for ^{99}Mo generation. It is not only the production volume output that is low but the specific activity, i.e. the quantity of radioactive ^{99}Mo per unit total mass of Mo is low; the neutron capture method typically generates 10 GBq/g compared to > 10^4 GBq/g with the fission process. Due to the low absorption of Mo onto alumina columns, only generators with extremely low activity can be assembled from this method and the quantities of eluted ^{99m}Tc would not be suitable for modern day ^{99m}Tc cold kits. Several methods such

as solvent extraction and distillation have been attempted; even the use of the Szilard-Chalmers extraction route has been attempted (4). One successful approach has been to use more molybdenum-acid gel materials which permit significantly more molybdenum uptake on the generator column. Materials such as zirconium molybdate and titanium molybdate gels have been successfully used in certain countries where lower numbers of generators with activities less than 37 GBq are needed to satisfy local markets. An international programme of research coordination meetings has been set up by the International Atomic Energy Agency (IAEA) to stimulate development of gel generator technology. In general this method requires much more target material, significantly more reactor irradiation space and new generator designs but avoids all the downside aspects of using uranium. In 2010, the United States Department of Energy (DoE) has awarded funding to General Electric (GE) Hitachi Nuclear Energy (5) to develop this method further using target irradiation in commercial power reactors.

2. Liquid core reactors

One innovative way of using the fission reaction for the production of ^{99}Mo is the proposal to develop aqueous homogeneous reactors (AHR). It has been reported (6) that over 30 different models of AHR's have already been designed and built in the USA and other countries. More notably there is at least one report of generating ^{99}Mo material that satisfies the general pharmacopoeia standards (7). The current proposal is by the established United States nuclear utility operator Babcock and Wilcox Inc (8) who has a development agreement with the radiopharmaceutical supplier Covidien Inc. It is reported that this project has also received development funding from the United States DoE in 2010 (9). This Medical Isotope Production System (MIPS), shown in figure 1, does not use a traditional solid reactor fuel element but a circulation liquid containing salts such as uranyl nitrate containing low enriched uranium (LEU) at approximately 20% ^{235}U. The reactor arrangement is intrinsically safe and has a large negative reactivity with the aqueous fuel operating at 80° C and at atmospheric pressure. Further advantages of the design are a low power rating of 200 kW (cf. a research reactor of 20 to 140 MW) and extremely small dimensions. The ^{99}Mo will be generated continuously in the circulating fuel within the thermal neutron field of the AHR and this provides an extremely efficient access to the available neutron flux. The ^{99}Mo will be extracted regularly from the fuel by chromatographic methods, but radiochemical methods of extraction, purification and product finishing methods will need to be developed and licensed. Liquid fuel handling and waste management procedures will also be needed and it is claimed that one MIPS unit would be capable of producing approximately 37 TBq per week which amounts to around 7-8% of the current world demand for ^{99}Mo. Although several earlier AHR's have received operating licences in the USA, approval by the Nuclear Regulatory Commission (NRC) will be a major challenge. In addition, radiopharmaceutical licensing requirements by the Food and Drug Administration (FDA) will pose further obstacles for commissioning this very innovative but untested alternative for producing ^{99}Mo.

3. Cyclotron produced Technetium-99m

Accelerators offer alternative production routes and using cyclotrons the reactions ^{100}Mo (p,2n) ^{99m}Tc and ^{100}Mo (p,pn) ^{99}Mo have been considered (10). Both have low cross sections necessitating high intensity cyclotron beams and the cyclotron energies required are 24 and 40 MeV respectively. The additional cyclotron technology demands have ruled out the (p,pn) route, but the (p,2n) reaction method has been recommended by the Canadian Expert Review Panel on Medical Isotope Production. It is judged that a centralized manufacturing facility will not have the capacity to supply large geographic markets with the short lived ^{99m}Tc radionuclide but a distributed national network of individual

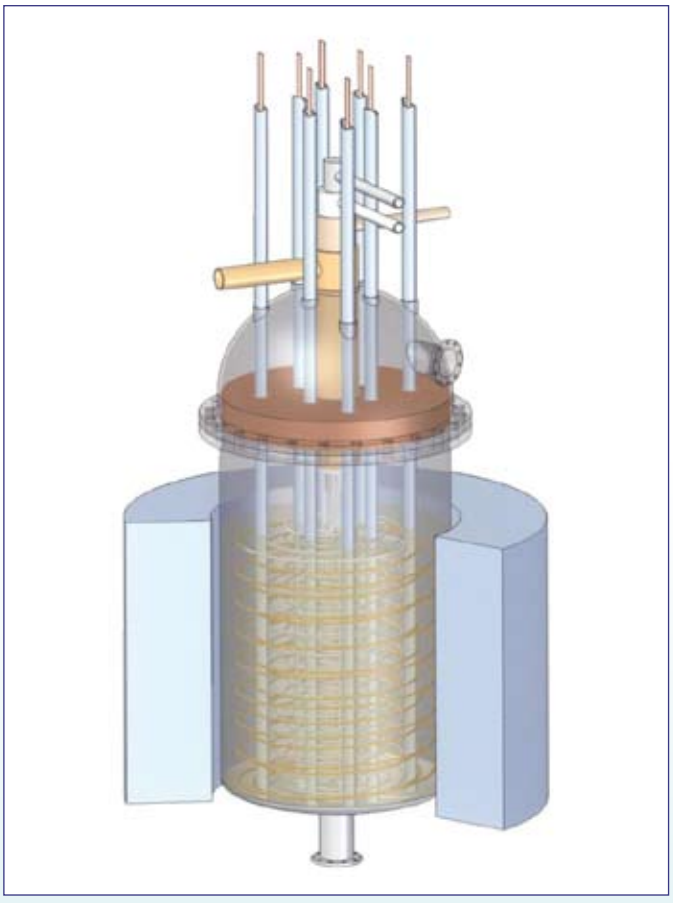

Figure 1.
Schematic of MIPS, the Medical Isotope Production System (Courtesy of B&W Inc.), showing the helical structure of the aqueous reactor core, its cooling system, its biological shield. The small dimensions of this reactor allow installation in a small sized facility.

centres may be appropriate. It has been estimated that 3 or 4 dedicated cyclotron facilities could meet all Canada's national need for ^{99m}Tc which represents some 5-6% of the global demand. In fact, because of the vast geographic separation of Canadian cities, it is likely that 8 to 10 cyclotron sites would be needed. Proof of concept studies have been carried out at TRI-University Meson Facility (TRIUMF) (11), and the Vancouver based company Advanced Cyclotron Systems Inc has a suitable design, as shown in figure 2, for a 24 MeV, 500 µA compact cyclotron (12). The starting material for this reaction is ^{100}Mo which is not readily available and has a natural abundance of only 10%. The supply of 98% enriched ^{100}Mo supply will require significant isotope separation capacity. The ^{100}Mo bombardment targets are likely to be small, i.e. 1 to 3 grams and molybdenum will be a robust target material due to its high melting point and stability. Rapid radiochemical extraction of the short lived ^{99}Tc from the ^{99}Mo target will have to be optimized as well as the recovery of the expensive ^{100}Mo. Careful attention to the radionuclidic impurities in the ^{99m}Tc will be needed before a pharmacopoeia standard is agreed. The levels of ^{99}Tc present in the final may influence the design of processing and delivery schedules. Radioactive waste arising from this method will be low and an efficient logistical delivery system will have to be created. It is clear that a production system of this type will become available in Canada in the near future.

4. Photonuclear production of Molybdenum-99

In the effort to design higher production output systems for ^{99}Mo, the photonuclear reaction route (13) has been proposed: ^{100}Mo (γ,n) ^{99}Mo. High power electron accelerators are used to bombard high heat-capacity, high-Z convertor targets and the resulting photon field or bremsstrahlung radiation is directed at a secondary production target of ^{100}Mo. Advantage can be taken of the high cross section of the large dipole resonance reaction, as shown in figure 3, which occurs at photon energies of around 15 MeV which would require incident electron beam energies of 35 to 50 MeV. These technical requirements are not so far removed from available equipment and the latest proposal (14) recommends the use of two systems using 35 MeV electron linacs each with a 100 kW beam capability bombarding either liquid mercury or water cooled tungsten convertor targets. The ^{100}Mo production targets could be as small as 30 grams each, with dimensions of approximately 2 cm diameter by approximately 2 cm long. It has been proposed to extend the design of an existing linac supplied by Mevex Corporation to deliver a 100 kW beam load, which would require electric power consumption of 600 kW. Two such systems are estimated to be capable of supplying the whole of the Canadian national requirement for ^{99}Mo, and a different automated chromatographic separation technique has been proposed for selectively separating the ^{99}Mo from the technetium.

5. Photofission production of Molybdenum-99

An extension of the previous method has been suggested (13) which would employ the photofission reaction Uranium-238 (^{238}U)(γ,fission) ^{99}Mo. In this case the starting material would be the much safer uranium isotope ^{238}U. Again the system would be a high power electron beam incident on a high heat capacity target, the resulting photons striking a small ^{238}U production target creating fission reactions with the same

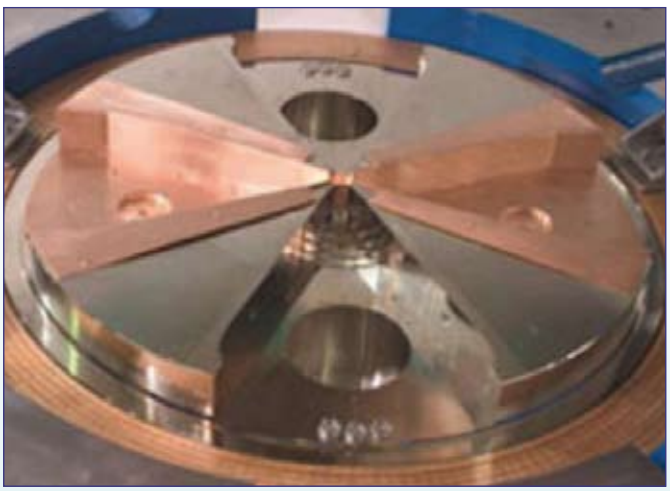

Figure 2.
Photo of the TR-24 Cyclotron magnet system, (Courtesy of Advanced Cyclotron Systems Inc.) demonstrating a relatively simple 'hill and valley' magnet design with fourfold symmetry. The TR-24 cyclotron will be capable of producing SPECT and Positron Emission Tomography (PET) radionuclides.

