4 The Tc-99m supply chain is technically complex and characterised by market imperfections

Supply of Technetium-99m (Tc-99m) is a just-in-time activity requiring continuous production in a complicated and aging supply chain that combines a mix of governmental and commercial entities. Governments control the availability of enriched uranium required for medical isotope production and also largely control the regulatory framework and the legislation around health care provider payment for nuclear medicine diagnostic scans. The central steps of the supply chain, including processing and generator manufacturing are mainly commercial. Processors and generator manufacturers wield market power and market concentration has increased in these parts of the supply chain, while supply continues to be supported by some government funding of nuclear research reactors that perform irradiation and of some processors. The resulting inability by reactors to increase prices sufficiently for full cost recovery and insufficient outage reserve capacity at various steps of the supply chain leave security of supply vulnerable and the market economically unsustainable.

4.1. Introduction

This Chapter describes the global supply chain for Mo-99/Tc-99m. It breaks the supply chain down into the main steps, between irradiation of uranium targets in nuclear research reactors (NRRs) and Tc-99m administered to patients, and describes the structure of the industry and product market at each step. It then explores historical factors that contributed to market imperfections and an economically unviable supply chain. The Chapter concludes with an assessment of the viability of the supply chain based on current estimates.

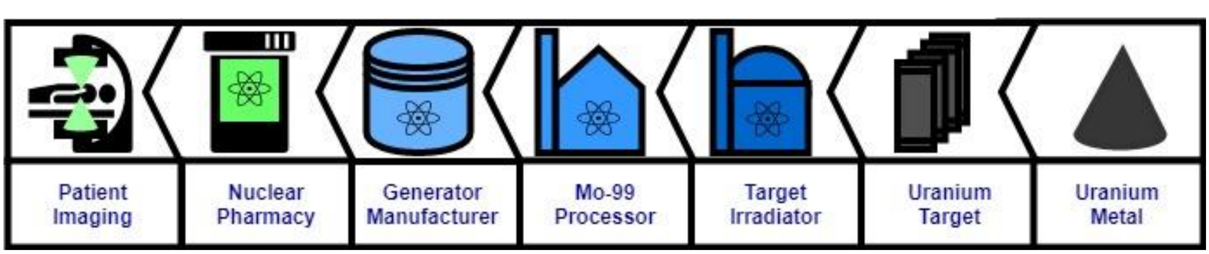
4.2. Overview of the supply chain

Patients are the ultimate beneficiary of the medical isotope supply chain. As described in Chapter 1, there is substantial value to health care from successful diagnosis of medical conditions, the assessment of patients for future therapeutic interventions and the monitoring of their treatment in real-time.

The short half-life of Mo-99 requires continuous production and just-in-time delivery. Overall, the Mo-99/Tc-99m supply chain is complex and faces a number of significant challenges, both in the short- and long-terms. An ever-present factor in the supply chain is the need to get the product to patients quickly to minimise decay and the related loss of its value. Given the short half-lives of Mo-99 (66 hours) and Tc-99m (6 hours), Mo-99 cannot be efficiently stored and Tc-99m must be prepared at least daily. In all practical terms, the economics and medical utility of Mo-99/Tc-99m imaging depends upon near continuous production of Mo-99, logistical efficiency and just-in-time delivery throughout the global supply chain.

Each radiopharmaceutical dose for a nuclear medicine imaging procedure is prepared locally on the day of use by independent nuclear pharmacies or by in-hospital radiopharmacy departments. They elute Tc-99m at least once per working day from Tc-99m generators and use it to label "cold kits." Tc-99m can also be used in a more limited way directly as pertechnetate. Cold kits are non-radioactive chemicals and bio-molecules that are specific to the organ system or anatomical area targeted in individual imaging procedures. The generators, which last for up to two weeks, are delivered on a number of prescribed days per week from specialist generator manufacturers, who produce and distribute them at a local or regional level, using bulk Mo-99 purchased from processor organisations that operate globally. Processors procure special uranium targets and arrange their irradiation in nuclear research reactors (NRRs) with suitable characteristics. Processors thus play the main co-ordinating role in the supply chain and have the primary responsibility for ensuring sufficient supply is always available. Figure 4.1 is a simplified illustration of the mains steps in the Mo-99 supply chain, from the uranium raw material to the patient scan.

Figure 4.1. Simplified structure of the Mo-99 supply chain



Source: Authors

4.3. There are five main steps in the current supply chain

This Section describes in some detail the structure and economics of the global Mo-99 supply chain. A sub-section is dedicated to each of the five main types of participants in the supply chain: patients and health care providers; nuclear pharmacies; generator manufacturers; processors and nuclear research reactors (NRRs). Each sub-section describes the structural characteristics of the industry and the main implications for the economics of the supply chain.

4.3.1. Patients and health care providers

Specialised health care providers perform NM diagnostic scans and require a continuous supply of medical isotopes. Details on the types of providers that perform scans in each country are provided in Chapter 3.

Individual patient doses are prepared against individual prescriptions on the day of use and administered shortly before the patient is scanned. Imaging facilities require a range of highly skilled medical staff, suites of imaging cameras and high power computing capability to collect, analyse and store the data created by the procedures. All the equipment is dedicated to the purpose of nuclear medicine imaging, with some even dedicated to a specific sub-set of procedures (e.g. cardiology) and the facilities must be built and equipped with specialist infrastructure to receive, store and use radioactive materials while also being subject to pharmaceutical regulatory controls.

The cost to set up, operate and regulate nuclear medicine imaging facilities is high, the equipment is expensive and cannot be repurposed, and the staff is specialised. Some providers operate independently, while others operate within larger departments that offer other types of medical imaging services.

Without a secure daily supply of medical isotopes, an imaging facility must immediately change, limit, or cease operations. During isotope shortages, staff must continuously work to manage the difficult balance between the continuing demand for patient examinations while making the best use of the limited and decaying stock of isotopes available. Staff often will go to extreme lengths and personal inconvenience to maintain as many services as possible. Chapter 1 of this report discusses the options and challenges associated with substituting Tc-99m – based scans with alternative diagnostic services during times of supply shortage.

4.3.2. Nuclear pharmacies

The role of the nuclear pharmacies varies significantly between countries

Doses, either as an individually named patient dose, or as multi-dose vial for further sub-dispensing within an imaging facility, are normally prepared in a specialist nuclear pharmacy, also referred to in some countries as “radiopharmacy.” The primary type of nuclear pharmacy model in a country has a strong influence on the way patient dose provision is arranged. This may also influence the cost of the NM imaging services.

