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Future Supply Options of ^{99}Mo and ^{99m}Tc

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ABSTRACT

Global efforts to decrease nuclear proliferation, shifts to full cost recovery (FCR), and impending end-of-service of key nuclear reactors are challenging current production methods, distribution, availability and cost of molybdenum-99 (^{99}Mo) and Technetium 99m (^{99m}Tc). Ge Healthcare has commercial interests across the nuclear medical diagnostics industry, spanning from: nuclear cameras, ^{99}Mo generators, radio-pharmacies, isotope and medical tracer production. GE Healthcare, including infrastructure units (Corporate Global Research, PET Cyclotrons, Nuclear Imaging, etc), took the opportunity to look across all elements of the developing landscape for ^{99}Mo and subsequent ^{99m}Tc production. Based on public reports information and our knowledge of the market, GE believes that the future of ^{99m}Tc will most probably evolve towards a combination of global distribution and local production, built on advancements from academia, national labs, and private industry. A review of the landscape and a potential future supply model is presented here. Technology, regulatory, and distribution advancements should enable secure and affordable patient access to this critical medical diagnostic capability.

Introduction:

The GE Healthcare portfolio allows a unique industry perspective in relation to supply chain issues, imaging agents and cameras for the nuclear imaging field.

GE Healthcare maintains a global installed base of over 5,500 nuclear imaging cameras, with multiple product offerings providing nuclear imaging cameras and combined nuclear imaging / computed tomography systems to its medical customers.

The Life Sciences Core Imaging business unit of GE Healthcare ("GELS") develops, manufactures, and ships thousands of ^{99}Mo generators, supplying over 38 countries globally. From June 1st, 2014 and following the approach recommended by the US Food and Drug Administration (FDA), GELS is now supplying generators for the production of sodium pertechnetate; technetium (^{99m}Tc) injection to its chain of 31 radio pharmacies in the US. Overall, it is responsible for more than 30 percent of the world's supply of radioactive tracers.

GELS provides a broad portfolio of ^{99m}Tc-based products, helping to ensure accurate disease diagnosis and enabling subsequent appropriate patient management.   Figure 1 highlights some of the disease areas covered by these products.

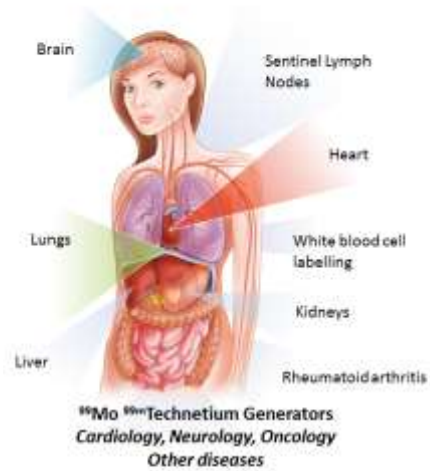

Figure 1: Medical uses of GE Life Science ^{99m}Tc-based products

The GE Radio-pharmacy Cyclotron business in Uppsala, Sweden supports a growing global installed base of over 330 PET medical cyclotrons.

Technetium-99m (^{99m}Tc) is a key isotope for cardiology, oncology, and other nuclear imaging applications. Therefore, the impact of Full Cost Recovery (FCR), transition to Low Enriched Uranium (LEU) from High Enriched Uranium (HEU) and aging irradiation/processing infrastructures must be considered in the future supply model. Analysis of past and current global supply for Molybdenum99 (^{99}Mo) and the medical demand for it have been presented by several authors, e.g. (Ballinger, 2010), (Pillai, 2013) (NOORDEN, 2013). Since 2009, predictions of supply, regulatory, economics, and alternate technology maturity have reduced the risk of supply not meeting demand; however secured supply is still not yet guaranteed. Through a campaign to improve usage efficiency, OECD suggests the predicted demand for ^{99}Mo has decreased by 20%, while sustaining a prediction of 2-5% growth in global medical procedures (OECD, 2010), (OECD N. , 2014). This efficiency gain sets baseline market need as 10,000 six-day curie of ^{99}Mo, or approximately 115,000 doses of ^{99m}Tc doses daily[1], with a predicted 3% annual growth.

Figure 1: GE product portfolio in Molecular Imaging associated with ^{99m}Tc

Current and Projected Centralized Distribution Production

The current process map for ^{99m}Tc generation has been evaluated in many references in the past 5 years. (Sciences, 2009) A simplified illustration is presented in Figure 2. The estimated supply volume of main irradiation is summarized in Table 1.

