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Is the Global Shortage of Mo-99 Over?

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Concerns regarding an adequate supply of the widely used medical isotope, technetium-99m, the radioactive daughter of reactor produced Mo-99, were raised when the decision to withdraw the availability of highly enriched uranium (HEU) from commerce was made for security reasons. Would the substitution of low enriched uranium (LEU) result in a lower yield, and thereby precipitate a drug shortage? As studies addressing whether or not LEU produced Mo-99 was feasible were being conducted, the aging Canadian Chalk River Reactor, which at one time produced the majority of the global supply of Mo-99, had an unexpected outage. This precipitated a crisis! The theoretical fears surrounding a fragile supply chain became real. In response to this global drug shortage, global governments, industry, and professional organizations addressed the problem in a variety of ways. The author will review the recent history, and make the case that the global shortage is essentially over.

1. Introduction

My relationship with ^{99m}Tc began in 1970, as a graduate student, when I learned that ^{99m}Tc was a new medical isotope, described as the ideal nuclide, with good imaging energy, a short half-life, and very good chemical characteristics that made it easily labeled to many drugs. Most important for the medical community, it was easily available. Little did I know that this modest radionuclide would eventually account for as much as 80% of global nuclear medicine procedures.

In 2007 my relationship with ^{99m}Tc was reestablished, as I testified on behalf of the Food and Drug Administration (FDA) at a hearing of the National Academy of Sciences (NAS). The Academy was investigating if conversion from highly enriched uranium (HEU) to low enriched uranium (LEU) would be feasible? The report eventually concluded that it was feasible. The driving force behind this conversion has been and continues to be the reduction of risk associated with nuclear terrorism, and has been part of the mission of the Department of Energy's (DoE) National Nuclear Security Administration (NNSA).

At this point in 2007, the NAS review was focused on potential regulatory hurdles associated with changes in manufacturing. Any changes in the entire manufacturing process for the FDA approved drug, ^{99m}Tc, in this case the conversion from HEU to LEU in the production of ^{99}Mo, have to be filed with FDA as a New Drug Application (NDA) supplement. The committee was concerned about how long such approvals would take, possibly delaying the HEU-LEU conversion by years. These concerns eventually proved unfounded.

2. The Shortage and Global Response

The initiatives to eliminate HEU from commerce for security reasons dates back to the Energy Policy Act of 1992. Later on, The Energy Policy Act of 2005 focused on ensuring that the security initiatives did not jeopardize the supply of medical isotopes. Concerns became reality when in 2009 the largest source of ^{99}Mo, the Canadian reactor at Chalk River, the National Research Universal (NRU), shut down for 14 months, precipitating the global shortage.

In response to the shortage, Canada and the United States, as members of the Organization of Economic Cooperation and Development (OECD), through the OECD's Nuclear Energy Agency (NEA) created the High Level Group on the Supply and Security of Medical Radioisotopes (HLG-MR). I had the privilege to participate in many of these meetings as part of the US delegation to the HLG-MR twice yearly meetings in Paris.

The problem was not that the aging Chalk River Reactor, commissioned in 1957, had an unanticipated shutdown, the aging reactor would intuitively need more maintenance and more downtimes. The plans were to replace the NRU with two new reactors, the Maple reactors. When these reactors proved to be unsafe and would no longer replace the NRU, the plan was to continue to allow the NRU to continue to operate. This set the stage for the predictable and inevitable increase in outages, one of which eventually triggered the shortage. Eventually, because of safety, economic, and political reasons, the government of Canada decided to exit as a major global supplier of ^{99}Mo.

Also historically relevant, the OECD, which today consists of 35 countries, is an outgrowth of the post-World War II European Marshall Plan, which provided economic assistance to Europe after WW II. The OECD was formally established in 1960 as an organization dedicated to global economic development.

3. Leadership and Partnerships to Forge a Solution

The HLG-MR provided the global leadership to forge a solution. This solution involved many important players which included government agencies, scientific and professional organizations, industry and other stakeholders. Some focused on security issues, while others were concerned with the clinical availability of ^{99m}Tc.

In the United States the DoE's NNSA has provided a critical leadership role over the years, whether it is funding, or seeking out the appropriate partners both domestically and internationally. The NNSA has forged a broad coalition of diverse professionals and organizations. Government Agencies such as the DoE and the national laboratories, the Department of Health and Human Services' (DHHS) FDA and Centers for Medicare and Medicaid Services (CMS), the Department of State, the Office of the U.S. Trade Representative, the Department of Transportation, the Nuclear Regulatory Commission (NRC), and the White House Office of Science and Technology Policy (OSTP). The professional and industrial societies also played major roles in making their constituencies aware of what was happening. The Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the Council on Radionuclides and Radiopharmaceuticals (CORAR) played major roles for their nuclear medicine constituencies.

