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Production of ^{100}Mo for Cyclotron conversion to ^{99m}Tc

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ABSTRACT

The new cyclotron production route to manufacture ^{99m}Tc for medical imaging has made substantial progress over the past few years. Its commercial viability has now been proven and is based on a full capital cost payback, requiring no subsidy, with a much lower environmental and political profile than reactor-based ^{99m}Tc manufacturing.

^{100}Mo-isotope enriched material is vital to the cyclotron method. This enrichment can be performed at relatively low capital and operating costs using ASP technology.

ASP technology is an aerodynamic process that is a lesser-known embodiment of the principles of centrifugal separation labelled as a stationary wall centrifuge - no moving parts. It extends the stationary wall centrifuge idea which resides in the public domain, by utilising novel extensions to achieve successful isotope separation.

The much lower cost of production of enriched ^{100}Mo via ASP augments a low cost of ^{99m}Tc production along the cyclotron route that is also green.

1. Introduction

Healthcare inflation in South Africa is a runaway phenomenon that is plaguing the provision of quality and affordable medical services to all of our population. Tariffs paid to doctors and hospitals have consistently increased over the past 2 decades at rates that are substantially above consumer price index (CPI). Furthermore, the cost of cancer treatment doubled between 2010 and 2013; numbers as supplied by Discovery Health [1]. The main drive for this increase is a combination of higher treatment costs and the higher rates of cancer incidence.

The health sector in SA is peculiar in that only 18% of the population has access to medical insurance and the balance of population depends on the public health system that has been traditionally underfunded. The new National Health System (NHS) intends to urgently address the shortcomings of the current system both in terms of the standard and availability of service as well as its funding. It is, furthermore, imperative that the cost of medical services should decrease so that more of the population can have access to the specialised technologies and

services. Cancer is the fourth biggest killer of South Africans, in spite of the fact that the most common cancers are treatable if detected early enough; says the National Cancer Registry (NCR). According to South African cancer stats for the "insured population", 100,000 cases are diagnosed each year with 60,000 deaths from cancer each year (reference year 2013) [2]. Radio-pharmaceutical imaging is a very useful tool in the early diagnosis of cancers and other diseases.

It is befitting to reference the USA market for medical imaging market to assess the potential near-term future South African market for radiopharmaceuticals. The USA hospitals and clinics perform ~20 million scans per annum in a population of ~321 million; this translates to 3 million scans for the ~52 million local population. The current number of annual scans in SA is ~67,500 [3] and this is performed with ~130 SPECT scanners distributed across the country; an average of 2.3 patients per day, which is too low a utilization number for commercial acceptance.

The global cost of technetium-99m radio-isotope, the most frequently used isotope for medical imaging, is substantially subsidised and not suitable to serve the medical needs of all the South African population.

2. The Cyclotron Route for Technetium-99m Production

Alternative routes to the nuclear reactor production of technetium-99m isotopes for medical imaging have progressed greatly over the past few years. In particular the use of a cyclotron as proton accelerator to instigate a nuclear reaction has advanced to the commercial phase with astonishing technological elegance spearheaded by the outstanding work of the group at Triumf in Canada [4]. The nuclear reaction employed to directly produce ^{99m}Tc by proton irradiation inside a cyclotron utilises the following nuclear reaction: ^{100}Mo(p,2n)^{99m}Tc. The target material is the stable molybdenum isotope ^{100}Mo and this is bombarded by hydrogen nuclei, which is actually protons; in the reaction ^{99m}Tc is directly formed and two neutrons are released. The nuclear reaction that occurs inside the cyclotron is schematically pictured in figure 1.