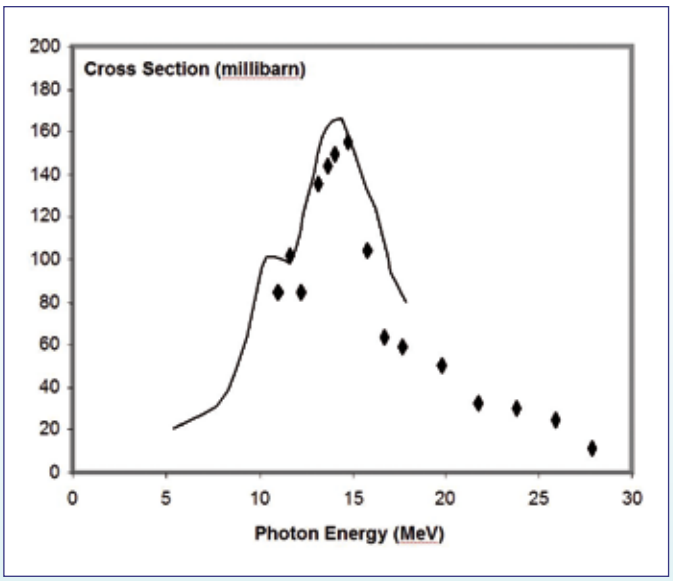

Figure 3. Graph of the Large Dipole Resonance cross-section with high values for the reaction cross section at around a photon energy of 15 MeV.

radioactivity generation profile as with the traditional ^{235}U starting material. A conceptual design has been developed for this photofission route, shown in figure 4, which could use a 50 MeV superconducting linear accelerator operating at a frequency of 704 MHz with a beam current of 100 mA. The 5 MW electron beam would strike one or more convertor targets to produce the photons and the ^{238}U production target could be as small as 2 cm in length. This system would be capable of supplying all the ^{99}Mo requirement for Canada but would draw electrical power of approximately 12 MW. The actual technology does not exist today, but constructing such a linac and designing an appropriate target would not be impossible to develop. The process would benefit from readily available and inexpensive ^{238}U, the fission radiochemistry would be similar but radioactive fission waste would be produced. In summary, this concept has major technical challenges and the economics of building and designing such a system do not look attractive.

6. Accelerator bombardment of Uranium-235

Several proton accelerator methods have been reported. The latest design from the Belgian company IBA, uses proton induced fission with LEU targets using the company's established cyclotron technology (11). The accelerator would be a new design for a 200 MeV cyclotron with a 1.5 mA proton beam, i.e. a beam power of 300 kW, and the target would be a sub-critical structure with an effective multiplication factor (k_{eff}) of 0.45, consisting of a series of 0.5 mm ^{235}U LEU foils separated by 1 mm in water, the neutron reflector being either water or beryllium. Estimates of the ^{99}Mo production output indicate that up to 74 TBq at 6 day reference may be possible. Another design concept (15) from the French company Advanced Accelerator Applications uses the Adiabatic Resonance Crossing invention from CERN where a high power proton beam, i.e. 1 GeV and 1 mA, would be incident on an 'activator' target containing a liquid lead target and graphite buffer with the starting material being enriched ^{98}Mo. The idea is that the target design can access the neutron capture resonance reactions with high cross-section values at approximately 10 keV for the reaction ^{98}Mo (n,γ) ^{99}Mo. Computational estimates indicate that high levels of ^{99}Mo can be produced albeit at low specific activity. Further calculations show that for this large accelerator arrangement commercial quantities of ^{99}Mo are possible if the target material is LEU or HEU.

7. Other methods of Molybdenum-99 Production

The 2009/2010 ^{99}Mo crisis situation has triggered numerous innovative proposals which may be realized in production facilities which could be much smaller than the traditional research reactor facilities. MIPOD Nuclear Inc of Nevada USA has proposed a new patented technology (16) for regional or hospital production of ^{99}Mo with a machine of 2 m by 2 m dimension using a D-T neutron generator (17) to produce fast

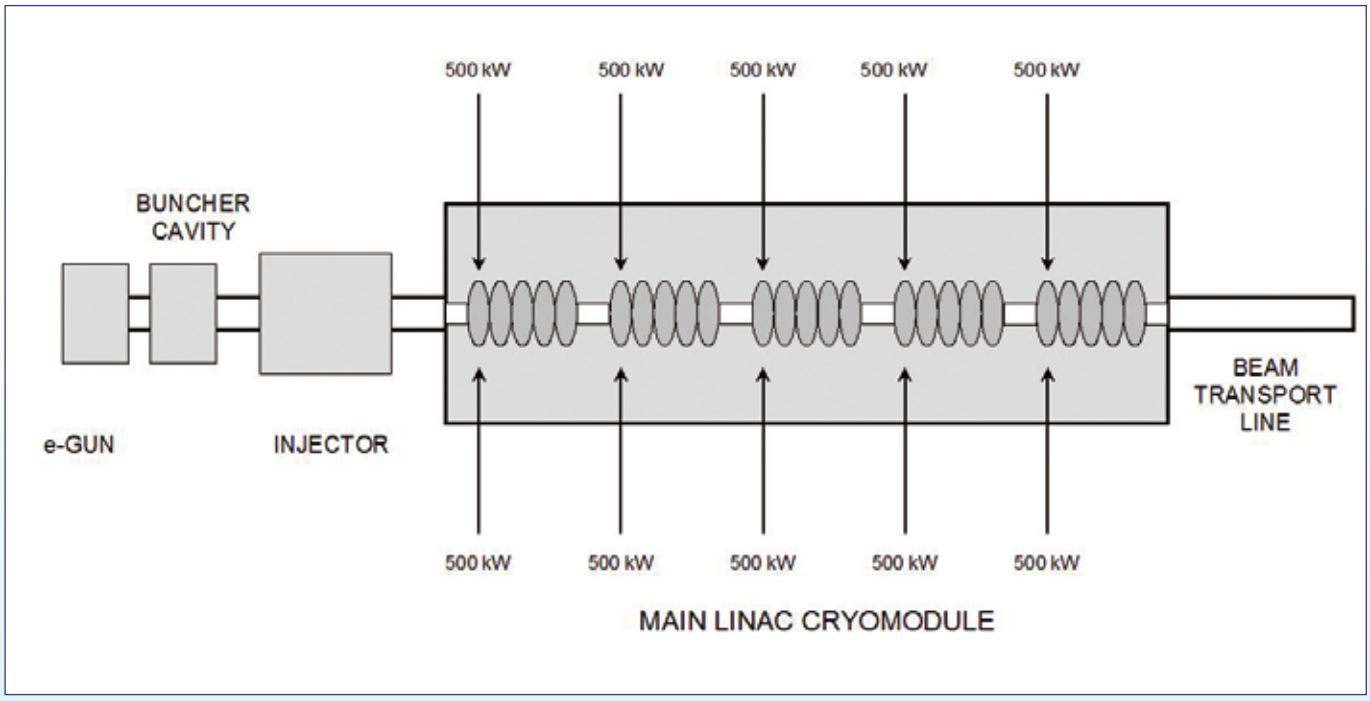

Figure 4.
Schematic of the possible linear accelerator: Courtesy of The TRIUMF Report, 2008: "Making Medical Isotopes: Report of the Task Force on Alternatives for Medical-Isotope Production."

neutrons which would be moderated an then irradiate ^{235}U in LEU form. Advanced electrolytic separation would be used to obtain the ^{99}Mo. Phoenix Nuclear Laboratories from Wisconsin USA, have another design using a neutron generator as the radiation source. Advanced Medical Isotope Corporation (AMIC) in Washington USA, is well advanced in the design of an accelerator-driven ^{99}Mo production system (18) using a sub-critical LEU solution reactor. Their design requires an electron accelerator of approximately 30 MeV to bombard a high-Z target. The resulting photons then irradiate a vessel containing ^{235}U LEU targets dissolved in deuterium oxide. Fission reactions occur in this non-critical assembly. The fast neutrons are moderated in the heavy water and the ^{99}Mo can be extracted continuously from the vessel. The system facility design is intended to have a small footprint for the production facility.

Conclusions

From a technical perspective, fission generation of ^{99}Mo in research reactors remains the most efficient method of production for very large quantities that would meet at significant fractions of the global market demand. However, replacement costs of new research reactors, the complexities of continuing to use HEU targets and the high level or radioactive waste arisings are serious negative factors and many of the alternative methods do avoid some of the issues. Nevertheless, these alternative routes invariably pose their own additional technical risks plus high development costs and so it is likely that the current research reactor fission method may well continue to be used in the future. However it is clear that small, efficient, dedicated medical isotope reactors would best meet the needs of the nuclear medicine community. But the remaining nuclear industry capacity and the various franchises between certain Governments and the manufacturers means that it is now unlikely that any single organization, whether Government or industry, would undertake the investment risk of building a reactor dedicated only to the production of medical isotopes.