The NAS, founded in 1863 by Congress to provide independent and objective advice to the nation on matters of science and technology, is a nonprofit, non-governmental organization. It has consistently provided the essential scientific and expert opinions upon which policy depends.

When the Chalk River NRU shut down, precipitating the global shortage, it was the Canadian and US governments who acted. The shortage was not only a North American concern, it was global, and therefore needed to be addressed at the global level. They requested that the OECD's Nuclear Energy Agency (NEA) take on this task. With the creation of the HLG-MR, the global community took this on collectively.

The response of the European Association of Imaging Producers and Equipment Suppliers (AIPES) has to be one of the most effective mitigating actions taken by any single group! These actions ensured a continuous supply and availability of ^{99}Mo. By routinely surveying and making available the planned reactor schedules, effective management and adjustment of these schedules minimized the risk of potential periods of overlapping planned outages. Whenever a critical period was identified with few reactors online, the global supply chain was made aware, and contingencies were planned due to the increased risk.

4. Demand and Supply

Demand: In 2009 the global demand for ^{99}Mo was estimated to be about 12,000 6 day Curies, with modest growth estimates ranging up to 5%. Opinions vary, but because of reaction to the shortage, a global economic recession, and changing health care practices in the U.S, demand for ^{99}Mo dropped by 25% from 2009 to 2017. Current demand estimates are 9,000 6 day Curies. This reduction in demand has clearly relieved the pressure for increased supply at this point in time, but ^{99m}Tc still accounts for about three-fourths of the global demand for radiolabeled drugs. Estimates for global growth remain weak, but continue to be positive for the foreseeable future.

Current Supply: For this discussion I assumed that the NRU reserve capacity is zero, despite their commitment to providing potential reserve capacity as "a supplier of last resort" through March of 2018. Therefore, the actual number of net operational reactors have increased to 6, not the 7 if Chalk River was included, from the previous 5 major irradiators, or reactors.

The 2009 major suppliers of fission based ^{99}Mo were the NRU, HFR, BR-2, OSIRIS, and SAFARI. Despite the effective loss of two of these major reactors, the Canadian NRU and the French OSIRIS, their output has been replaced by 3 new reactors, the Australian OPAL, the Polish MARIA, and the Czech Republic's LVR-15. OPAL is the newest reactor, while MARIA and LVR-15 are older reactors, but new entrants into the supply chain.

The actual total available ^{99}Mo production capacity per week, if all 6 reactors were operating 100% of the time, is 24,800 6-day Curies per week, clearly exceeding the 9,000 6-day Curie estimates for demand of ^{99}Mo by a factor of 2.75. This estimate incorporates the new capacity of 3,500 6 day Curie/week for OPAL, and excludes NRU capacity completely. Even though these reactors operate about 67% of the time, there is clearly a very large overall reserve capacity, enough to assure ^{99}Mo availability. Clearly the operational capacity and stability of the remainder of the supply chain must be maintained, but the fundamental availability of ^{99}Mo is not an issue.

Potential Producers of ^{99}Mo.

The following potential global producers are not included in the current operating reserve capacity estimates.

Argentina currently operates an LEU based RA-3 reactor, which will be replaced by their RA-10 reactor around 2020, this will replace their current production of about 400 6-day Curies to 2,500 6-day Curies.

Brazil is planning on building the RMB reactor, with plans to produce 1000 6-day Curies, but this is still in the early planning phase.

Canada is currently developing accelerator based programs for domestic ^{99m}Tc production. The four projects consist of (1) Canadian Isotope Innovations (CII), (2) Prairie Isotope Production, a (3) consortium between Advanced Cyclotron Systems and the University of Alberta, and (4) Canada's national laboratory for particle and nuclear physics and accelerator-based science, TRIUMF

France, as part of an international consortium, is currently building the Jules Horowitz reactor with a 2021 target date. This replaces the OSIRIS reactor which shut down in 2015.

S Korea is building the Kijang Research Reactor (KJRR) with projected ^{99}Mo capacity of 2,000 6-day Curies/wk.

The Russian Federation has provided HEU derived ^{99}Mo both domestically and regionally for many years. They have expressed an interest in supplying up to

20% of global demand using LEU. ROSATOM, the Russian government agency currently operates 3 reactors using HEU with plans to switch to LEU, and future plans to expand capacity to 1000 6 day Curies.