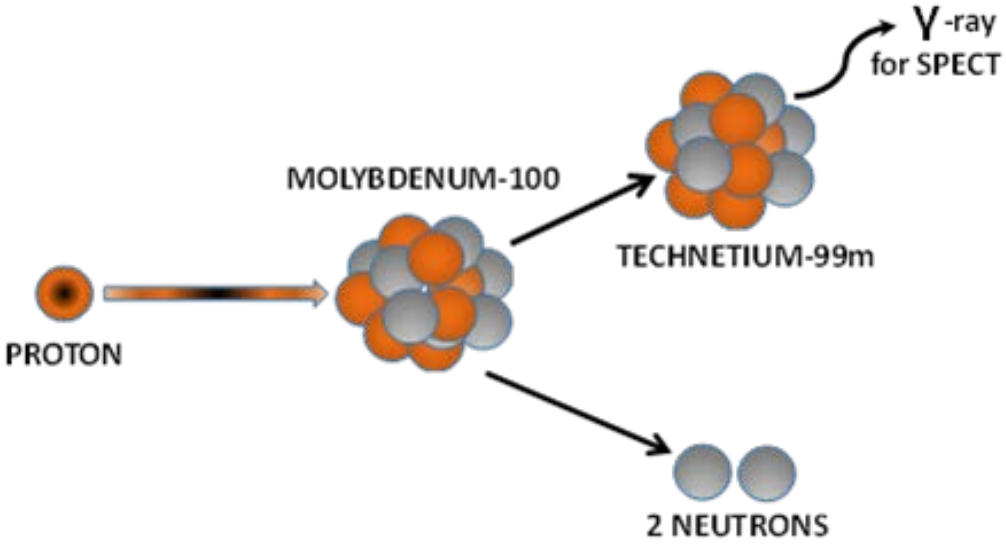

Figure 1. Proton interaction with ^{100}Mo-isotope forms ^{99m}Tc.

The production of technetium-99m isotopes is the first step in the synthesis chain to produce the radio-active labelled pharmaceuticals for SPECT scan imaging: In its natural state the metal molybdenum has 7 completely stable isotopes; i.e. they show no radio-activity. A characteristic feature of the "cyclotron route" of technetium production is the starting material, which is 99% pure ^{100}Mo; i.e. this isotope must be separated from all the remaining isotopes and the isotopic abundance of the desired isotope increased from 9.63% to 99%. Klydon developed a proprietary technology breakthrough separation process called the ASP Process (derived from Aerodynamic Separation Process) that is ideally suited for this purpose.

3. ASP Technology

ASP technology was developed from genesis technology, first detailed in the scientific media in the mid-1970s [5]. Adequate narratives can be found in patents and a leading reference for separation technologies, whilst an industrial scale enrichment plant for uranium was constructed utilising the so-called "stationary-wall centrifuge" [6-8]. The development of ASP over the past 18 years culminated in a much more advanced device that can compete handsomely on an industrial and commercial scale. The schematic presentation in figure 2 serves to highlight the current state of performance and the understanding of several important features of such a device. This separation device separates both gas species and isotopes in a volatile state via an approximate flow pattern as show cased in figure 2.

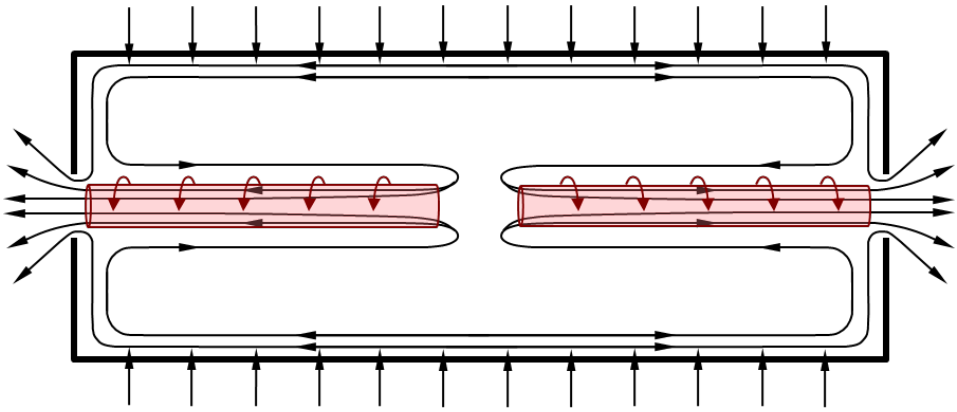

Figure 2. Gas flow pattern inside ASP separation device.

The process gas enters the vessel container after tangential injection through carefully placed and sized openings at the surface of the containment; then it follows a flow pattern that concludes in two mini-centrifuges around the geometrical axis of the separator as shown. Each of the centrifuges is fed material that becomes separated in the radial dimension as a result of the spin speed reaching several hundred meters per second. An axial mass flow component in each centrifuge feeds isotope material to the respective ends of the vessel where the harvesting of the portions is accomplished. The technology is classified as "dual use technology" and in terms of International Atomic Energy Agency protocols detailed information is controlled.