About the author

Professor Dewi M. Lewis is Industry Advisor to CERN in Geneva and was formerly Head of Physics for Amersham Health and GE Healthcare. He is an accelerator physicist with experience in isotope production and medical imaging Research & Development with over 30 years experience in the radiopharmaceutical industry. He is also Vice President of the European medical imaging industry association (AIPES) based in Brussels and has various university appointments and Government advisory roles in the UK.

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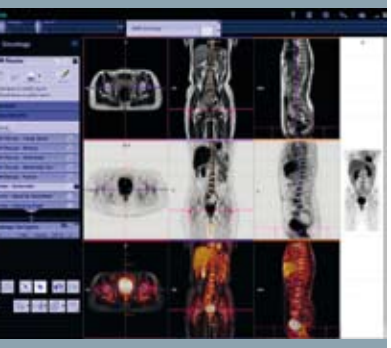

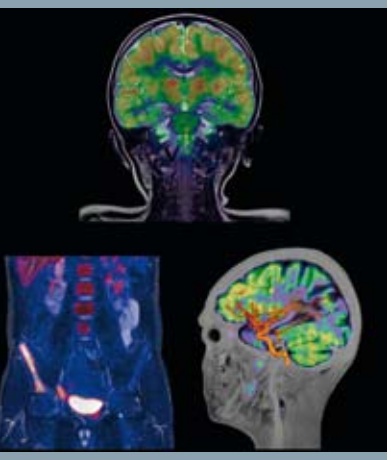

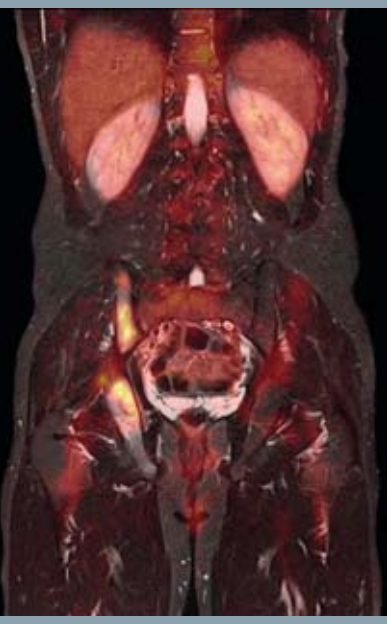

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Molybdenum-99 supply shortage: is cyclotron-produced Technetium-99m a realistic alternative?

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Abstract

Zimmermann RG, Geets J-M. Molybdenum-99 supply shortage: is cyclotron-produced Technetium-99m a realistic alternative? Alternative methods for manufacturing Molybdenum-99 (^{99}Mo) or Technetium-99m (^{99m}Tc) based on cyclotron technology have been explored several times in the literature. Most of these publications extensively describe the technical feasibility of this approach at small scale, but never addressed the technical and economical impact associated with the scaling up. These issues including impurity profile control, regulatory constraints, pharmaceutical aspect, logistics and customers interest are developed here. Unfortunately the discussion leads to the conclusion that the cyclotron-generated ^{99m}Tc is not an economically viable alternative to the well-established ^{99}Mo/^{99m}Tc generator. Even from a technical point of view the development of a cyclotron for large scale production of ^{99m}Tc will be difficult to concretise. Despite its huge initial investment, the best option from an economical point of view will definitely remain the reactor route. This conclusion is provided by experts working with IBA/CISbio, a company having a long standing experience in both cyclotron development and radiopharmaceutical manufacturing and distribution.
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Introduction

When the company Ion Beam Applications (IBA) was created in 1986, its major aim was to produce and sell one large (30 MeV) cyclotron per year. Very quickly customers became interested in adapting this tool for the production of new radionuclides and new targets were developed for this purpose. In parallel new cyclotrons with different energies were also developed and presently more than 200 IBA cyclotrons are in daily operation worldwide. About ten years ago, IBA decided to run their own centers and became a fluor-18 fluorodeoxyglucose (^{18}F-FDG) producer. The company controls today the largest network of cyclotron-based radiopharmacies. By doing this, IBA/CISbio acquired a double expertise in both cyclotrons and pharmacy. In order to improve efficacy, IBA also developed integrated solutions for the manufacturing of high quality fluorinated tracers.
Based on this technical and commercial well-established knowledge, it would be possible to develop a similar network for the production of ^{99m}Tc-labeled molecules. However, from its long experience, IBA knows also that any new tracer must take into account non-technical constraints as well, including the economical, market, regulatory and the safety aspects. From a general point of view and in most of the cases any alternative to cyclotron-produced radionuclides is usually less expensive in terms of development and operating costs. This certainly applies for ^{99}Mo and ^{99m}Tc manufacturing, when compared to the reactor processes. Even if the huge initial investment is included, the reactor route will remain the most economically viable solution. The cyclotron technologies for these two radionuclides have been described several times in the literature and a complete report on the topic was generated as early as 1999 (1-3). Most of these publications extensively describe the technical feasibility of this approach demonstrating their achievability on small scale production and confirming the quality equivalence of the radionuclide. However it never addressed the real constraints and limitations of scaling up in terms of operational and economical impact. From target handling to final drug supply, developers and producers of Cyclotron-originating-Technetium-99m (C-^{99m}Tc) will have to face - and solve - some issues that will be described here and compared to Generator-originating-Technetium-99m (G-^{99m}Tc).

Technical issues

A few research centers have employed the cyclotron technology at a local level and could produce ^{99m}Tc of a satisfying quality for labeling standard kits (1-4). The equipment used to manually produce this radionuclide is definitely not well adapted for large scale manufacturing. In the development of cyclotron/target there is a large gap to cross between a pilot project and a routine high-yield industrial manufacturing tool (figure 1).

Figure 1.
An 18 MeV cyclotron (IBA Cyclone®) with beam line for solid target. This equipment could be adapted to produce ^{99m}Tc provided it is cost-effective.

In the specific case of a ^{99m}Tc manufacturing dedicated cyclotron, the following will have to be considered (figure 2):

- Develop a process for ^{100}Mo target preparation that will sustain the 500 µA on target to produce the required daily amounts of ^{99m}Tc, (low power tests - up to 50 µA at 15-17 MeV - had so far only limited success) (5)
- Develop and validate the automated process for Mo/Tc target separation and purification from contaminants (monography limits)
- Guarantee the quality of the highly pure ^{100}Mo, but also secure access to commercial ^{100}Mo at an affordable price
- Develop and validate the separation and recycling process of ^{100}Mo (enriched material is very expensive) with large amounts of target mass and confirm that ^{99m}Tc generated with recycled ^{100}Mo remains within specifications
- Develop an adequate Good Manufacturing Process (GMP) unit that can assure pharmaceutical grade quality of ^{99m}Tc with shelf-life greater than 8h (specific activity issue)

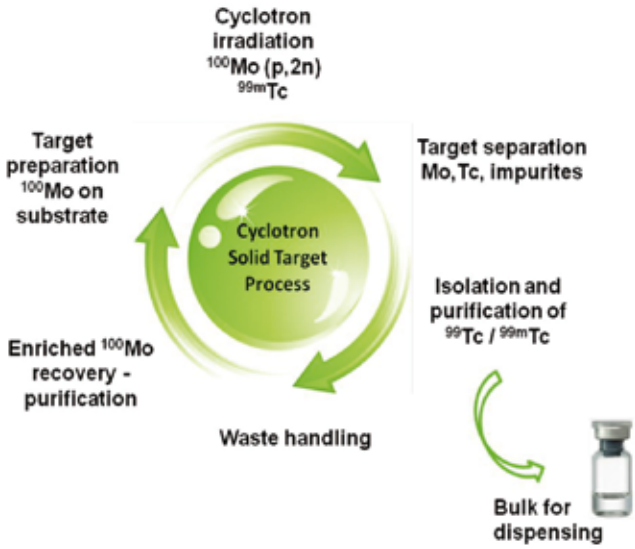

Figure 2.
Cyclotron Solid Target process: each step of the process for the manufacturing of ^{99m}Tc requires the development of adapted tools taking into account the specific properties of ^{100}Mo and ^{99m}Tc as well as the handling of large amounts of these products.

While technically theoretically feasible, most of those issues will have to be addressed and solved by the producer of C-^{99m}Tc. The cyclotron developer remains only in charge of the targetry and its expected upper supply limit. Each of these steps will generate additional development costs if the solution is not evident.

Impurity issues

A distinct route generates other impurities. As a consequence complying with the existing specifications will not be sufficient for the health authorities to approve the use of the final radionuclide for labeling. All data provided so far about the impurity content and elimination processes are based on low energy, low current and small-size target experiences and cannot be extrapolated to large scale processes. Scaling up will affect the ratio of impurities and undesired side-products will be generated from target material modification, content concentration, use of higher temperatures or time of irradiation.
Moreover presently G-^{99m}Tc is used for labeling within one hour after milking. C-^{99m}Tc will be used several hours post-purification and contain supplementary impurities generated during transport conditions (higher content of ^{99}Tc and impurities due to interaction with container), issues and constraints to be overcome by the C-^{99m}Tc producer.
Impurities such as ^{99}Mo, Niobium-97 (^{97}Nb), Technetium-95 (^{95}Tc), Technetium-96 (^{96}Tc) and Technetium-95m (^{95m}Tc) have already been identified (4) in C-^{99m}Tc besides ^{100}Mo. Excess of molybdenum is probably of less concern as its removal via column separation is an easy well-known step in the

generator process measured by the breaking point. However, validation of the (non radioactive) ^{100}Mo content will be needed as it is a new major impurity compared to the G-^{99m}Tc process.