Nuclear pharmacies may be an integrated part of a hospital or clinic providing only local services or may be independent organisations that provide commercial services to multiple imaging providers. Nuclear pharmacies may compete fiercely where imaging providers can source patient doses from a number of commercial nuclear pharmacies. This is in stark contrast to the dynamics of an in-house local radiopharmacy model, where pharmacies do not compete. There are many shades between competitive models and where such competition is completely absent. In France, for example, independent nuclear pharmacies do not exist. In the United States, competing commercial nuclear pharmacies are the predominant suppliers. Some countries, such as the United Kingdom, have the full range and publicly owned nuclear pharmacies that serve their local hospital may also compete with independent commercial services.

Nuclear pharmacies can have market power in some countries

Nuclear Pharmacies may operate in large chains and these chains can have significant market power. Generator manufacturers who supply commercial nuclear pharmacies with significant market shares are faced with customers that have market power. For example, the largest nuclear pharmacy chain in the United States, supplies around 50% of all demand in the United States and consumes more than 20% of all Mo-99 produced worldwide.

In some large markets, the number of Tc-99m-based imaging examinations has declined since 2010. For example, in the United States the nuclear medicine scan rates per 1 000 enrolled Medicare beneficiaries declined by 25% in the period from 2010 to 2014 (Levin et al., 2017[1]). Worldwide revenue of the two manufacturers that dominate the United States market declined by 11.3% between 2012 and 2013[1] and the number of commercial nuclear pharmacies operating in the United States also declined in that period. A declining market with strong competition among nuclear pharmacies created further price pressure upstream in the supply chain.

Nuclear pharmacies drive the efficiency of Tc-99m use through patterns of delivery and elution

To provide patient dose services, nuclear pharmacies purchase generators from specialist pharmaceutical companies. Generators are sold in a wide range of activity sizes, based upon their Mo-99 content at a specified time point. That time point, referred to as *pre-calibration*, is often a fixed number of days after the generator's delivery to the nuclear pharmacy. Pre-calibration was originally developed when Mo-99 supply was both plentiful and cheap and has since become entrenched in the industry. It was often a feature used in product marketing but the practice also serves to conceal the true amount of material required by the market to provide the necessary imaging services. Pre-calibration thus understates the actual Mo-99 content of the generator at the time of delivery and understates the amount of material that must be produced every week by the supply chain to maintain imaging services.

To nuclear pharmacies, product value depends on the total Tc-99m that can be eluted during the usable lifetime of the generator, which directly determines the economics of generator use. The timing of the delivery of the generator to a facility, the length of time elapsed since it was produced by the generator manufacturer and the timing of the first usable elution are all factors that play a role in determining the maximum usable activity of Tc-99m. The activity from the first usable elution can be used to calculate the maximum theoretical activity of Tc-99m that can be obtained from that generator and is therefore the single most important metric to nuclear pharmacies.

The total cost of a generator compared to its theoretical maximum usable activity of Tc-99m can be used to compare input costs between different nuclear pharmacies. The actual use of that theoretical maximum activity in terms of patient doses eluted can be used as a metric of generator use efficiency. These factors were investigated in the in Study on Sustainable and Resilient Supply of Medical Radioisotopes in the European Union (SMER) funded by the European Commission (EC).

However, it is the actual operational practice within an individual nuclear pharmacy (factors like – single or multiple elution per day, single week use, or elution during the second week and the total number of generators per week used in the facility) that will determine the actual efficiency of use of the generator. Efficiency of use is important in determining the cost of an average patient dose made by an individual nuclear pharmacy. The wide range of nuclear pharmacy practices leads to a wide range of effective efficiency of use and, combined with different generator selling prices in different markets, leads to a wide range in average cost per patient dose.

4.3.3. Generator manufacturers

Technetium Generators are delivered at least weekly

Generator manufacturers were mostly established through the development of nuclear medicine in a specific country and are, as a result, well distributed around the world. Many are now purely commercial organisations but may have governmental origins and some remain linked to semi-governmental organisations. Some are vertically integrated with processors. Partly due to their origins, generator manufacturers today fall into two main categories, those that primarily supply a country or a local area and produce a relatively small number of generators and those supplying large numbers of generators internationally. Market concentration has increased in recent years, with the consolidation of two of the larger suppliers into one commercial organisation (Curium) that maintains three production facilities in France, the Netherlands and the United States. The manufacturer historically based in the United Kingdom (GE Healthcare) has ceased production recently and entered a supply agreement with Curium. This has further concentrated the market, with the largest supplier now holding dominant market positions in many large countries and representing around 50% of all global generator production.

Generators are highly regulated products; they must be produced according to the conditions of their medical licence as well as under strict regulated controls for handling radioactive material. Generator manufacturers typically source bulk Mo-99 from a number of processor organisations to provide operational flexibility and to have back-up options in the event of supply problems. Not all processors can produce and supply material every week of the year. The problems experienced in the 2009-2010 period of Mo-99 supply crisis led to increased multi-sourcing by generator manufacturers and multi-sourcing subsequently became more common throughout the supply chain.

Multi-sourcing is important for security of supply, but brings additional costs; medical licences must be maintained for each separate supplier, even if that supplier is only used infrequently. The addition of a new processor to a medical licence can be a time consuming and expensive process for both the generator manufacturer and the prospective supplier. Likewise, the adjustment of medical licences can be necessary as a result of upstream changes in the supply chain, such as an adjustment to the manufacturing process, and these can also be burdensome. The complexities of medical licencing in the Mo-99/Tc-99m supply chain have been clearly demonstrated during the process of conversion from high enriched uranium (HEU) to low enriched uranium (LEU) targets in recent years.

Generator manufacturers typically have production runs on a number of different days of the week. The production days have a regular pattern based upon the preferred delivery days of their primary markets. The timing of the receipt of bulk Mo-99 is synchronised as much as possible with the regular generator production days to minimise delays and waste through product decay. The cost of decay loss of the bulk Mo-99 during distribution and during any waiting period (approximately 1% per hour) is borne by either the generator manufacturer or by the processor providing the bulk product. With the global distribution of bulk Mo-99 often taking place by a combination of surface and air transport, the level of the decay loss incurred between the end of processing and the time that a completed generator is shipped can be significant and can represent a substantial cost.