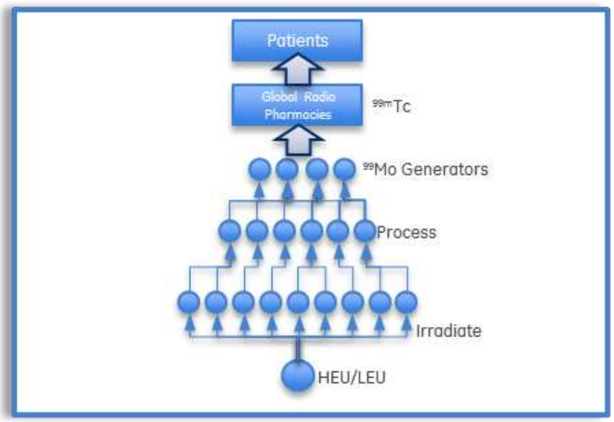

Figure 2: Simplified Illustration of today's 99mTc Supply Chain. (Representative of 90% production volume)

Reactor	Location	Age	Est. % Supply
NRU	Canada	55	33%
HFR	Netherlands	53	33%
BR-2	Belgium	53	9%
Safari-1	South Africa	49	15%
OSIRIS	France	48	<5%
OPAL	Australia	8	<5%
Others	-	-	<5%

Table 1: Estimation of current supply chain irradiation volume division.

The OECD is predicting that centralized irradiation and processing capability will meet global isotope demand through 2020. This is assuming a minimal disruption of supply during this period and a maximum requirement of 35% outage reserve capacity (ORC), if needed. After this, the introduction of alternate production techniques, existing reactor/processor capacity increase and new reactors into the market is predicted to meet, and potentially exceed, medical demand beyond 2020.

The main projected losses in ^{99}Mo supply are from:

- the removal of irradiation capability from OSIRIS, France (2015[2])
- the removal of irradiation and processing capability from Chalk River, Canada (2016)

Together, these two account for approximately 38% the current world ^{99}Mo supply and Chalk River [NRU] is currently the major contributor to the USA market supply.

However, increases in traditional fission irradiation and processing capabilities from production at the Ansto/Opal facility, increased irradiation volume at BR-2, and the introduction of FRM-II in Munich and JRH in France [2020], should be capable of offsetting some of the supply decreases.

The OECD prediction stated above also requires success from new irradiation and processing programs in the United States (SHINE, MURR/Northstar), LINAC Production (Northstar), and other entries and improvements from research reactors. (OECD N. , 2014), (Galea, 2013)

Each approach is built on sound scientific principles and, on the assumption that regulatory, financial, and engineering risks can be overcome successfully in a timely fashion.

Potential Future Supply Model

One of the main concerns in the period of 2015 to 2020 is Outage Reserve Capacity (ORC). Centralized production and processing sites have inherent sensitivity to a single point of failure, influencing short-term isotope availability. Average demand may be met over the calendar year, but a period of 2 to 3 weeks may have limited isotope availability. In 2010, due to unexpected reactor issues and prolonged 'down' time, ^{99}Mo was only available to the medical community in limited quantities for multiple days and weeks. To access ORC in the short-term, the community turned to research reactors. However, the introduction of unused capacity from research reactors to ^{99}Mo irradiation workflow leads to integration challenges in processing protocols, regulatory considerations and distraction from the core mission of the research reactors.

One path to abate the supply risks in the 2015-2017 interval, to decrease reliance on new developing irradiation and processing sites, and further improve ORC in the future, is to leverage the current and future global cyclotron network. Over 500 mid-energy PET cyclotron installations have the potential to be modified to directly produce ^{99m}Tc. Even with a shorter distribution range, inherent of the 6 hour Tc-99m half-life, a single 100 - 250 µA, 16 MeV

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[2] License Extension being considered by the French Government.

cyclotron has the potential to provide sufficient nuclear imaging coverage to a population size close to 1-2 million people.[3] (see Section: Direct Production of ^{99m}Tc on PET Cyclotrons)

Figure 3 shows a potential evolution of the supply chain presented in Figure 2. In this new model, the majority of the market would be served by the ^{99}Mo generator current supply chain infrastructure. During outages, cyclotron operators could shift isotope output to ^{99m}Tc production. A local community could be served by a cyclotron to increase PET Radio pharmacy asset utilization. Using New York State as an example, most rural regions and large population centers (New York City Metro Area 20M) may be served by ^{99}Mo generators, as is common practice today. Mid-sized regions, such as the capital district (~1M) may be primary served by cyclotron production of ^{99m}Tc. During times of single or dual central irradiation outages, production in existing ^{99m}Tc cyclotron production sites would increase, in combination with ORC from primary PET cyclotron centers enabled with ^{100}Mo Targets and chemistry capability.