Regulatory issues

As the manufacturing process is changed, the final drug C-^{99m}Tc is to be considered as a drug product which will need its own Marketing Authorization (MA). Therefore the manufacturing sites must be GMP-approved. If several cyclotron centers are using the same process, then one MA will be sufficient per company, and only variation filings will be needed for each newly opened center.
Moreover, all the marketed ^{99m}Tc-kits rely on existing MA's that describe labeling with G-^{99m}Tc. The new source of ^{99m}Tc will require at least an internal validation of the labeling process for each marketed product. Unless there is a high demand, cold kit manufacturers will have no special incentive to invest in these validation steps which is normally their duty. In certain countries, health authorities may even request the individual kit dossiers adapted through variations, representing further additional costs to kit manufacturers.
In absence of existing radiopharmaceutical industry's interest to reinvest in already marketed products, cyclotron owners will have to deeply evaluate on a case by case basis the real interest of local customers. From an economical point of view this will make little or no sense as long as cheaper generators with longer shelf-life will remain the competitive technology.

Operational issues

Theoretical evaluations (6,7) showed that two times 6 hours bombardment time could lead to 2.75 TBq of ^{99m}Tc corresponding to approximately 800 doses of ^{99m}Tc-radiolabeled radiopharmaceutical (based on 0.9 GBq injected per patient). Our experience with ^{18}F-FDG manufacturing shows that on top of these 12 hours, time must be spared for cooling down, target exchange, cleaning and maintenance, leaving limited time for production of other radionuclides. Nevertheless the major drawback in using a cyclotron around the clock is simply that customers request access to several radiotracers at the same time during working hours. Even if time allows it with e.g. cameras running overnight, a high power cyclotron with an energy range of 24-30 MeV is not well-suited for producing short half-life radionuclides such as Copper-11(^{11}C) or ^{18}F. Such machines are usually dedicated to high power long- term irradiation of solid-gas SPECT targets, while PET tracers are easier to produce with much simpler fixed low energy cyclotrons.

Economical issues

The economical aspect of a C-^{99m}Tc can be easily evaluated on a single-site model if one disregards the one-shot development investment. A dedicated high current 24 MeV + cyclotron with its radiopharmaceutical infrastructure will cost at least €12 million. From our experience in running 18 MeV and 30 MeV cyclotrons, we can estimate that the daily operating costs for a site producing twice (2x6 hours beam) a pharmaceutical grade ^{99m}Tc should be above €9,000. Amortization of the equipment is also very high (€3,600 if based on €12 million investment amortized over 15 years and 220 working days/year). With an expected maximum of 800 daily produced doses (4), the cost for C-^{99m}Tc will be above €15. By comparison one G-^{99m}Tc dose is estimated at about €3.50 (a non-optimized use of a €1,000 generator could produce more than 300 doses over a week). And this figure has the margin already included. Even if the price of ^{99}Mo rises, generators will remain competitive for a long time.

Conclusions

A major distinction should be made between a long-term secure supply of ^{99}Mo and compensating for a transient manufacturing issue. Unfortunately there is no adequate short term solution except when substituting ^{99m}Tc by ^{18}F-labeled tracers, ^{201}Tl or Rubidium-82 (^{82}Rb) whenever possible. Any new technology proposal will need at least 5 years of development and long authorization processes before it reaches the market. We strongly believe that by 2015 the ^{99}Mo-shortage crisis will have been solved with an adequate reactor network. By September 2nd, 2010, as a first step, IBA, the Belgian Institute for Radioelements (IRE) and the French Atomic Energy Agency (CEA) announced a partnership to secure the supply of ^{99m}Tc relying on the new CEA reactor Jules Horowitz (JHR) under construction in Cadarache (France), the renovated IRE's manufacturing facilities in Fleurus (Belgium) and IBA CISbio's new generator manufacturing lines in Saclay (France). Provided time being of essence and all options presented so far based on long-term solutions (8,9), now we need to put a maximum of pressure on politicians and to persuade decision makers to invest in other reactors.

About the authors

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Jean-Michel Geets holds a Master degree in electrical engineering. After being involved since 2002 in project management for IBA (Ion Beam Application), he moved to IBA Molecular Equipment as product manager dealing with cyclotron and target development in PET and SPECT applications.

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advertentie de wildt

Delft University of Technology working on short and long-term solutions to the molybdenum crisis

Prof. H. Th. Wolterbeek *Faculty of Applied Sciences, Delft University of Technology, The Netherlands*

Introduction

Global shortage of the medical radioisotope Molybdenum-99 (^{99}Mo) occurs frequently. This is because there are only five major commercial producers, all of which also use old reactors. Additional production facilities would therefore be very welcome.
Delft University of Technology (TU Delft) has responded to this by allowing its research reactor to act as a back-up production facility for ^{99}Mo in the event of severe shortages. The required technical alterations to the research reactor are minimal. The main consequence for TU Delft is that some of its regular nuclear research will have to be temporarily halted if the back-up production is required. Regular molybdenum production tests will also need to be conducted. In TU Delft's view, however, these disadvantages are negligible compared to the wider social importance of supplying enough ^{99}Mo to hospitals around the world.

In September 2010, the Dutch Ministry of Health, Welfare and Sport accepted TU Delft's offer and asked the university to adapt the research reactor for isotope production; this is currently being carried out. As soon as the necessary permits have been issued, the reactor will be used to produce medical isotopes in the event of an emergency. This should be ready in 2011.

In the future, the research reactor will act as back-up for reactors such as the High Flux Reactor in Petten, which accounts for 30 percent of the global production of ^{99}Mo. In terms of capacity, the reactor in Delft can for example take over slightly more than the total Dutch requirement for ^{99}Mo. This equals about one thousand procedures per day and 5 to 10 percent of the production normally conducted in Petten. This does not mean of course that isotopes produced in the Netherlands will necessarily be used within the Netherlands.

OECD report

TU Delft's initiative matches with the recent, critical report by the Organisation for Economic Co-operation and Development (OECD) on global molybdenum production. The report indicates how the molybdenum crisis could be alleviated, at least using regular production technology: have the major producers work at slightly less than their full capacity. This would mean that there is room for production to be increased if supplies are cut off from one of the other producers.
A second option, however, is to create a number of smaller (sleeping) back-up producers, such as is now the case with the TU Delft research reactor. TU Delft is the first party in the world to come up with such an initiative. According to TU Delft's Reactor Institute Delft, there are plenty of reactors around the world which could do the same. If a dozen or so back-up facilities could be created, the current supply problem could be reduced dramatically.

Molybdenum-98

In the back-up scenario, TU Delft will produce ^{99}Mo using standard technology, i.e. by splitting highly enriched uranium. One of the by-products of splitting Uranium-235 (^{235}U) is ^{99}Mo. In the long term, however, an entirely different solution to the molybdenum crisis is possible. In fact, studies are being conducted into various alternative production methods for ^{99}Mo. TU Delft is focusing on one of these alternatives, which has already been patented. This method uses Molybdenum-98 (^{98}Mo): a stable, naturally-occurring molybdenum isotope. This ^{98}Mo is irradiated with neutrons in order to make ^{99}Mo out of it.
The molybdenum atoms are not just activated (turned into ^{99}Mo) by the neutron capture, the recoil energy transferred to the molybdenum nuclei also detaches them from the surrounding atoms (figure 1). This means that this isotope can be collected in high concentrations (high specific radioactivity).

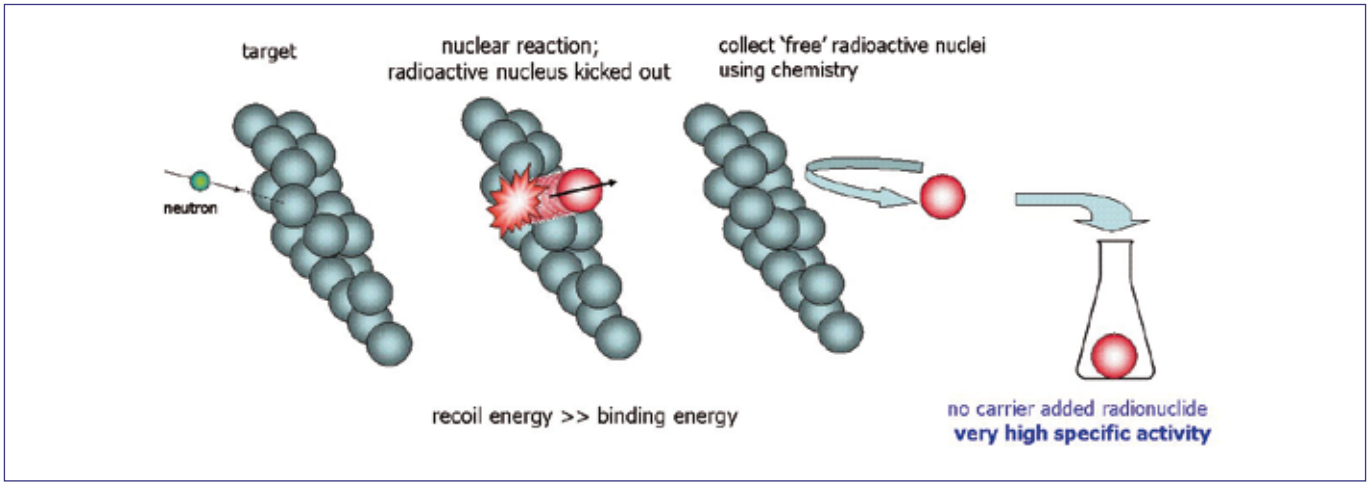

Figure 1. Production Molybdenum-99 using Molybdenum-98

Benefits

The production of ^{99}Mo from ^{98}Mo is a highly elegant method with a number of major benefits. A uranium target is no longer required for production. The production process using ^{98}Mo as its basic material creates much less radioactive waste, which otherwise has to be processed and removed (as is the case for ^{235}U). Moreover, ^{98}Mo is relatively simple to obtain via mining. ^{98}Mo accounts for about one quarter of all naturally-occurring molybdenum. In addition, it is relatively easy to prepare the ^{98}Mo target material for repeated use in the production of ^{99}Mo.