"Package deals" determine market prices and generators are often loss leaders

Generator manufacturers typically provide other products to the nuclear pharmacies such as the "cold kits" needed for preparing the final Tc-99m imaging dose, as well as supplying other short-lived medical isotopes. These are often offered as a *package deal* for the combination of the generator and the other products and can have economic advantages as the other products typically "travel for free" when they are delivered with the generator. Supply contracts typically have a term of at least one year, and often of multi-year periods.

In some markets the practice of package deals led to the use of the generator as a *loss leader* product, with the objective of establishing the regular supply of the generator (often at a low profit margin or loss) in order to earn profits from the supply of the other products with higher profit margins. The practice of using generators as loss leaders has tended to keep downward pressure on generator prices, and this has continued in some markets despite increasing costs of production. In many respects, the loss leader model has collapsed in recent years with most cold kits becoming generic, implying sharp decreases of prices and profit margins. The loss of income to some companies from generic competition for cold kits has been profound and has reduced the ability of those companies to counterbalance the low margins historically associated with generators.

4.3.4. Processors

Processors are the main co-ordinators of Mo-99 production

Generator manufacturers purchase bulk Mo-99 from processors based on long-term, often multi-year, contracts that determine many important aspects of supply, including who pays for the decay loss during the delivery process. While contracts will typically contain general agreements about the overall average quantities and planned schedules of bulk Mo-99 delivery, actual daily/weekly demand fluctuates.

The processor industry is relatively concentrated. Among a total of eight processor organisations worldwide, the four largest ones collectively account for nearly 90% of global capacity and the largest one for 32% alone. While the largest one is a commercial organisation, the other three main processors are governmental or semi-governmental. Table 4.1 shows the main characteristics of processors to provide a structural overview of the industry.

Table 4.1. Overview of the processor industry

Processor Name	Country	Average no of Mo-99 production weeks/year	Maximum capacity per week (6-day Ci ^{99}Mo)	Share of annual total world capacity	Type of Organisation[1]	Importance of Mo-99 processing to the organisation[2]
ANM	Australia	43	3 500	18%	Governmental	Very High
CNEA	Argentina	46	400	2%	Governmental	High
Curium	Netherlands	52	5 000	32%	Commercial	High
IRE	Belgium	52	3 500	22%	Semi-governmental/ commercial	High
NorthStar	United States	52	750	5%	Commercial	High
NTP	South Africa	44	3 000	16%	Semi-governmental	Very High
Rosatom (RIAR and KARPOV)	Russian Federation	50	890	5%	Semi-governmental	Low

Notes: 1. Types of organisation in increasing level of commercialisation: governmental, semi-governmental, semi-governmental/commercial and commercial.
2. Level of importance of the Mo-99 processing as an activity in terms of relative importance to the organisation as a whole, from: low, moderate, high and very high.
Sources: NEA reports and analysis; Table reviewed by the named organisations.

Some generator manufacturers may have a primary processor of choice that will supply the majority of the material they need and they will only take occasional limited quantities of material from secondary suppliers. Other generator manufacturers will spread their demand more evenly between a number of processors. Some may rely upon a single processor to supply them on the basis that this processor is also responsible for sourcing extra material in the event that they have insufficient processing capacity of their own. Extensive cross-supply and co-operation arrangements exist between different processors, either as part of commercial supply agreements, or as formal or informal reserve capacity arrangements.

Bulk Mo-99 is shipped in special transport containers either by surface transport or by air. The timing of the shipments is critical as any delay is costly and could lead to a supply shortage, as the quantity of material shipped reduces by approximately 1% per hour.

Each processor carefully plans production levels to match the variable demands made on them by their generator manufacturer customers and it is the responsibility of the processors to manage the production level needed to achieve this. Each processor arranges the availability of their own enriched uranium targets and determines the schedule of irradiations that are performed under contract by nuclear research reactors (NRRs). After the scheduled irradiation, targets are delivered by surface transport to the processors in special transport containers carried in customised vehicles by specially licenced transport companies. Air transport of irradiated targets is not practicable, so the transport of irradiated targets is a loco-regional activity conducted by surface transport only. The scheduled end of each irradiation, the associated specialist transport logistics to the processor site and the processing of the targets are all led and co-ordinated by the processor organisations.

Processors contract with nuclear fuel fabricators in a highly regulated environment

Un-irradiated enriched uranium is a strategic material and must be purchased from a limited number of government repositories, making it a highly regulated market with only a small number of players. Nuclear fuel fabricators are contracted to produce special enriched uranium targets for Mo-99 production in bulk quantities. The purchase and delivery of enriched uranium and the production of enriched uranium targets is very specialised and covered by many nuclear safeguards; much of the market is supplied by a single fabricator located in France. Prior to irradiation, the fabricated targets are shipped in special transport containers and stored securely for the processor at contracted NRRs that have the technical and operational capabilities including licences to hold, store and to irradiate those targets.

4.3.5. Nuclear Research Reactors

Irradiation and processing are geographically close or integrated except in Europe

Nuclear research reactors (NRRs) perform the primary irradiation services. Most irradiations are performed by NRRs located close to processor facilities. In some cases (Argentina, Australia and South Africa), the NRR and the processor are co-located within the same organisational structure and the single local NRR is the sole irradiator for the processing facility. Thus, if the NRR is out of operation for a period, the processor cannot operate and if the processor is out of operation, the output from the NRR cannot be processed. The transport of irradiated targets to the processing facility is less difficult when both facilities are on the same site. In Russia two processing locations in different parts of the country each work with their respective NRRs, but co-operate formally to provide a continuous supply of bulk Mo-99 through a single commercial outlet.

The main exception is in Europe, where presently an informal network of four NRRs (located in Belgium, the Czech Republic, the Netherlands and Poland) supply two processors (located in Belgium and the Netherlands). In this informal “network” model, even when a NRR is located in the same country as a processor, the NRR and the processor do not operate within the same organisational structure and, in the case of Belgium, are not located on the same site.

Table 4.2 shows the main characteristics of irradiators to provide a structural overview of the industry.