There are three operating parameters that most critically describes the separation performance of any device; the isotope enrichment factor per single step of the device, the associated "cut" per step of enrichment, which is the ratio of the mass flow of the desired isotope in the product stream relative to the same quantity in the feed stream; and the mass flow of the isotopes through

the device. The enhanced isotope enrichment factor for ASP compared to other separation processes for the oxygen-18 system was previously reported [9]. Mathematical analysis of cascade theory in an isotope enrichment plant also reveals that the cut is one of the most important parameters for cost minimization. Accordingly this parameter was studied intensely over several years. It is crucial to operate the separation device at a symmetrical cut, i.e. 50% mass flow in both the product and waste streams of the separation configuration. The genesis technology demonstrated a low cut of 4-6% [10], which for molybdenum enrichment is insufficient. In figure 3 the remarkable improvement in the cut parameter obtained in our program over time is reflected.

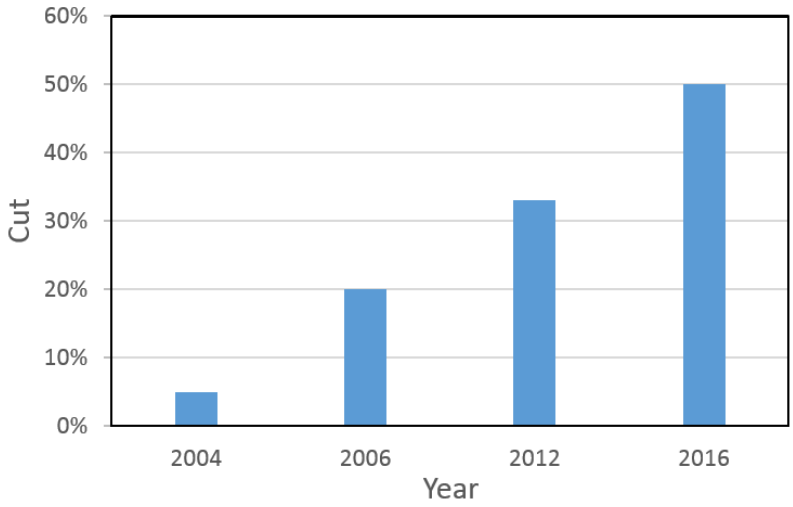

Figure 3. The "cut" parameter of ASP technology.

The ASP technology is a truly profound technology with many applications in isotope and gas separation systems. The advantages of ASP technology can be summarised:

- The ASP technology separates gases and isotopes.
- The separation process occurs inside a closed cylindrical container and is a volume technology, i.e. the process efficiency is not effected by poisoning of surface contaminates as is the case for surface separation processes.
- ASP operates most efficiently at molecular masses below 100 atomic mass units.
- ASP easily separates hydrogen gas from other gas components, e.g. harvesting hydrogen gas from carbon monoxide and carbon dioxide, and altering the ratio of syngas mixture.
- ASP clean-up natural gas
- With the right material choice ASP handles even the most corrosive gases.
- ASP can separate any isotopes that have a gaseous or volatile chemical compound.
- For low volatility chemical compounds ASP is operated at elevated temperatures with great success.
- The ASP process is easily scaled to industrial level and most of the subsystems are procured from shelf items in market.
- The capital cost of an ASP plant is relatively low.
- Commercial viability is achieved at small plant level.
- An ASP plant can be constructed in any country that adheres to the International Atomic Energy Agency (IAEA) protocols for the protection of dual use technology.

4. Molybdenum-100 Isotope Enrichment Plant

A typical ASP isotope enrichment plant is schematically pictured in figure 4 to explain the main systems in plant design. For the case of molybdenum-100 isotope enrichment the process gas is molybdenum hexafluoride (MoF_6) which has a sufficiently high pressure at ambient temperatures. The molybdenum bearing molecule is mixed with helium gas through a mixing station (at 1 in the diagram) to a combined molecular mass of 20-35 grams/mol; this is to enhance the separation factor by achieving a higher spin speed in the device than with MoF_6 on its own. The feed point of process gas mixture is between the enrichment and stripping sections of the cascade respectively labelled by 3 and 2. Both the enrichment and stripping section handles a forward flow and a backward flow of mass to conserve mass at any point in the cascade. An outstanding feature of the ASP cascade is that the feed can be any isotope concentration and the same blocks can handle different isotope concentration profiles.