These arguments for switching to a different production method will become increasingly important. This not only applies for molybdenum: recoil-based separation of radioisotopes from their targets (basic materials) may become the answer to many of the the requested high-specific-radioactivity radioisotopes in hospitals throughout the world.

TU Delft is currently working together with Urenco on upscaling the ^{98}Mo technology. The university is constructing a test radiation facility to further develop the method. TU Delft can see no fundamental obstacles to putting the production technology into practice in the long term. If the current experimental technology can be applied on an industrial scale, many more factories could produce ^{99}Mo than is currently the case.

Oyster

TU Delft's research reactor is used for academic research in health, energy and materials. The Oyster programme (Optimised Yield- for Science, Technology & Education-of Radiation) is currently being conducted with a view to the reactor being able to meet the latest scientific challenges and respond to social issues (such as the production of ^{99}Mo) more precisely and flexibly. This programme will allow the production of ^{99}Mo to be increased even further as more neutrons will be available.

About the author

Bert Wolterbeek (1955) is full professor of Radiochemistry at the Faculty of Applied Sciences of the University of Technology, Delft, The Netherlands, and head of the research section Radiation and Isotopes for Health within the department Radiation, Radionuclides & Reactors.
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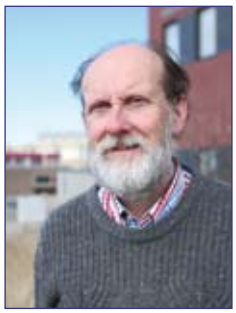
PALLAS: the new nuclear research reactor in the Netherlands



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Abstract

Van der Schaaf B, De Jong PGT. PALLAS: the new nuclear research reactor in the Netherlands

In the European Union, the first generation of research reactors is inevitably approaching operational retirement. Maintenance costs are increasing and continuity of operations is compromised by the aging of materials and components. The High Flux Reactor (HFR) in Petten, the Netherlands, is one such reactor.

Nuclear Research and consultancy Group (NRG), the current license holder and operator of the HFR, therefore plans to build a new research reactor called PALLAS. This will be a state-of-the-art reactor equipped to meet the growing world demand for both nuclear knowledge and services and the production of essential medical isotopes. It will have the capacity to be the world's largest producer of such isotopes.

The tender process for PALLAS began in 2007 and will continue through 2010-2011, following the EU rules for competitive tendering of complex, one-off design and construction projects. NRG is currently still actively pursuing the acquisition of funding for the project. In the exploitation of PALLAS there will be both public and private interests. Public interests have to do with research for sustainable energy and with guaranteed availability of isotopes for medical applications. Private interests are focused on commercial irradiations and the production of isotopes.

NRG welcomes the cabinet-council's support (1) for the building of a new reactor and is fortunate in having fast growing public acceptance and support for it too. The licensing process began in autumn 2009 with a, so called, Notification of Intent to conduct an Environmental Impact Assessment for PALLAS. Public hearings have been held to inform the public about PALLAS. This summer (29 June 2010) NRG received the so called *'Richtlijnen Milieueffectrapport'* (2), the final guidelines for the Environmental Impact Assessment.

The PALLAS project team in Petten will guide the design and construction processes, is responsible for the licensing and commissioning and will manage the design and construction of the reactor infrastructure.

This chapter gives an understanding of progress made towards the realization of PALLAS and its role in securing the European supply of radioisotopes for nuclear medicine. **Tijdschr Nucl Geneesk 2010; 32(4):624-628**

Introduction

The middle decade of the 20th century saw the start of the design and building of a large fleet of research reactors in the range from "zero" to over 100 megawatt (MW) thermal power. In the EU the first generation of the larger types of research reactors is now being phased out after operational lives of 40 years and more. Maintenance costs are increasing and continuity of operation is compromised by the aging of materials and components.

The High Flux Reactor in Petten, one of this generation of reactors, was built in the fifties and began full operation in 1961. A recent shut down for repairs of the primary cooling water systems (extensively described elsewhere in this journal issue by De Widt) underlines the aging of this reactor. These ageing issues, together with economic considerations left Nuclear Research and consultancy Group (NRG), the current license holder and operator of the HFR, with the choice of either undertaking a second vessel replacement or building a new reactor.

In 2004 NRG took the initiative to start working on the design and construction of a new nuclear reactor: PALLAS. This reactor is not only intended to function as a centre of research (material testing, development of nuclear fuels and components etc.), but also as a workhorse for the pharmaceutical sector (medical isotopes).

Reactor Requirements

The requirements for PALLAS are derived from the vision in three strategic areas:

- **Health care** for the world population which is increasing both in age and standard of living, stimulating increasing demand for existing isotope diagnostics and therapies and development of new isotope-based treatments.
- **Safety and Environment** in relation to nuclear energy generation with existing nuclear power reactors and the partitioning and transmutation research to reduce remnant waste.
- **Energy and security of supply** to satisfy rising energy demand with even more effective power plants and fuel cycles, such as the thorium fission cycle and the tritium generation technology for fusion reactors.

Together with this threefold vision, almost 50 years of experience with the HFR has delivered a great deal of input for the technical requirements. The main feature of PALLAS is its operational flexibility. On the one hand, the reactor responds to the changing demand for research and development activities. On the other hand, the core is so flexible that it can react immediately to the fluctuating demand for isotopes.

It must be possible at all times to respond to peak demand or special irradiations efficiently. No research study or development activity should obstruct the production of medical isotopes, and vice versa. Moreover global production capacity is extremely limited, so reactors must have the capacity to take over the production of medical isotopes from each other very quickly if unexpected maintenance is required or malfunctions occur. PALLAS has this capacity to react quickly.

Other key elements in the design of the new PALLAS reactor are safety, reliability and efficiency of operation. The design foresees a tank in pool design with a flexible reactor core. To allow production capacity increase and reduction reacting to market demand, the reactor core and reflector zone are flexible in space. This flexibility can be expressed in the power which ranges from 30 to 80 MW. The core and reflector design allow ample space for isotope production, in positions less attractive for most experiments. So there is always a dedicated place for baseline isotope production in the reactor. The driving fuel assemblies will contain low enriched (less than 20% uranium) uranium silicide in the early years of operation. Later, as soon as it has been qualified, low enriched uranium molybdenum (UMo), fuel will be used. UMo has more attractive properties in the core and in the re-processing phase. The core design allows the use of either HEU en LEU targets for the production of Molybdenum-99 (^{99}Mo) isotopes for Technetium-99m supply. Further major requirement details are given in (3).

The tendering process

The tender procedure adopted has followed the EU rules for complicated one of a kind design and construction projects. The procedure began with a qualification of potential tenderers. Three were qualified; they were the consortia AREVA Ballast Nedam, KAERI - KOPEC - DOOSAN (figure 1) and INVAP-ISOLUX (figure 2). Following this there was a dialogue and consultation phase comprising sessions of several days during which each potential tenderer provided additional information and asked more than 400 formal questions. Only one major requirement had to be adjusted. The fast neutron flux specification had to be reduced by about 30% in order to allow for sufficient flexibility in reactor operation. The reduction in fast neutron flux gives a more even distribution

Figure 1. What might PALLAS look like? An artist impression provided by one of the three consortia, the KAERI – KOPEC-DOOSAN consortium, involved in the first (2008-2009) tender procedure. A second tender procedure is expected in 2011-2012.

Figure 2. Architectural rendering of PALLAS reactor concept as proposed by the INVAP-ISOLUX consortium, involved in the first (2008-2009) tender procedure.

of neutrons in the core. This improves the flexibility of irradiation facilities for both experiments and isotope production, counterbalancing the customer loss for the fast neutron facility. Fast neutron customers may be served in future research reactors in the EU dedicated to fast neutron research.
The procedure allowed NRG to produce the final employer requirements in summer 2008. The accompanying criteria for granting of the tender concentrated on: licensability of the design, treatment of safety and health physics aspects, production capacity and quality, investment costs, and cost of operation. After the draft contract was completed in agreement with all parties, NRG received the tenders in May 2009. Prior to this NRG teams had visited all three vendors in Korea, Germany and Argentina respectively.
In summer 2009 NRG analysed the valid tenders. It was clear that the technical requirements could be met, though the solutions were very different. NRG selected the most economically advantageous tender. However, the contract could not be granted because, in the meantime, the requirements for the financing of the reactor design and build changed, affecting the timetable to such a degree that a new tender exercise was inevitable. A new tender procedure is expected in 2011-2012.

Funding

Construction will require an investment of several hundreds of millions of Euros. Currently NRG is still actively pursuing the acquisition of funding for the project. The goal is to have the reactor operating within ten years (2020), subject to funding and regulatory approvals.

Sourcing of assured funding for the total project is still ongoing. In the exploitation of PALLAS there will be both public and private interests. Public interests have to do with research for sustainable energy and the guaranteed availability of medical isotopes for the treatment and diagnosis of patients. Private interests are focused on commercial irradiations and the production of isotopes.

The building will rely on:

- Public funding for the pre-competitive research and science development carried out in PALLAS.
- Private funding for the investment needed for the commercial production of isotopes.

A recent 'Communication' from the European Commission states: "The possibility of financing mechanisms to ensure a sustainable supply of radioisotopes in the interest of public health and an equitable share of public expenditure by all Member States will be explored together with the Council and European Parliament, and the Commission will ensure appropriate follow-up to the Council Conclusions on this matter. The needs will be established on the basis of the conducted technical and economic studies and of a reference scenario for the replacement of reactors of age." In this same paper the Commission envisages three possible financing mechanisms: Euratom loans, European Investment Bank loans and guarantees and Joint Undertaking (4).