Table 4.2. Overview of Nuclear Research Reactor irradiators

Reactor Name	Country	Average no of Mo-99 production weeks/year	Maximum capacity per week (6-day Ci ^{99}Mo)	Share of annual total world capacity	Type of Organisation[1]	Importance of Mo-99 irradiation to organisation[2]
ANSTO (OPAL)	Australia	43	3 500	16%	Governmental	High
CNEA (RA-3)	Argentina	46	400	2%	Governmental	High
NCBJ (MARIA)	Poland	36	2 200	9%	Semi-governmental	Moderate
NECSA (SAFARI-1)	South Africa	44	3 000	14%	Semi-governmental	Very High
NRG (HFR)	Netherlands	39	6 200	26%	Semi-governmental/ commercial	High
RC Rez (LVR-15)	Czech Republic	30	3 000	10%	Semi-governmental/ commercial	High
Rosatom (RIAR and KARPOV)	Russian Federation	50	890	5%	Semi-governmental	Low
SCK-CEN (BR-2)	Belgium	21	6 500	15%	Semi-governmental	Moderate
University of Missouri (MURR)	United States	52	750	4%	Independent non-profit	Moderate

Notes: 1. Types of organisation in increasing level of commercialisation: governmental and independent non-profit, semi governmental, semi-governmental/commercial and commercial.
2. Level of importance of the Mo-99 processing as an activity in terms of relative importance to the organisation as a whole, from: Low, Moderate, High and Very high.
Sources: NEA reports and analysis; Table reviewed by the named organisations.

There is a range of different commercial arrangements between processors and NRRs, with the relationship between a processor directly linked within the same organisational structure generally being different to that between a processor and NRRs acting in an informal network of supply (i.e. in the informal 'European model'). In linked facilities, the processor has a direct obligation to sufficiently fund the activities of the NRR, whereas with a network, the processor can choose between different irradiators and holds market power. In principle, the commercial arrangement between a processor and a NRR should make provision for the supply and payment for outage reserve capacity (ORC) services, but this is not yet universally the case (NEA, 2017[2]). Holding sufficient paid ORC services ensures the flexibility to manage periods of supply problem and payment for the provision of ORC services is essential for the NNRs to achieve full cost recovery (FCR) for the whole range of services they provide.

Two main operating patterns dictate the flexibility and efficiency of irradiations

NRRs do not run continuously and normally operate following two main patterns. The first pattern is relatively long operating cycles of around one month or more, where targets can be loaded and unloaded at any time during the cycle. The second pattern is relatively short cycles (usually of less than a week); where the targets can only be loaded and unloaded during stop periods. NRRs that follow the first pattern provide more flexibility to processors as they can unload targets more than once per week and can adjust the irradiation period, or if needed, add extra targets, at short notice. This added flexibility allows for the most efficient use of freshly irradiated targets on multiple processing days per week.

NRRs that follow the second pattern of short cycles can only efficiently provide irradiation services for material needed shortly after the end of the fixed cycle plan. This either restricts the availability of freshly irradiated material to a processor to certain days of the week, or demands that the NRR operator arranges the cycles specifically to align with the needs of the processor. An advantage of operating shorter cycles is that the NRR may have a greater number of operational weeks per year.

All NRRs require maintenance periods. Some maintenance can be performed in the periods between operating cycles, but most take extended planned stops for more extensive preventive maintenance work. NRRs normally operate predetermined cycle programmes with major preventive maintenance plans being established some years in advance. Many NRRs have a range of purposes aside from medical isotope production, which include nuclear technology testing, fundamental scientific research and industrial isotope production. Some of these activities are undertaken on a commercial basis; however they are most commonly funded by governments, in part or in full. The long-term planning of NRR operations is needed with regard to efficient operation of the NRR for all of its purposes and not solely for medical isotope production. Generally, when a NRR has a large number of purposes not related to medical isotope production, it has less flexibility to adjust operating plans.

4.4. Irradiation capacity is co-ordinated globally

In the period around the 2009-2010 supply crisis, only five reactors produced around 90% of global Mo-99 supply and, at that time, they were all over 40 years old. Following the supply crisis, additional NRRs became involved in the supply chain (in the Czech Republic, Poland, and Russia), however these were also relatively old. Only one newer NRR, the OPAL in Australia has joined the international supply network and further investments in new processing facilities in Australia have recently increased the overall level of supply available from that NRR. Since the supply crisis, important NRRs in Canada and France have ceased operation. Their planned closures took place in 2017 and 2015 respectively, with a commensurate reduction in the total irradiation capacity available.

The overall planning of NRR operating cycles and the extended maintenance periods is critical and has to be co-ordinated between all NRRs providing irradiation services to avoid periods of supply shortage. The global co-ordination is today managed through the Nuclear Medicine Europe (NMeu)[2] Security of Supply Working Group (SoS). NMeu is an independent European Economic Interest Group funded by the medical imaging industry and includes all NRRs involved in Mo-99 production around the world as associate members. NMeu-SoS meets regularly to discuss long-term reactor scheduling. During this process, potential weaknesses in global supply are identified and requests are made to individual NRRs to investigate the possibility of cycle adjustments. It is this extensive and *not-for-profit* co-ordination activity of NMEu that allows the industry to ensure sufficient NRR capacity is continuously scheduled.

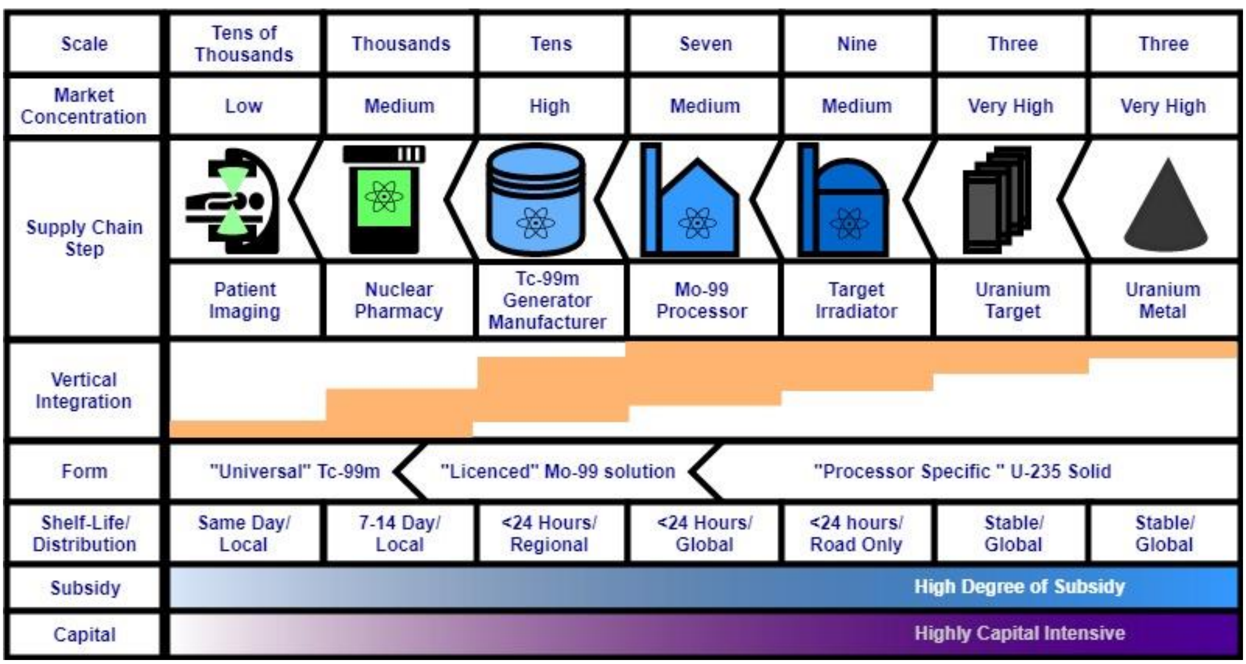
If an unplanned event occurs that could lead to supply disruptions, NMeu-SoS calls together at short notice a so-called Emergency Response Team (ERT) that represents NRRs, processors and generator manufacturers globally. It is primarily the responsibility of the processor organisations to identify potential supply weaknesses and for the ERT group to discuss the risks and propose potential planning adjustments that could alleviate the problem. The ERT group also takes a prime responsibility in communicating the risk of any potential supply problem to governments and to stakeholders. ERT communication is co-ordinated through the NMEu directorate to the Euratom EU Observatory co-ordinator and through the secretariat of the NEA HLG-MR. ERT communication activity has proven invaluable during recent supply problem periods. For example, starting from November 2017 the ERT convened and communicated to stakeholders on more than 45 occasions during the approximate one-year period that NTP (South Africa) experienced operational problems.