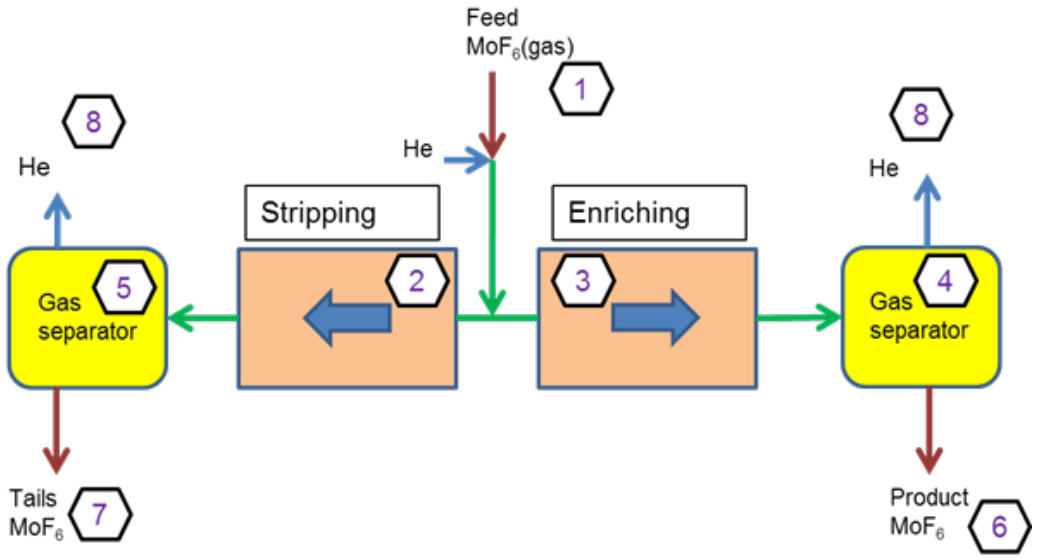

Figure 4. Schematic presentation of ^{100}Mo enrichment plant by ASP.

At the top end of the enrichment section the MoF_6 and helium is separated by a gas separator, at 4, and the helium recycled, point 8, and the product withdrawn from the plant at 6; the ^{100}Mo concentration is larger than 99%. An atomic mass difference of 2 separates the desired isotope from the next lower lying mass of ^{98}Mo. It is the even lower mass isotopes that are unwanted in the cyclotron irradiation step and this elimination is effectively achieved with ASP. Similarly, at the bottom end of the stripping section the MoF_6 and helium is separated, point 5, into the tails portion, point 7, and the helium is recycled into the cascade.

Gas separation of the helium and MoF_6 (or any other gas species) can be easily accomplished by utilising the ASP separation element optimised for the molecular mass range pertinent to this specific application. An appropriate gas separation demonstration for helium at atomic mass 4 and SF_6 at molecular mass 146 is show cased in figure 5; this data simultaneously reports the separation ability of the device and the operation at elevated temperature of 200 ^{o}C referenced to ambient temperature results. In the nomenclature the parameter Beta (β) is the heads enrichment

factor derived from the abundance ratio between feed gas flow and enriched flow [11], Alpha (α) is the enrichment factor between feed flow and waste or tails flow, and Gamma (γ) is the abundance ratio between feed flow and waste flow. Elevated temperature clearly has no practical waning effect on separation performance as illustrated in the data. The separation of helium and MoF_6 the latter at molecular mass 214 is even much more pronounced than for the illustrated case.