Licensing

In The Netherlands six Ministries constitute the Competent Authority for the Dutch Nuclear Energy Law (KEW). In early 2008 the first project information exchange was held between NRG and the coordinating Competent Authority for the KEW, the Ministry of Housing, Spatial Planning and the Environment (VROM). VROM takes the IAEA framework as the basis for its policy, extended by rules pertinent to the Netherlands particular circumstances. For research reactors with a thermal power over 30 MW several rules will be similar to those established for nuclear power reactors in the Netherlands. An amendment that NRG is anticipating is a requirement for a supplementary shut down/observation room. (The supplementary shut down and observation room are back-up facilities possibly required in the future by the authorities for managing emergency conditions of the reactor). Other preconditions are:

- withstand high internal pressure
- withstand high speed, heavy aircraft crash
- long 'grace period' in the event of an accident
- Core damage frequency (CDF) ≤ 10^{-6}

In 2009 NRG published the Initial Memorandum (5), informing the public about its plans for PALLAS and how it will analyse and control its environmental impact. The formal submission of the Initial Memorandum to VROM triggers the Environmental Impact Assessment (EIA) procedure. The public hearings, organised by VROM, were held in the two candidate locations: the communities of Zijpe and Zeeland. The views of the Netherlands' public gathered during and after the meetings are used by the EIA committee to set the themes for the analyses and report. The committee gave its final guidelines in June 2010. NRG has now started working on the EIA procedure, and expects to complete it by the end of next year.

The final reference license basis and the final operational limits and controls need to be agreed with the regulator as soon as possible, in order that the design and license application can be completed. Transparent and strict communication lines between regulator, license applicant and vendor will be essential for the speed and quality of the work needed. The building can only be started after the license has been issued.

Project organisation

The PALLAS project team in Petten will direct the realization of PALLAS on NRG's behalf. It will review and assess the design and construction processes provided by the vendor, and it will have primary responsibility for defining

the employer's requirements, the licensing and the commissioning of PALLAS, with the supporting design and safety systems supplied by the vendor. The major projects the team will have to manage are:

- Control and supervision tasks for the design & license phase
- Evaluation and verification of nuclear design codes of the vendor.
- Netherlands Environmental Impact Assessment: Milieu Effect Rapportage
- Netherlands Nuclear Law: KernenergieWet, building and operational license
- Operation and Commissioning preparation
- Experimental irradiation devices design and embedding in the reactor core
- Isotope irradiation devices design and embedding in the reactor core
- Site layout
- Infrastructure: adapt power, gas, water, sewerage, data supply, etc. to PALLAS.
- Cooling water supply including licenses. Studies to use the remnant heat in the cooling water are underway. The continuous heat production requires heat buffers that are quite costly. The potential is thus there, but finding sufficient customers to justify the extra investments needed for the delivery of the heat is not simple in a sparsely populated area.
- Remnant heat processing and disposal

The project team has a director and project manager, leading the lead engineers of the major projects. The core team now consists of nine members. They will be supported by experts from NRG and some third parties. Subcontractors will supply the design and hardware needed to accomplish the goals of the projects. The PALLAS team will detail the scope and planning for the design and construction for the infrastructure needed and will control the contract management.

With the formal framework in place and continuation of the professionalism, enthusiasm and dedication already shown by all members of the team, PALLAS will bring forward great innovations in the field of technology and science by means of research for the medical sector, the energy sector and consultancy on high tech materials.

PALLAS and the EU

Over the past years the nuclear industry and politicians (European and Dutch) produced an extensive set of future strategies to strengthen the nuclear research infrastructure and security of supply of medical isotopes. Below there are some important conclusions concerning PALLAS.
The thematic network "Future European Union Needs in Materials Research Reactors", FEUNMARR, already stated in 2001 that "given the age of current Materials Test Reactors there is a strategic need to renew Materials Test Reactors in Europe". Continuity in irradiation capacity for research and development for fission and fusion power plants is essential for securing energy production in the EU and the world as a whole (6).

The European Strategy Forum on Research Infrastructures (ESFRI) followed in 2006 with a note that the next prominent nuclear facilities such as the Réacteur Jules Horowitz (JHR) in France are primarily designed for research projects that serve scientific, industrial and public needs. PALLAS and JHR will be complementary (7).

In 2008, the Committee for Netherlands' Roadmap for Large-Scale Research Facilities (Commissie van Velzen) of the Ministry of Education, Culture and Science carried out an international peer review of PALLAS resulting in very positive advice for the go-ahead of the project. In early 2009 PALLAS was added to the list of the Netherlands' National Roadmap Large Scale Research Facilities (8).

The Sustainable Nuclear Energy Platform's (SNETP) Strategic Research Agenda (May 2009) makes the need for PALLAS clear with statements such as "To hold on to its leadership in reactor technology, Europe must maintain its efforts towards the realization of a European Research Infrastructure Area" and "the PALLAS project will provide an innovative irradiation facility and reinforce the supply of radio-nuclides for medical application in Europe" (9).

In a letter for the Dutch Parliament issued 16 October 2009 the Netherlands government clearly expressed their positive vision on the building of Pallas (1). The letter stipulates that the replacement of the HFR by a state-of-the-art reactor will satisfy both the need for nuclear research, and the security of radiopharmaca supply. The letter expresses the vision that the multipurpose reactor provides sufficient flexibility for fulfilling these tasks, building on the existing Netherlands knowledge infrastructure in the fields of nuclear technology and radio-isotopes.

French Atomic Energy Commission (CEA), Belgian Nuclear Research Centre (SCK-CEN), Technical University, Munich (TUM) and NRG have recently written a position paper called 'Scenario for sustainable ^{99}Mo production in Europe". In this paper the major European reactor operators underline the importance of a joint approach and the need for a set of common principles "to ensure the conditions necessary for security of European ^{99}Mo supply" (10). This position paper has been positively referenced by the EC Directorate-General for Energy in a recent advice to the European Parliament.

September 2010 an OECD-NEA report, prepared by the High Level Group on security of supply of Medical Radioisotopes (discussed elsewhere in this journal issue by Seeverens)

highlights the current absence of "sufficient financial incentives for new ^{99}Mo production infrastructure without government assistance" (11).

Conclusions

1. The role of PALLAS in the EU's future research and isotope utilization is well established.
2. The tender process has lead to offers that technically seem feasible. The competition and dialogue procedure for the tender was most effective in arriving at stable requirements and clear offers. The tender process will be continued later this year/early next year.
3. Although progress has been made only limited funds are available at the moment. The financial arrangements for the design and construction phase of the project have not yet been concluded.
4. The licensing path has been started with the Environmental Impact Assessment, based on the results of public hearings following the Netherlands practices.
5. The project organisation for the PALLAS project is ready for the next phase: the design and license preparation, followed by construction and commissioning as soon as the construction and operating license has been awarded.

About the authors

Bob van der Schaaf holds a degree in Physical Metallurgy obtained from the Delft University of Technology. Since 1971 he was involved in materials science and engineering of neutron irradiation effects on matter, resulting in about 100 publications. His project experience is in the range of managing the European fusion materials development program to leading the design and construction of the Jaap Goedkoop nuclear research laboratory. He held line management positions with ECN and NRG until 2007, when he became manager of the PALLAS project.

Paul de Jong has a degree in Applied Physics at Delft University of Technology. He managed the development of ultra-centrifuges and the design & construction of uranium enrichment plants. As Managing Director Urenco-NL he was responsible for Almelo operations. He was involved in preparing and executing of the Urenco investment projects. In 2009 he was appointed by NRG-Petten as PALLAS Project Director.

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Department of Nuclear Medicine and Molecular Imaging (2010)

University Medical Center Groningen

The University Medical Center Groningen (UMCG) is the second largest academical center of the Netherlands, the largest employer of the North of the Netherlands and the only Dutch center with permission for all organ and tissue transplantations. The total number of beds is 1,339 and the total number of employees is 10,085, of which 1,871 are part of the scientific staff. The central focus of the UMCG is 'Healthy ageing, building the future of health'.

Department of Nuclear Medicine and Molecular Imaging

The history

The UMCG and University of Groningen are pioneers in the application of radio-isotopes in medicine. In 1953, Dr M.G. Woldring founded the central isotope laboratory, where the first in vivo and in-vitro measurements were performed. For in vivo measurements, external detectors were used initially; and later, a linear scanner. Radio-immunoassays were developed on a very large scale. The first gamma camera was installed in 1965 and with the availability of the ^{99m}Tc-generator, new in-vivo diagnostic procedures were set up. Positron Emission Tomography (PET) became possible in 1972 after installation of a large cyclotron at the university's Nuclear-Physics Accelerator Institution (KVI). The founding father of this PET development in Groningen was Prof. A.M.J. Paans. Pioneering PET studies were performed in a close cooperation between Nuclear Medicine, the KVI and the University Laboratory of Organic Chemistry. This led to financing by the Dutch government of a fully equipped PET Center on hospital grounds in 1988. Nuclear Medicine (headed by Dr D.A. Piers) and PET Center (headed by Prof. W. Vaalburg) developed individually during the 1990s. Because of the clinical potential of nuclear imaging in diagnostics and radionuclide therapy, Nuclear Medicine and the PET Center were re-united in 2005 and renamed as Nuclear Medicine and Molecular Imaging (NMMI), headed by Prof. Rudi A.J.O. Dierckx. In 2009 and 2010 the department was completely renovated and new cameras and a new GMP-laboratory were installed. The installation of the new camera systems was guided by our clinical physicists Anne Paans, Antoon Willemsen and Johan de Jong, and Hans ter Veen, head of the technicians, was involved also.