4.5. Despite progress, the supply chain remains unviable

Although progress has been made to overcome some of the issues described in Section 4.5.1, product markets along the main steps of the Mo-99/Tc-99m supply chain depart significantly from the idealised model of perfectly competitive markets. The main structural characteristics of the Mo-99/Tc-99m supply chain are shown in Figure 4.2. Supply progresses from right to left starting with bulk enriched uranium supply, through target supply, NRR irradiators and processors to generator manufacturers, then on to nuclear pharmacies, providers of imaging services and finally patients.

Market concentration is high, in particular upstream. Steps on the right side of Figure 4.2, where the product is in the form of a uranium metal target, all have very limited numbers of players and very high market concentrations. There is a somewhat higher number of players in the central steps of the chain, from irradiators through processors and generator manufacturers, but market concentration is still medium and high. From nuclear pharmacies onwards the numbers of market players increase substantially and market concentration is lower. However, as noted above, in some countries such as the United States, commercial nuclear pharmacies can also hold large market shares and wield market power.

Figure 4.2. Structural characteristics of the Mo-99/Tc-99m supply chain



Source: Authors

High capital intensity creates barriers to entry, in particular upstream on the right hand side of the Figure. These organisation rely more significantly on government subsidies.

Logistical requirements also constrain the ability for market players at various steps to exploit competition among suppliers. While solid uranium is stable, un-irradiated enriched uranium is a strategic material, the supply of which is completely controlled by governments. As the product is transformed into bulk Mo-99 and finally Tc-99m, decay becomes an issue so that geographic proximity between NRRs, processors, generator manufacturers and nuclear pharmacies is a relevant factor that constrains competition.

There are many instances of vertical integration within the supply chain, with for example the steps from irradiation through to bulk Mo-99 processing and generator manufacturing all being performed within a single organisation and even on the same site. There are also examples of vertical integration of fewer steps in the chain, with examples of vertical integration at every level of the supply chain up to the imaging provider. In general, vertical integration protects subsequent steps in the chain from competition and often implies reduced transport distances and reduced decay loss with the associated economic benefits.

4.5.1. Some historical barriers to full-cost recovery remain

Historical irradiation prices were too low to cover costs and support investments

The NEA (2010[3]) Economic Study concluded that the *"overall impact of the historical market development on the current situation is that there is currently not enough reliable reactor capacity and there are constraints on processing capacity"* (p.11). This was *"caused by a market structure that developed around an unsustainable economic model that did not remunerate reactor operators and processors sufficiently well enough to provide incentives to invest in new infrastructure to meet growing demand or to maintain reserve capacity"* (pp.11-12). It concluded that *"lack of investment resulted in a system reliant on older reactors that have had reliability concerns over the last decade. The shortage seen in 2009 and 2010 is a symptom of this economic problem"* (p.12).

The report also warned that, *"once the shutdown reactors return to operation and the short-term supply becomes stable again, it is important to stress that although the symptom has been addressed, the underlying problem – the unsustainable economic structure – has not."* (p.12)

The observations in the NEA 2010 Economic Study were well founded and subsequently many stakeholders reported that the market did *"return to historical market behaviour"* in the period after supply had stabilised and information in a number of publically available annual reports for generator manufacturers identified that major new contracts were won on the basis of price reductions.

Irradiation prices were also too low to cover costs and support infrastructure investments

Prior to the 2009-2010 supply crisis period, irradiation services were seen as a by-product, with historical NRR capital costs already paid off or fully justified. Most processors originally contracted target irradiations in multipurpose NRRs constructed and operated with 100% government funding. As a result, the historical pricing of irradiation services reportedly included only limited direct marginal costs and did not account for replacement costs and full direct and indirect marginal costs. The historical non-inclusion of those costs resulted in the prices charged for target irradiation being too low to sustainably support the portion of NRR operations that could be attributed to Mo-99 production. They also did not contribute sufficiently to covering the costs of replacing or refurbishing ageing reactors. Also, with historical pricing set too low at the irradiation step, all further steps in the supply chain were likely to be priced too low to support full-cost recovery (FCR) pricing at the irradiator step of the supply chain.

A further historical factor complicating the achievement of FCR was the existence of excess irradiation capacity while the economic value of outage reserve capacity (ORC) was not recognised. Although a certain level of excess capacity is essential for reliable supply, it is difficult to determine the difference between essential reserve capacity and overcapacity when ORC services are not properly valued or paid for. The NEA established a minimum guideline of market demand +35% ORC to establish a safe minimum level of paid ORC that should be held at all levels in the supply chain. This was identified as a level that should be sufficient for the supply chain to manage the single unplanned outage of a major reactor or a processor.