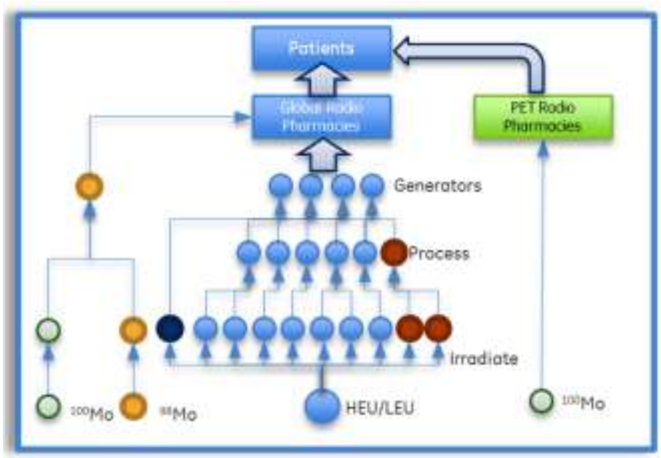

Figure 3 Potential Simplified Future Supply Chain of 99mTc

A rough estimation of this model suggests daily operation of 100, 250 μA, 16 MeV cyclotrons producing ^{99m}Tc, would increase the irradiation and processing ORC by >15 points.[4]

Direct Production of ^{99m}Tc on PET Cyclotrons:

Cyclotron produced ^{99m}Tc has been presented since 1970. (Beaver JE, 1971) Two groups:

- TRIUMF, British Columbia Cancer Agency, Lawson Health Research Institute, and Centre for Probe Development and Commercialization; and

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[3] Estimate assumes 5% of the population receives one 25 mCi dose per year, 10 Ci produced per 6 hour production run of 16 MeV, 130 microamps , 50% loss in chemistry, processing and delivery. 5 production days per week for 50 weeks.

[4] Assumes: 30M, 25 mCi ^{99m}Tc annual scans are performed annually. (mCi on a Cyclotron)/(mCi used in 1 week of scans) = (100*5 Ci*5 days)/((30M)/(52 weeks)*(25mCi)) = 17%. This illustration does not account for global cyclotron distribution versus patient usage.

- University of Alberta, Centre Hospitalalier Universitaire de Sherbrooke and Advanced Cyclotron Systems Inc.

are actively retiring the technical, economic and regulatory risks of this process. 16 MeV, 19 MeV and 24 MeV cyclotrons have been proposed for ^{99m}Tc generation. ^{99m}Tc production on 16 MeV systems will have fewer by-products at a lower production rate. (Celler, 2011) It is suggested, at higher energies the minority Molybdenum contaminants in the ^{100}Mo target will produce different Technetium radioisotopes which cannot be separated chemically from the ^{99m}Tc, increasing the radiation dose on the patient and lowering the specificity of the desired radiotracer. (Quaim, 2014)

There are over 900 cyclotrons worldwide serving the PET scanner base. An estimated of the install base, distributed by vendor and energy, is shown in Figure 4a. One of the main functions of this network is the generation of ^{18}F. The global distribution of the GE installation base is shown in Figure 4b.

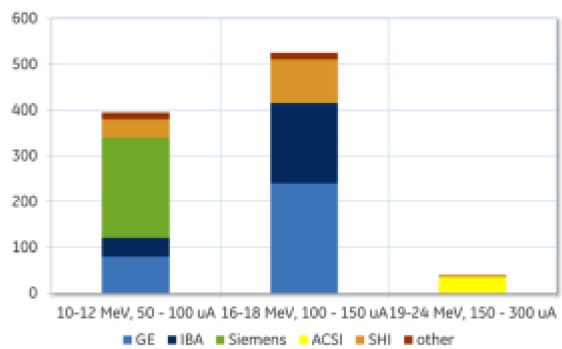

Figure 4A: Distribution of PET Mid-Energy PET Cyclotrons by Energy & Vendor. Data provided by Siemens, IBA, and ACSI. Sumitomo data is estimated. (Left)

Figure 4B: Global Distribution of GE Cyclotrons. (Right)