The priorities

The theme of the department is fully consistent with the theme of the UMCG: 'Radionuclides for healthy ageing'. Within this theme three priorities are defined, which can be recapitulated with the following three terms (in Dutch forming the letters 'KLM'):

Quality

Since 2000, NMMI is already in possession of the NEN-EN-ISO-9001 certificate, but the department has the potential to achieve more goals in the next years:

- Realize a fully Good Manufacturing Practice (GMP)-compliant facility for the production of radionuclides.
- Strengthen and intensify working following Good Clinical Practice (GCP).
- Aiming for the EFQM (European Foundation for Quality Management) acknowledgement.

Linking with other modalities

Multimodality imaging (SPECT/CT, PET/CT, PET/MRI), both in humans and in small animals, remains a priority for NMMI because of the enormous implications for clinical routine, research and education purposes. The multidisciplinary approach and the cooperation with other professions such as radiology and radiotherapy are necessary for optimal effectiveness.

Molecular Targeting

More than ever molecular targeting emphasizes the difference between nuclear medicine and other imaging modalities. NMMI focuses on molecular targeting for both clinical as well

as preclinical research, including a close collaboration with the industry. Our highly equipped radiopharmacy lab facilitates this. The radiochemistry is runned by Philip Elsinga, together with Erik de Vries and Gert Luurtsema, and the clinical pharmacy by Marjolijn Lub-de Hooge and Hendrikus Boersma. The main topics in the following years are neurology, cardiology, oncology and inflammation. In the next coming years a new cyclotron will be installed.

The medical staff

The medical staff consists of five Nuclear Medicine specialists, each with their own area of interest. Rudi Dierckx is the head of the department and responsible for the specialization of the residents and promoter of a number of PhD-students. His own research focuses on the brain. Jan Pruim is the deputy head of the department, the deputy trainer of the residents and focused the last years on the implementation of all new equipment and the growing collaboration with radiology. He will also further develop radiotherapy research and is responsible for the industrial contract research projects. Starting from 2005 he was also the medical coordinator of the department, a position that will be transferred to Adrienne Brouwers (this position is alternating within the group). Her main areas of attention are endocrinology, oncology (including neuro-endocrine tumors) and therapy. Riemer Slart is responsible for the education of students and is mainly focused on cardiology and osteoporosis. Andor Glaudemans is the most recent staff member (since 2008) and focuses especially on inflammation and infection, but also on the areas of oncology and therapy. Ha Tan-Phan assists with clinical duties one day per week. Bert Piers, although in retirement for a couple of years, is still educating the residents in all the aspects of conventional nuclear medicine. Together with the residents, we hope to form a complete group in all clinical fields related to nuclear medicine. Of course, once in a while it is time to relax, eat together or drink a beer (see the photo).

Most doctors of NMMI and some foreign guests (May 2010)

Facts and figures

Nuclear medicine examinations (2009):

• Conventional nuclear medicine	12,469
• PET	2,517
• Therapy	180

Staff (2010):

• Nuclear Medicine specialist	5
• Resident in training	6
• Clinical physicist	3
• Clinical physicist in training	4
• Radiochemist	3
• Pharmacist	2
• Biologist	2
• Manager	1
• Technician/lab	30
• Administrative staff	7

Equipment for small animal imaging (2010):

- Small animal imaging laboratory at DM-II level
- MicroPET Siemens Focus 220
- MicroCT MicroCat II
- MicroSPECT Milabs USPECT II

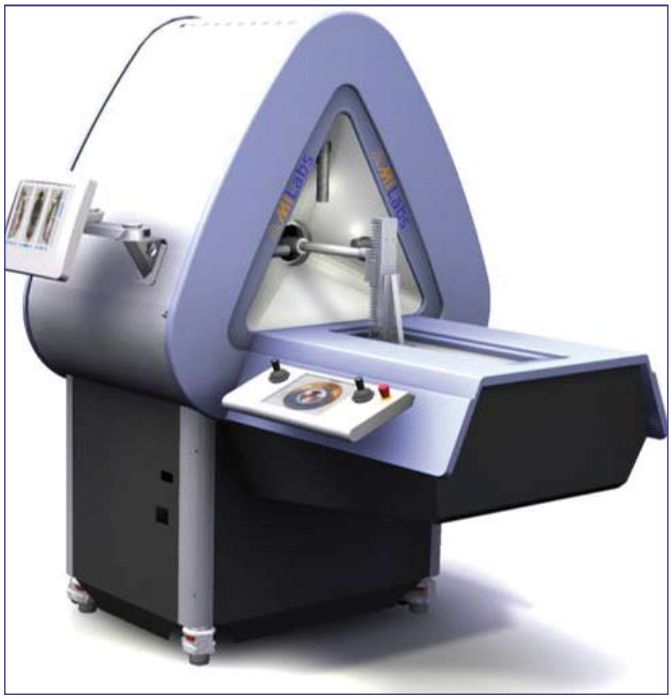
Laboratory facilities (2010):

- Cleanroom PET (11 hot cells, 3 laminar flow cabinets)
- Cleanroom SPECT (including 3 laminar flow cabinets and a dedicated hot cell for ^{89}Zr-labeling)
- PET research lab (6 hot cells, 8 shielded fumehoods)
- Research lab for long-lived isotopes, metabolite analysis and in-vitro experiments

Equipment for human use (2010):

- Scanditronix MC-17F cyclotron
- Siemens mCT (time-of-flight, HD, 64-slice CT)
- Siemens Ecat Exact HR+ PET camera
- Siemens Symbia T16 SPECT-CT (16-slice CT)
- Siemens Symbia T2 SPECT-CT (2-slice CT)
- 2 Siemens Symbia S1 gamma camera
- Hologic Discovery Bone densitometer

Siemens mCT (time-of-flight, HD, 64-slice CT)



MicroSPECT MiLabs USPECT II

Education

The Department of Nuclear Medicine and Molecular Imaging provides education within the wide range of molecular imaging, primarily to trainees, university students, graduate students and postdocs. The contribution of our department to the normal university curriculum has increased in recent years. We now participate in the educational programs of general medicine, pharmacy, technical physics (biomedical technology), and life sciences. Nuclear medicine residents play an important clinical role at the department and are mainly involved in reporting clinical studies and supplying therapy to patients, under supervision of a nuclear medicine specialist. From the year 2011 on, when the new trainee curriculum starts, NMMI will offer a training year in a general hospital, for which co-operation has been sought with the Isala Clinics in Zwolle and the Medical Center in Leeuwarden. We expect a growth in number of residents in the next years because the OOR N-O (Dutch Education and Training district North and East Netherland) assigned our department two new residents each year. The department also participates in the training of clinical physicists, internal medicine physicians, cardiologists and radiotherapists. Students and residents can participate in clinical procedures at the department or can be involved in (pre)clinical research. Recently, one of our technicians started her training for physician assistant (PA) in nuclear medicine.

Collaboration

NMMI has collaborations in research with academic hospitals in the whole world, for example with the University La Sapienza in Rome and the University of Gent (with Alberto Signore and Christophe van de Wiele as visiting professors, respectively).

Other hospitals we are collaborating with are the Tokyo Metropolitan Institute of Gerontology, Peking University, the University of Bari, the University of Sao Paulo, Royal Marsden Hospital in London, University Hospital in Munster Germany, and the Ottawa Heart Institute. We collaborate closely with VU Medical Center Amsterdam and the University Medical Center Nijmegen in a so called Dutch Hub together with Roche. Our Department is also part of the European Network for Diagnostic Molecular Imaging (DIMI) and strives to promote interuniversity collaboration also with these institutions.

The 'new' opening and future

On Thursday the 18th of November we celebrated the completion of the renovation of our department, the installation of new camera systems, and a new GMP-laboratory.
We are preparing new plans for the acquisition of a second PET/CT camera and a new IBA cyclotron is already ordered and will be installed in the next couple of years. The group wants to contribute to the development of nuclear medicine internally in Groningen, in the Netherlands and internationally. We want to provide a platform for that and to be considered a reliable and enthusiastic partner to collaborate with.

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- Mw. Dr. Ir. L. Poot (klinisch fysicus), secretaris
- Drs. R. Lange (ziekenhuisapotheker), penningmeester
- Prof.dr. W.J.G. Oyen (nucleair geneeskundige), lid
- Dr. A.D. Windhorst (klinisch radiochemicus), lid
- Drs. J.J.G. van den Heuvel (ziekenhuisapotheker), lid/ kwaliteitszaken

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E-mail: info@nvmbr.nl
Internet: www.nvmbr.nl

Studiedag voor Assisterende MB&RT
20 januari 2011
Locatie: Vergadercentrum Vredenburg 19 te Utrecht

Studiedag voor leidinggevenden en opleiders
10 februari 2011
Locatie: Antropia Cultuur- en congrescentrum te Driebergen

Workshop ECG
21 maart 2011
14 september 2011
Locatie: NVMBR te Utrecht

Workshop Ergometrie
30 maart 2011
2 november 2011
Locatie: NVMBR te Utrecht

Workshop Feedback
10 mei en 24 november 2011
Locatie: NVMBR te Utrecht

Nascholing Nucleaire Geneeskunde
22 maart 2011
Nascholing 1 SPECT CT

14 april 2011
Nascholing 2 Opleiden

22 september 2011
Nascholing 1 SPECT CT

1 november 2011
Nascholing 2 Opleiden
Locatie: congrescentrum de ReeHorst te Ede

NVMBR Jaarcongres
19 en 20 mei 2011, Hart van Holland, Nijkerk

Symposia 2011
22 september 2011
Symposium MRI

6 oktober 2011
Symposium Echografie

1 november 2011 Symposium Radiologie

12 november 2011
Symposium Radiotherapie
Locatie: congrescentrum de ReeHorst te Ede.