Waste management is an important issue for processors; it is generally agreed that a full economic model that incorporates the final treatment and disposal costs of the radioactive waste from LEU or HEU target irradiations is still not available and that final waste disposal costs are still not fully included in bulk Mo-99 pricing. The enforced conversion to LEU targets since the 2009-2010 supply crisis period has reinforced this concern; with increased waste volumes resulting from the LEU processes, the related costs are likely to increase, but those costs are not fully accounted for.

Some governments continue to subsidise irradiators

Most processors originally contracted target irradiations in multipurpose NRRs constructed and operated with 100% government funding. A question raised in the NEA (2010[3]) Economic Study economic survey was, *"If the supply chain pricing structure was such that the irradiation services were unable to be offered on an economically sustainable basis, why did reactors continue to irradiate targets?"* (p.52). The answer at that time identified the relationship that governments had established with NRRs and the medical community in the historical social contract. That is, governments subsidised the development of NRRs, the related infrastructure and its operation, including waste management, and NRR operators used part of this funding to produce Mo-99. In return for this use of taxpayer funds, citizens would receive a reliable supply of medical isotopes.

However, governments were not always aware of the extent to which Mo-99 production relied on subsidies. Although NRR operators were aware that government financial support was increasingly used for Mo-99 and other isotope production, this development may not have been transparent for some governments. In some cases, the magnitude did not become evident until there were requests to subsidise the refurbishment or the construction of a new NRR. Some governments were essentially subsidising the production of Mo-99 that was exported to other countries, thus subsidising imaging services in importing countries.

Governments have questioned the historical social contract and while they have encouraged the supply chain to achieve FCR, there has not been universal agreement on what a new social contract should be. As a result, some governments have faced a choice between providing continued support to some irradiators and processors in order to keep them financially viable or otherwise closing a loss making activity. Closing the activity could potentially result in a substantial shortage; this has been seen as unacceptable by some. In this regard, the social conscience of some governments has led to decisions to continue subsidies rather than taking the risk of triggering shortages.

Other countries have decided to allow older facilities that were operating below FCR to cease operations and have not subsidised extensions of their working lifetime. While this increased the risk of insufficient supply or challenged reserve capacity, decisions to end the operation of facilities unable to achieve FCR have been helpful in achieving the six NEA policy principles (see Foreword) by removing subsidised services from the market. These actions also reduced the level of subsidised reserve capacity and reduced perceived overcapacity within the market.

Some countries have decided to provide support in a number of ways to the development of domestic alternative technologies. These technologies are well described in a 2016 publication by the US National Academy of Sciences (Committee on State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium et al., 2016[4]). New technologies fall into areas including accelerator-driven systems, alternative uranium fission processes and new chemical separation technologies. Some alternative technology projects use more than one new technology. However, with the exception of the licencing in 2018 of the RadioGenix® generator system, those initiatives have yet to provide new capacity. Also, it has not yet been demonstrated that the new technologies are economically viable at present market prices.

Processors have market power

Processors were initially also funded by governments as part of their efforts to develop the use of medical isotopes, having recognised their utility in health care. In some markets in the 1980s and 1990s, the processors were separated from NRR operators and commercialised. Although that commercialisation process was originally thought to benefit all parties, NRR operators were disadvantaged in the process. In the NEA 2010 Economic Study, interviewees indicated *"that governments created the commercial contracts based on historical perceptions of cost and pricing structures, this resulted in long-term contracts with favourable terms for the commercial processors"* (NEA, 2010, p. 9[3]). The separation of activities often did not lead to a change to commercial prices charged for the irradiation step in the supply chain and once these long-term contracts had been established, they set the standard for potential new entrants.

The partial commercialisation process helped establish market power of some processors. There were examples of contracts that provided for an exclusive relationship between the processor and the NRR, creating a situation of monopsony whereby NRRs had only very limited avenues for selling Mo-99-related irradiation services to other buyers. The restriction to surface transport of irradiated targets also creates a geographic constraint, severely limiting the processors that an irradiator can supply. This market power has historically contributed to maintaining low prices for irradiation services.

Conversion to low enriched uranium increased costs

The NEA (2010[3]) Economic Study report identified that conversion to LEU targets for the production of Mo-99 had been agreed by most governments for security and non-proliferation reasons, but that while LEU conversion was agreed to be necessary, it was not financially supported by the market. This was identified as one of a number of issues within the industry that could increase the impact of the economically unsustainable supply chain, stating that, *"Industry stakeholders are being faced with possible additional economic pressures as a result of the conversion to LEU targets and changing levels of government financial support for overall and reserve capacity"* (p.14). It also identified the risk following LEU conversion, of an *"increase in costs per curie of product produced"*, as there would be *"a need for some degree of additional irradiation and processing capacity to continue to produce the same quantity of Mo-99 globally, depending on the uranium density that can be achieved in the target"* (p.15) and that *"there may also be an increase in waste management costs (capital and operational) since more total uranium waste and liquid wastes will need to be managed"* (p.15).

These observations have held true. Efficiency losses, increased waste and increased costs have been reported as a direct result of LEU conversion and these additional costs remain largely unrecognised downstream in the supply chain. Special uranium targets were previously made using HEU with enrichment levels often above 95% U-235. LEU, on the other hand, has enrichment of <20% U-235. This implies lower overall efficiency of Mo-99 production and more waste from LEU targets, leading to higher waste management costs. LEU targets are more difficult to make than HEU targets as they contain a higher total load of uranium (approximately 4.5 times higher) that must be securely embedded in metal plates using the minimum possible plate material. In January 2018, the Curium processing facility in the Netherlands announced a 100% change to the use of LEU targets. With that change, more than 70% of all of the world supply of Mo-99 was produced using LEU targets.

Some financial support has been provided from governments to individual processors to support the costs associated with the research, development, licencing and implementation of conversion projects that required capital investments. However, this has not covered the full costs associated with LEU conversion, with the remainder to be absorbed by processors and the market for bulk Mo-99. Since LEU conversion, a number of NRRs have reported irradiation efficiency losses of around 20% in terms of the activity of Mo-99 produced per target.

Irradiation price increases were not absorbed in the downstream supply chain

The historical undervaluation of the Mo-99 cost component in generator pricing and *loss leader* strategies described in Section 4.3.4 had a feedback effect on upstream prices. Manufacturers continue to compete on price and were not willing or able to absorb the upstream price increases needed to achieve FCR and paid ORC within their generator prices.