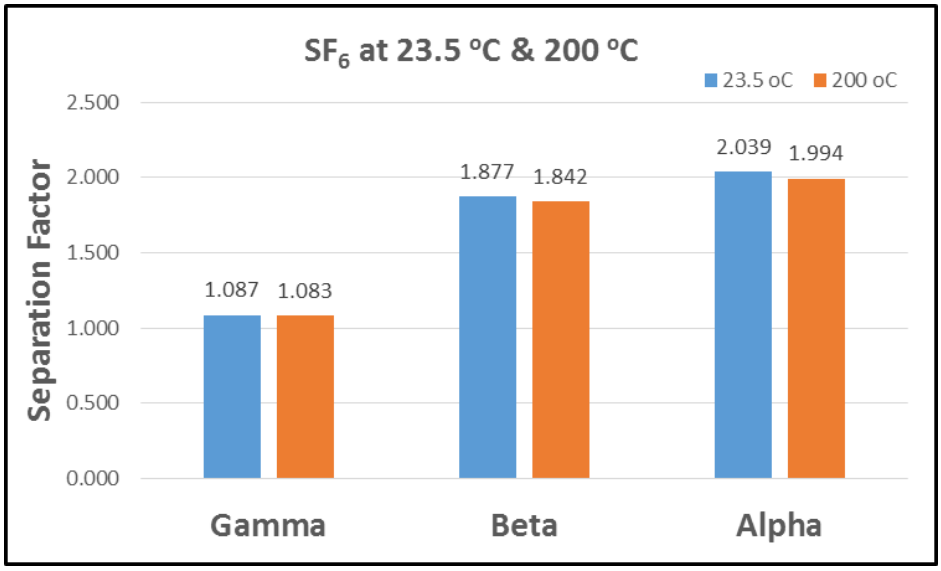

Figure 5. Gas separation of helium and SF_6.

The separation elements per enrichment stage (or depletion) are housed together in a common vessel and each stage has 2 vessels; a primary separation vessel, and a secondary vessel. After each primary separation the pressure is sufficient to drive another separation step, which enhances the separation performance per stage by ~30%. In figure 6 the two housings are shown in an ASP plant. An ASP plant has a small footprint as is shown in figure 7; put another way it earns substantial revenue per square meter of footprint.

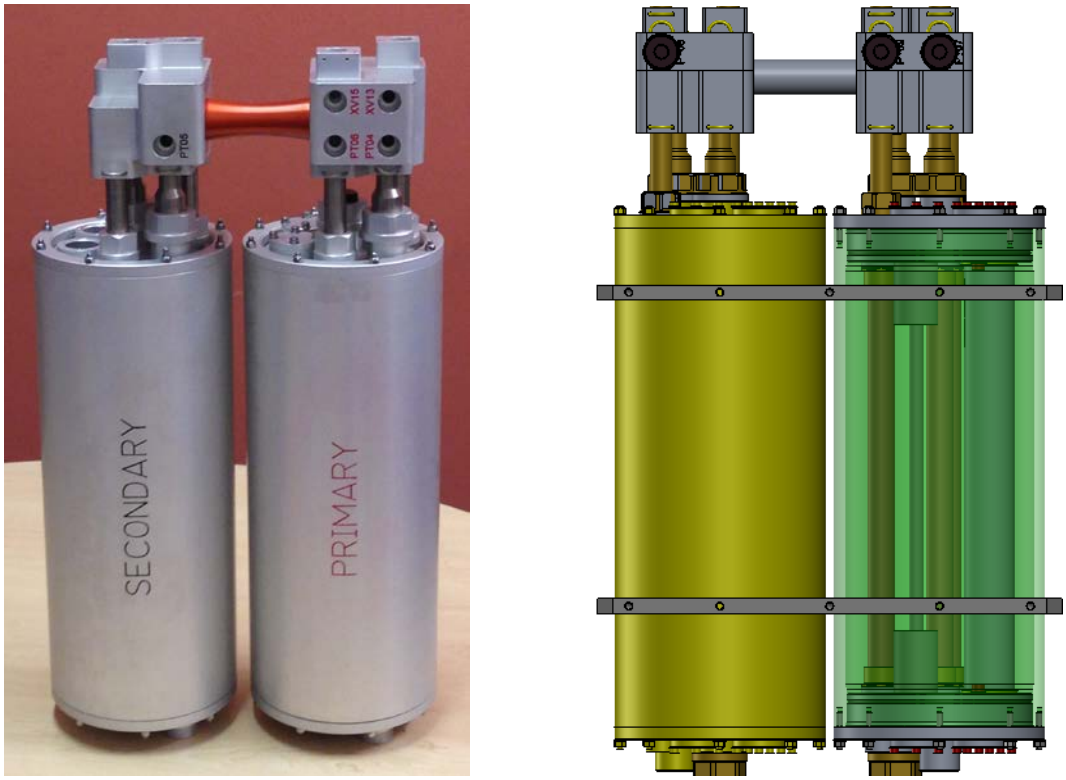

Figure 6. Primary and Secondary ASP separating element assemblies.