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Nummer 1 1 januari 2011
Nummer 2 1 april 2011
Nummer 3 1 juli 2011
Nummer 4 1 oktober 2011

Cursus- en Congresagenda

2011
NKRV Workshop
21 January, 2011. Eindhoven, The Netherlands. www.nkrv.nl

Learning Course for Nuclear Cardiology in Practice at National Heart and Lung Institute
31 January – 4 February, 2011. Londen, Great Britain .
7 – 11 February, 2011. Harefield, Great Britain. www1.imperial.ac.uk/medicine/about/divisions/nhli/nhli_events/shortcourses/

15th scientific meeting ISORBE
31 March – 2 April, 2011. Nijmegen, The Netherlands. http://www.umcn.nl/isorbe

SPECT-CT EN PET-CT: Functionele beeldvorming van de toekomst
7- 9 May, 2011. Luxembourg, Luxembourg. www.belnuc.be/nl/luxembourg-2011/luxembourg-2011-overview.html

ICNC10
15 – 18 May, 2011. Amsterdam, The Netherlands. www.escardio.org/congresses/ICNC10/Pages/welcome.aspx

ESGAR 2011
21 – 24 May, 2011. Venice, Italy. www.esgar.org

2011 IRCC International Conference on Molecular Clinical Oncology
26 – 28 May, 2011. Turin, Italy. www.cancercoop.org

17de symposium voor verpleegkundigen en paramedici
26 May, 2011. Amsterdam, The Netherlands. www.nki.nl/symposium26mei2011

SNM Annual Meeting 2011
4 – 8 June, 2011. San Antonio, USA. www.snm.org/index.cfm?PageID=9182

19th International Symposium on Radiopharmaceutical Sciences
28 August – 2 September, 2011. Amsterdam, The Netherlands. www.isrs2011.org

ASNC 2011
8 – 11 September, 2011. Denver, USA. www.asnc.org

EANM'11
15 - 19 October, 2011. Birmingham, Great Britain. www.eanm.org

2012
ESGAR 2012
12 – 15 June, 2012. Edinburgh, Great Britain. www.esgar.org

ASNC 2012
6 – 9 September, 2012. Baltimore, USA. www.asnc.org

Adreswijzigingen

Regelmatig komt het voor dat wijziging in het bezorgadres voor het Tijdschrift voor Nucleaire Geneeskunde op de verkeerde plaats worden doorgegeven. Adreswijzigingen moeten altijd aan de betreffende verenigingssecretariaten worden doorgegeven. Dus voor de medisch nucleair werkers bij de NVMBR, en voor de leden van de NVNG en het Belgisch Genootschap voor Nucleaire Geneeskunde aan hun respectievelijke secretariaten.
De verenigingssecretariaten zorgen voor het doorgeven van de wijzigingen aan de Tijdschrift adresadministratie.
Alleen adreswijzigingen van betaalde abonnementen moeten met ingang van 1 januari 2011 rechtstreeks aan de abonnementenadministratie van Kloosterhof Neer B.V. worden doorgegeven: Kloosterhof Neer B.V., t.a.v. administratie TvNG, Napoleonsweg 128a | 6086 AJ Neer of per E-mail: nucleaire@kloosterhof.nl

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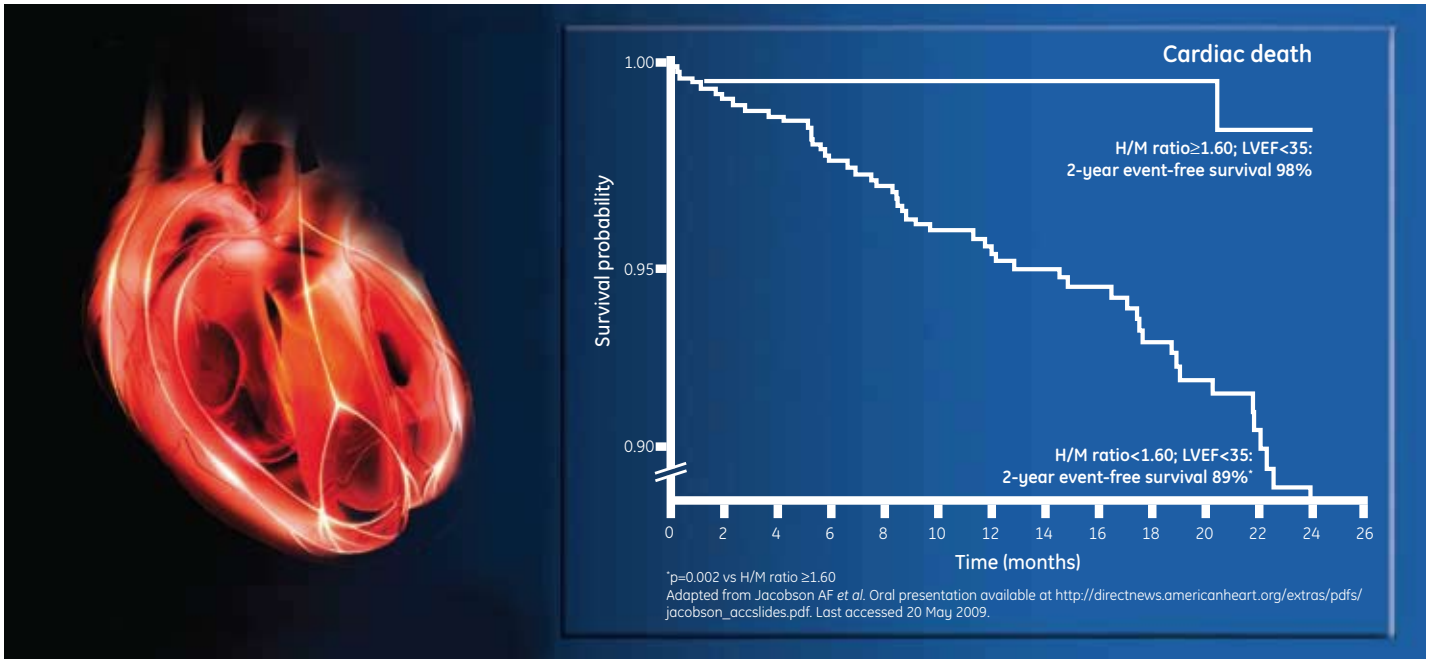

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1. Jacobson AF *et al.* Oral presentation available at http://directnews.americanheart.org/extras/pdfs/jacobson_accslides.pdf. Last accessed 20 May 2009.

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Pheochromocytomas and neuroblastomas are sensitive in approx. 90% of patients, carcinoids in 70% and medullary carcinoma of the thyroid (MCT) in only 35%. • Functional studies of the adrenal medulla (hyperplasia) and the myocardium (sympathetic innervation). **DOSAGE AND METHOD OF ADMINISTRATION** For adults the recommended dosage is 80-200 MBq, higher activities may be justifiable. Children under 6 months: 4 MBq per kg body weight (max. 40 MBq), the product must not be given to premature babies or neonates. Children between 6 months and 2 years: 4 MBq per kg body weight (min. 40 MBq). Children over 2 years: a fraction of the adult dosage should be chosen, dependent on body weight (see SPC for scheme). No special dosage scheme required for elderly patients. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. Must not be given to premature babies or neonates. **WARNINGS AND PRECAUTIONS** This medicinal product contains benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old. Administer dose intravenously over several minutes. Monitor the patient constantly during administration as, in theory, iobenguane uptake in the chromaffin granules may induce a hypertensive crisis due to noradrenaline secretion. Image 24 and 48 hours after administration. Drugs known or expected to reduce the iobenguane(^{123}I) uptake should be stopped before treatment (usually 4 biological half-lives). Thyroid blockade is started 24-48 hours before the iobenguane(^{123}I) is administered and continued for at least 3 days. Blockade by potassium perchlorate is achieved by administration of approx. 400 mg/day. Blockade by potassium iodide, potassium iodate or Lugol solution must be performed with an equivalent of 100 mg of iodine/day. Radiopharmaceuticals should only be used by qualified personnel with appropriate government authorisation and should be prepared using aseptic and radiological safety requirements. **INTERACTIONS** Decreased uptake was observed under therapeutic regimens involving the administration of reserpine, labetalol, calcium-channel blockers (diltiazem, nifedipine, verapamil), tricyclic antidepressives (amitryptiline, imipramine and derivatives), sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine or phenylpropanolamine), cocaine and phenothiazine. These drugs should be stopped before administration of iobenguane (^{123}I) (usually for four biological half-lives to allow complete washout). Nifedipine (a Ca-channel blocker) is reported to prolong retention of iobenguane. **PREGNANCY AND LACTATION** Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Only imperative investigations should be carried out during pregnancy, when likely benefit exceeds the risks incurred by mother and foetus. If administration to a breast feeding woman is necessary, breast-feeding should be interrupted for three days and the expressed feeds discarded. Breast-feeding can be restarted when the level in the milk will not result in a radiation dose to a child greater than 1 mSv. **UNDESIRABLE EFFECTS** In rare cases the following undesirable effects have occurred: blushes, urticaria, nausea, cold chills and other symptoms of anaphylactoid reactions. When the drug is administered too fast palpitations, dyspnoea, heat sensations, transient hypertension and abdominal cramps may occur during or immediately after administration. Within one hour these symptoms disappear. 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Maintain a high urine flow to reduce the influence of radiation. **INSTRUCTIONS FOR USE** Swab stopper with suitable disinfectant before removal of dose, then store at 2-8°C, use within one working day **MARKETING AUTHORISATION HOLDER** GE Healthcare Limited, Little Chalfont, UK. **CLASSIFICATION FOR SUPPLY** Subject to medical prescription (POM). **UK MARKETING AUTHORISATION NUMBER** PL 00221/ 0140.
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