The cost of the Tc-99m component in the costs of final patient doses and imaging procedures is also one factor among many that determine the setting of health care provider payment rates for Tc-99m-based imaging procedures. An unsustainably low price of the Tc-99m component may have historically led to low prices of Tc-99m-based procedures. In turn, procedure prices may have had feedback effects that have helped maintain low prices in the upstream supply chain.

The NEA Third Self-Assessment showed that in many countries there had been little or no increase in provider payment rates for Tc-99m-based diagnostic procedures for a number of years (2012-2016). In some countries, this represented a price reduction in real-terms as even inflation was not accounted for. Health care provider payment is discussed in detail in Chapter 3.

4.5.2. Progress has been made but FCR is not yet achieved

A further 40% price increase by irradiators is necessary to achieve FCR

Following the supply crisis and the work of the NEA HLG-MR, governments gained a better understanding of the historical levels of subsidies and agreement was reached through the adoption of the NEA HLG-MR six policy principles. The subsequent Joint Declaration (see Annex A) stated that the subsidy of the production of medical isotopes should end. Although countries have taken a number of different actions to help achieve that goal, it has not been fully achieved so far.

All of the players throughout the supply chain have been strongly encouraged to achieve FCR. The NRRs that responded to the NEA Third Self-Assessment indicated that they had substantially increased charges for irradiation services to processors in recent years. However, as of late 2016, reactors representing around 70% of the global irradiation capacity were yet to fully implement FCR pricing for irradiation services.

From the data available in 2016, the NEA estimated that the total global charge for irradiation services to processors needed to increase by at least a further 40% to achieve FCR at the irradiator level. While prices are assumed to have increased since 2016 and the gap to breakeven has likely narrowed, FCR is still not achieved at the irradiator level, especially within the informal European network.

Analysis for the NEA Third Self-Assessment identified that many market players have experienced cost increases beyond the ones described above as a result of the implementation of tighter security regulations (due to terrorist concerns) and emergency preparedness (in response to the Fukushima accident).

Outage reserve capacity is still undervalued

The processors that responded to the NEA Third Self-Assessment indicated that they had increased the contracting of ORC, but information received from NRRs in the European informal network indicated that ORC did not reach the minimum target. In some cases no payments were made for an irradiator holding ORC although those services were available and were actively used during periods of supply stress.

The insufficiency of ORC manifested itself during the extended unplanned outage of the NTP facility (South Africa) between late 2017 and early 2019. The outage led to extended periods of shortage, whereas the level of theoretical reserve capacity in the system should have been sufficient to cover the loss of the NTP capacity.

Market entry remains difficult and unattractive for new players

In the NEA 2010 Economic Study, interviewees indicated that incumbent market players created barriers to keep new entrants from entering the market and competing profitably. Such barriers included aggressive pricing strategies and exclusive contracts. These add to significant entry barriers already present in a highly regulated industry that is knowledge and capital intensive (see Section 4.5.1).

Since the supply crisis period, it has primarily been existing market players who have successfully added production capacity to the supply chain. It is reasonable to speculate that this has only been possible by existing players being able to leverage privileged positions, or by a reliance on further support by some governments during a transition period.

Market entry by new players has been hampered by a combination of technical delays and the time it takes to gain the licences needed to build and operate prospective new facilities and to gain medical licence approvals. One of the most significant impediments to entry, however, has been economic: new commercial investment has been difficult to justify. The historical economic and structural characteristics of the supply chain continue to determine the current market structure, its economics and the (in)ability of the market to adjust.

Latest estimates confirm that the industry is unsustainable

The 2010 NEA economic study presented a costing model for the period prior to the supply crisis based on information received during interviews with market participants at all stages of the supply chain. The model yielded a median estimate of about EUR 11 for the Tc-99m element of a patient dose (or USD 13 at 2018 exchange rates[3]). Although, the model was not universally accepted by all market participants, however, all participants agreed that the cost of the medical isotope was small compared to the overall cost of associated imaging procedures.

A review of publically available data and preliminary findings of the recent EC SMER study indicate that the average cost of a Tc-99m dose has increased in the last decade. This is likely in part a response to the supply shortage experienced in 2009-2010 and in part due to subsequent efforts to achieve FCR in the supply chain. The EC SMER study identified a wide range of generator prices in Europe and of activity eluted by nuclear pharmacies to prepare doses. These factors collectively result in a wide range of costs of an individual patient dose. Mean estimates are therefore only indicative illustrations of cost structures; no individual supply chain participant should expect to recognise their own cost in mean estimates.

Based on preliminary findings of the EC SMER study and publically available data, the average cost of an individual patient dose at the point of dispensing of Tc-99m from generators (i.e. at selling prices of generators to nuclear pharmacies, with no costs added for nuclear pharmacy staff, facilities or cold kits) is around USD 21 (EUR 18[3]). This suggests an overall world market value of technetium generators of around USD 630M per year.

Assuming a world market demand of around 9 000 six-day Ci Mo-99 at "End of Processing" (EOP) per week, recent disclosures by publicly listed generator manufacturers[4] indicate a global Mo-99 market value of around USD 230M per year at the selling point of bulk Mo-99 from processors to generator manufacturers. Assuming that around 30 million patient doses are dispensed per year, the overall average cost of a Tc-99m patient dose at the selling point of bulk Mo-99 from processors is around USD 8. This suggests an overall value added of around 170% between bulk Mo-99 supply and technetium generator delivery.

No data are publicly available to estimate the current cost per patient dose at the supply chain step between irradiators and processors. It is believed that this step in the supply chain does not fully meet FCR in all cases. However, processors have three main variable cost components: the cost of the target including the enriched uranium content, the cost of irradiation (performed by the NRRs) and the cost of their own processing activities including long-term management and waste disposal. Processors additionally have to cover fixed costs associated with developing processes, buildings, maintaining and licencing of facilities and staff needed to manage target processing, including all regulatory costs associated with maintaining both nuclear and medical licences. It appears unlikely that irradiation itself would represent more than 25% of the total cost of processed bulk Mo-99.This would imply that the average cost of a Tc-99m patient dose at the selling point of irradiation services to processors is unlikely to be above USD 2. This estimate is substantially higher than the cost of irradiation per patient dose suggested in the NEA (2010[3]) Economic

Study of USD 0.37, confirming that prices have increased and suggesting a present world market for irradiation services of around USD 58M per year.