Figure 7. ASP Separating Plant.

5. Techno-Economics for ^{100}Mo Production by ASP

An ASP enrichment plant to produce ^{100}Mo is currently under construction in South Africa. The production capacity of the plant is 10 kilogram of 99% isotopic abundance. Klydon completed, and it is operational, two ASP plants that respectively produces Oxygen-18 and harvest methane from natural gas. Accordingly, the confidence level in our techno-economic analysis for the molybdenum isotope plant is high. The production cost of enriched molybdenum isotope is somewhat sensitive to the cost of electricity as can be seen from the data of figure 8. The first case features the production cost and cost components for an electricity price of ¢3.7/kWh as may be applicable in Liechtenstein and Norway. The second case is for an electricity price of ¢15/kWh as may be appropriate for South Africa and several other countries. In both cases the isotope enrichment production cost is below $500 per gram. The unit production cost decreases as the plant capacity increases.

In a free cash flow model the capital cost of the enrichment plant is provided for by loan capital at a cost of 8% per annum and this is repaid over 10 years; the contribution of isotope to the unit production cost of a dosage of technetium is less than $10. The construction time of a 10 kilogram plant is 18-24 months and the plant is subject to regular IAEA inspection.

The USA is the main consumer of technetium-99m radio-isotope for medical imaging. An extrapolation of the numbers applicable in USA to the global market confirms that the potential market size is ~1400 kilogram of ^{100}Mo at 99% enrichment at 1.5 gram target material for each cyclotron irradiation. The two largest market sectors is China (700 kg) and India.

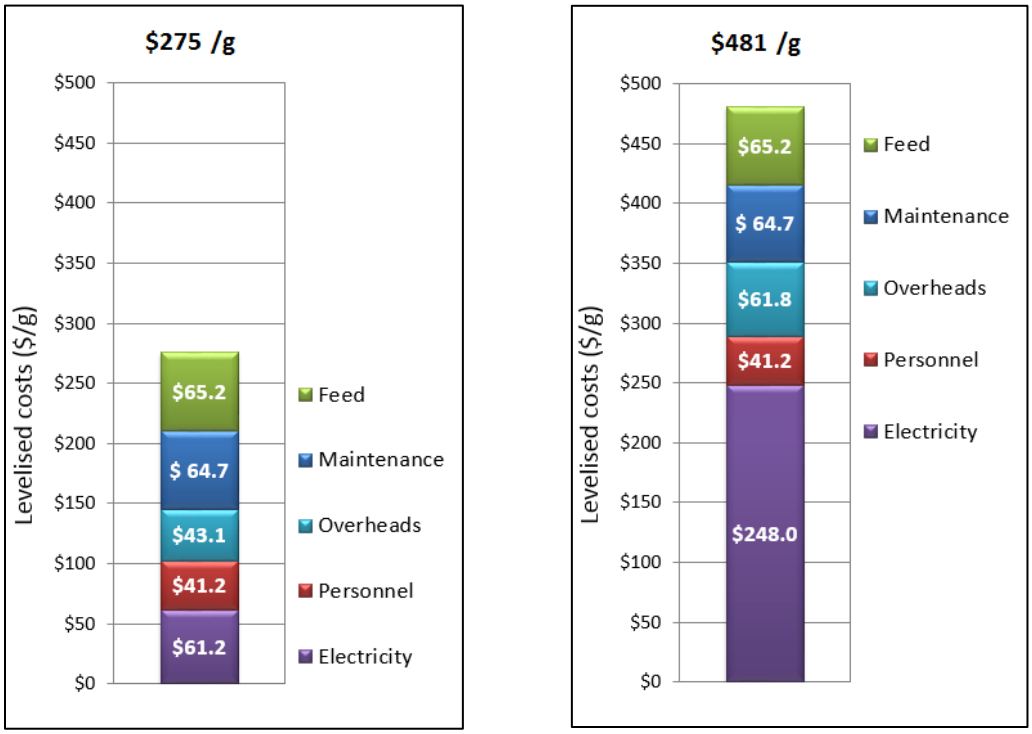

Figure 8. Production cost for enriched ^{100}Mo with ASP. The 2 cases show electricity price sensitivity.