Annually, 60 to 70 new cyclotrons are added to the installed base, as new capability or replacement units. The installation cost of a new cyclotron, chemistry center and supporting infrastructure ranges from 5 to 10 Million USD. Installing dedicated new capacity for ^{99m}Tc may be challenging from a customer business model and a cyclotron production rate. A more immediate solution to secure a cyclotron-produced ^{99m}Tc supply in the next 2-5 years would be to leverage existing site installations. D. Dick proposes (Dick, 2014) a cyclotron workflow leveraging the period between 12 pm and 10 pm in existing cyclotron centers for ^{99m}Tc. This would be done prior to the production of shorter half-life PET isotopes from 12 am to 6 am. Existing cyclotrons fitted with ^{100}Mo solid targets and appropriate downstream chemistry, combined with field upgrades to improve output capacity, can serve the next decade of ^{99m}Tc and PET isotope production. As cyclotron production becomes established, in parallel to the growth of PET isotope usage, new, higher current product offerings will continue to decrease production costs of ^{99m}Tc, approaching the cost of high volume, centralized production. An estimation of the production volume as a function of beam current is shown in Table 2.

Beam Current (uA)	Production Volume (Ci)	Estimated Number of 25 mCi dose per 6 hour run (assuming 50% loss)
130 (IB)	5	100
250 (IB Upgrade)	10	200
400 (Future)	15	300

Table 2: Estimation of Cyclotron production vs. beam current for a 16 MeV beam energy. (based on 5 Ci production at 130 uA, 16 MeV) (Schaffer, 2014) (Lawson and CPDC both demonstrated ~5 Ci production in 6 h irradiation runs at 130 µA)

^{99m}Tc generation capability and ^{100}Mo recovery has been demonstrated by both Canadian groups. (Guérin, 2010), (Gagnon, 2011), (Morley, 2012) (Bénard, 2014) ^{99m}Tc generation of 5 Ci on a 16 MeV, 6 hour, 130 µA production run has been shown. (Schaffer, 2014) (Zavodszky, 2014) Figure 5 shows the ^{100}Mo target produced at TRIUMF. The recovery of ^{100}Mo has shown to be feasible, obtaining at an efficiency of ~85%. (Morley TJ, 2012) The economic model of producing ^{99m}Tc on an existing installation must include elements of ^{100}Mo recycling and production costs, staffing and operating cost, cyclotron service cost from increased usage, chemistry cost and labor, dispensing, quality control, general lab expenses, handling, distribution, etc. As beam intensity increases, ^{100}Mo target recovery is established, and costs of cyclotron usage can be defrayed by parallel manufacturing of PET isotopes, cyclotron produced ^{99m}Tc may become cost competitive with the new base cost of ^{99}Mo set by LEU conversion and FCR.

Figure 5: (top left) TRIUMF-designed, GE PETtrace solid target capsule; (top right) (Schaffer, 2014) (SK Zeisler, 2014) with mounted ^{100}Mo target (bottom left) enriched ^{100}Mo target mounted on a copper test backing; (bottom right) enriched ^{100}Mo after 6hr, 130 µA irradiation (Schaffer, 2014)

The establishment of a PET cyclotron production base requires the solution to two main challenges; regulatory approval of cyclotron generated ^{99m}Tc and the development of an affordable, sustainable ^{100}Mo supply and reprocessing workflow. This may be addressed with international and domestic capability of ^{100}Mo enrichment and ^{100}Mo target fabrication, reprocessing and recycling.

Currently TRIUMF and GE are collaborating to establish technical feasibility of the production of ^{99m}Tc on two GE PET Trace 880 cyclotrons. (Schaffer, 2014) (Zavodszky, 2014) As the Canadian team develops the economic and regulatory solution to this workflow, it may serve as a model to other nations as a potential option to enhance outage reserve capacity; while meeting the production needs of mid-sized population centers.

Conclusions:

The past, current and upcoming global supply chain challenges of ^{99}Mo, FCR, and conversion to LEU production will stress the current medical imaging supply chain. As the decade continues, price increases and supply disruptions are probable, but with potentially less severity then originally projected in 2010. In a recent publication (OECD N. , 2014), OECD predicts entrepreneurial approaches and fission based LEU production will sustain the distribution model, with ORC challenges in 2017. GE Healthcare is positioned to maintain its current role as a provider of nuclear cameras, agents, ^{99}Mo generators, and radio pharmacies. With regulatory approval and support establishing a ^{100}Mo supply chain, a global introduction of cyclotron produced ^{99m}Tc may enable a stronger ORC position and local supply independence in 2017. This also creates additional tolerance to potential delays of the alternate production techniques entering the market from 2016 to 2020. Government, Industry, Academia and Entrepreneurs must collaborate to provide a stable supply of isotopes from today to beyond 2020.

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