It should be recalled that the cost structure of generator manufacturing typically includes fixed cost items for every generator for the recyclable and once-only use parts of the generator, the manpower involved in production, and the costs of distribution and, where done by generator manufacturers, costs of recovery for disposal and recycling. These items represent the full costs of producing, shipping and recycling generators, except the cost of the bulk Mo-99 loaded onto generators. The cost of the bulk Mo-99 depends on the quantity loaded onto the generator. The 170% value added by generator manufacturing estimated above includes all of these fixed cost items for every generator, as well as the variable cost of the quantity of bulk Mo-99 and a significant allowance for the cost of Mo-99 decay loss between bulk Mo-99 receipt by the generator manufacturer and the final activity of the generator delivered.

There are some specificities within the global estimates above. Japan, for instance, is an anomaly at the selling point bulk Mo-99 from processors to generator manufacturers. The majority of material in Japan is used in highly centralised Tc-99m production followed by national distribution, rather than in decentralised generator elution and dose distribution. National distribution of Tc-99m, which has a shorter half-life than Mo-99, increases the decay loss experienced in that supply model with greater supply distances for Tc-99m, so a greater quantity of bulk Mo-99 is required to service the number of individual patient doses. The resulting cost of each Tc-99m dose at the bulk Mo-99 delivery step is substantially higher in Japan. Conversely, the cost of the final Tc-99m dose does not include the costs for generator manufacture and recycling which are largely excluded in the Japanese model.

In other countries, the size and number of generators utilised by a conventional nuclear pharmacy are important factors. The EC SMER study confirmed that in Europe many nuclear pharmacies (around 75% of respondents) receive only a single generator per week and often only elute that generator once per day. European generators typically also have a relatively low Mo-99 activity content. In countries like the United States, where commercial nuclear pharmacies are predominant, higher Mo-99 activity generators are typical, with multiple generator deliveries per week to each pharmacy and multiple elutions per day. The EC SMER analysis also showed that the use of multiple generators per week and the multiple elutions of generators in a day make use of Mo-99 more efficient, further improving the financial economies of use when the generator activities are relatively large (e.g. in a centralised nuclear pharmacy). Market data indicate that the relative cost per individual patient Tc-99m dose at the point of dispensing from the generator is lower in countries with centralised nuclear pharmacies.

Generator distribution costs are also important. Within much of Europe, for example, where there are multiple and geographically spread generator manufacturing facilities, many generators are delivered close to their production point and only surface transport required. While larger generators lead to higher efficiency in Tc-99m use, in North America, on the other hand, generator distribution distances are typically much longer, except where imaging facilities are close to one of the two generator manufacturing sites. Delivery to more distant medical facilities is a combination of road and air. Some more remote locations in Europe (e.g. Scandinavia) have distribution challenges similar to North America.

4.6. Conclusion

Mo-99/Tc-99m supply is a just-in-time activity requiring continuous production in a complicated and aging supply chain that combines a mix of governmental and commercial entities. Governments essentially control both ends of the supply chain. They completely control the availability of enriched uranium required to make targets for medical isotope production and to fuel nuclear research reactors. Governments also largely control the regulatory framework, including medical licencing requirements, regulation of the use of nuclear materials and the legislation around health care provider payment for nuclear medicine imaging studies. The central steps of the supply chain are mainly commercial, in particular generator manufacturing and, in some countries, also nuclear pharmacies.

The current structure of the supply chain, with governmental or semi-governmental irradiators and semi-commercialisation of processors, was established by governments and bestowed market power on processors. Generator manufacturers also wield market power. The market was recognised as being economically unsustainable in the NEA (2010[3]) Economic Study. While progress has been made in all areas, the inability of achieving full cost recovery (FCR) by irradiators and insufficient outage reserve capacity (ORC) at various steps of the supply chain leave security of supply vulnerable and the market economically unsustainable. Continued market frailty was demonstrated from late 2017 to early 2019, with chronic shortages occurring regularly due to unplanned outages at the NTP facility. As of the end of 2018, only one alternative technology has been brought to market and then only in the United States.

Supply continues to be supported by some subsidies to irradiators and processors. Processors and generator manufacturers continue to wield market power, and market concentration has actually increased in these parts of the supply chain.

References

(n.a.) (n.d.), *X*. [5]

Committee on State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium et al. (2016), *Molybdenum-99 for Medical Imaging*, National Academies Press, Washington, D.C., http://dx.doi.org/10.17226/23563. [4]

Levin, D. et al. (2017), "After Nearly A Decade Of Rapid Growth, Use And Complexity Of Imaging Declined, 2008–14", *Health Affairs*, Vol. 36/4, pp. 663-670, http://dx.doi.org/10.1377/hlthaff.2016.0836. [1]

NEA (2017), *The Supply of Medical Radioisotopes: Results from the Third Self-assessment of the Global Mo-99/Tc-99m Supply Chain*, OECD Publishing, Paris, http://www.oecd-nea.org/med-radio/docs/sen-hlgmr2017-5.pdf (accessed on 15 May 2018). [2]

NEA (2010), *The Supply of Medical Radioisotopes An Economic Study of the Molybdenum-99 Supply Chain*, OECD Nuclear Energy Agency, Paris, https://www.oecd-nea.org/med-radio/reports/MO-99.pdf (accessed on 11 April 2019). [3]

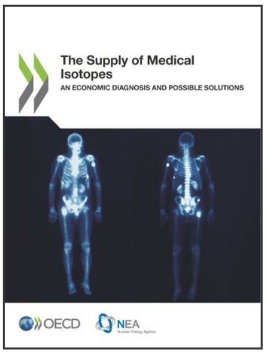
Notes

[1] See annual 10-K filings by Mallinckrodt and Lantheus with the U.S. Securities and Exchange Commission (SEC), available at http://www.mallinckrodt.com/investors/sec-filings/ and http://investor.lantheus.com/sec-filings.

[2] Formerly the *Association of Isotope Producers and Equipment Suppliers*.

[3] EUR 0.847 per USD 1 on average in 2018 (http://dotstat.oecd.org).

[4] See, for example, Lantheus 2018. Form 10-Q. http://investor.lantheus.com/sec-filings/sec-filing/10-q/0001628280-18-005734



From:

The Supply of Medical Isotopes

An Economic Diagnosis and Possible Solutions

Access the complete publication at:

https://doi.org/10.1787/9b326195-en

Please cite this chapter as:

OECD/Nuclear Energy Agency (2019), “The Tc-99m supply chain is technically complex and characterised by market imperfections”, in *The Supply of Medical Isotopes: An Economic Diagnosis and Possible Solutions*, OECD Publishing, Paris.

DOI: https://doi.org/10.1787/67dec9af-en

OECD