6. Dosage Price for Cyclotron Production

A comprehensive cost analysis based on current performance specifications of cyclotrons, on the market, in combination of the ASP production numbers paints a decisive picture of the commercial potential of the cyclotron route to produce technetium-99m dosages. The dominate performance parameters of the cyclotron is a beam energy of 16.5 MeV and beam current of ~500 microampere (μA). A single irradiation run of 6 hours manufactures 15 Curies (Ci) of useable ^{99m}Tc, which is diluted to an average dosage activity of 20 mCi and can be repeated 210 times per annum. Again the capital for the cyclotron is loan capital at 8% interest rate. The pie chart of the cost components in the unit production cost of technetium dosages is reflected in figure 9.

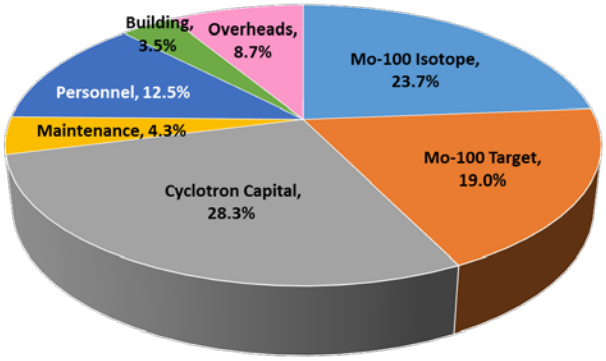

Figure 9. Cost components for technetium dosages produced by cyclotron route.

The potential market price for enriched ^{100}Mo isotope per gram can be highlighted by inspection of the selling price of technetium dosages relative to the current market price as quoted for Belgium; the only clear indication of price at $26 per dosage published [12].

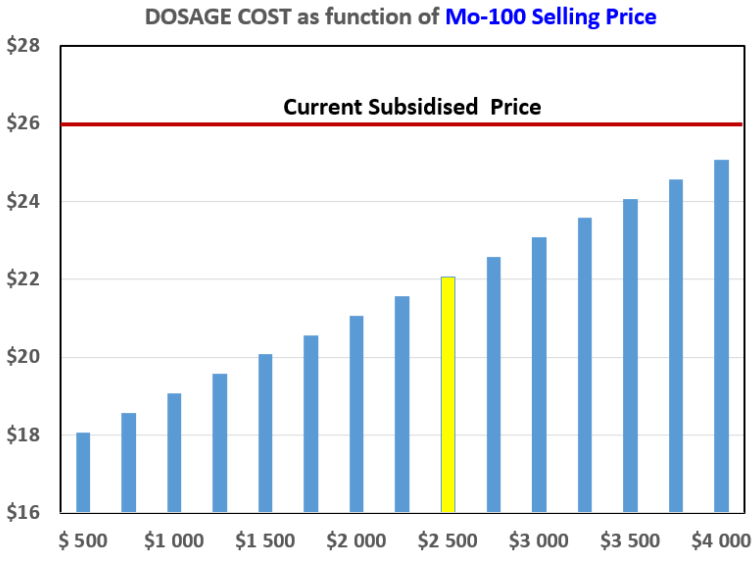

Figure 10. Dosage dependence on enriched ^{100}Mo selling price.

7. Conclusions

The production of isotopically enriched ^{100}Mo at commercially attractive cost is an important step and parameter for the cyclotron route of ^{99m}Tc manufacturing for application in medical imaging. The ASP isotope and gas separation process developed over the past decade and a half fills this request elegantly, whilst it simultaneously find profitable use in several medical isotope systems.

The production cost structure requires no monetary subsidy and the cyclotron route of technetium dosage manufacture can complete very favourably in the current price structure of the SPECT imaging modality.

8. Acknowledgement

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9. References

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