The following Potential Domestic sources are not included in the current operating reserve capacity estimates. Currently three active NNSA Cooperative Agreement Projects are in progress, and they use alternative technologies to produce ^{99}Mo.

NorthStar Medical Radioisotopes proposes using an accelerator based technology to produce ^{99}Mo, and has actually submitted a New Drug Application (NDA) to the FDA for a novel generator technology that produces ^{99m}Tc, although it has not yet been approved.

SHINE Medical Technologies is developing an accelerator based technology.

General Atomics, a partnership between the University of Missouri Research Reactor Center (MURR) and Nordion, is working on a reactor based gaseous extraction process. Both SHINE and General Atomics are still several years from completion.

In addition to the NNSA funded Cooperative Agreement Projects, the following aspirants also plan on entering the supply chain:

Coqui Pharmaceuticals is a proposed reactor complex dedicated to radiopharmaceuticals, with a potential for 7,000 6 day Curie/week capacity.

Eden Radioisotopes is a New Mexico based company, proposing a novel reactor design that they claim could provide total U.S. and global ^{99}Mo demand. They are currently in the process of raising funds to submit a license to the NRC.

Flibe Energy, Huntsville, Alabama, is developing a liquid fluoride thorium reactor (LFTR) for power and ^{99}Mo production.

Niowave, Lansing, Michigan, is planning on building an accelerator based ^{99}Mo production facility.

Northwest Medical Isotopes, Corvallis, Oregon, plans to use regional reactors to produce ^{99}Mo, initially at Oregon State University, and MURR.

The University of Missouri Research Reactor Center (MURR) is involved in several of the above projects with NorthStar, General Atomics, and Northwest Medical Isotopes.

5. Discussion: The Supply Chain, Reimbursement, and Full Cost Recovery

Since the shortage, the members of the Supply Chain Community have learned some valuable experiences. Although every link in this supply chain is critical, the experiences have been different, and have resulted in modifications of business and professional practice to reduce the risks, while improving the overall reliability of the supply chain.

Once the uranium is irradiated, ^{99}Mo needs to be chemically extracted from the fission products. This next step is managed by the 5 global suppliers of processed

^{99}Mo. They are currently ANSTO (Australia), IRE (Belgium), Mallinckrodt (Netherlands), Nordion (Canada), and NTP (South Africa). In the past, each of these producers obtained their irradiated uranium from single sources. During the shortages, they learned that to reduce their future risk, they needed to enter into contracts with multiple reactors, in case their primary source had an unplanned outage. This reduced their risk of not being able to obtain irradiated uranium from their primary source. Today, if additional capacity is anticipated, some companies will actually purchase these future irradiation slots.

The generator companies are the next step along the supply chain. They are ANSTO Health, GE Healthcare, IBA Molecular, Lantheus Medical Imaging, Mallinckrodt Pharmaceuticals, and NTP Radioisotopes. The generator companies also learned the value of multi-sourcing for the processed ^{99}Mo. This ensured the availability of processed ^{99}Mo when their primary source could not provide the necessary ^{99}Mo. They also shared their limited supply of ^{99}Mo with their customers by redistributing the ^{99}Mo among their generators, reducing the number of larger generators, and providing more smaller generators, allowing the existing supply to be rationed among more customers.

The generator companies' customers are the nuclear pharmacies. Many nuclear pharmacies are local, but there are also four national nuclear pharmacy companies or groups in the United States, they are Cardinal Health™, GE Healthcare, Triad Isotopes, and United Pharmacy Partners (UPPI, LLC). The nuclear pharmacies were able to increase yield from their generators by eluting more frequently. This was another mitigating factor during the shortage that enabled getting more patient doses from a fixed amount of ^{99}Mo activity.

The nuclear pharmacies were subjected to financial stresses during the shortage, when many pharmacies apparently had longer term contracts with hospitals than they did with the generator companies, and were particularly vulnerable to price changes between their generator suppliers and their hospital customers. While generator prices increased, there were apparently no restrictions in such price increases being passed on to the pharmacies. However the pharmacies were legally obligated to continue to sell the radiolabeled drugs at previously agreed upon prices to the hospitals. To address this problem in the future they now multi-source their generators to ensure supply during loss of a single vendor, and have increased their bargaining powers by creating alliances, and writing smarter contracts. This is similar to what energy and water companies do today, where the cost of the energy or water are paid separately from the services.

The last link in the supply chain are the hospitals and clinics, where the patients are. The flexibility in how patients are managed is a critical short term action that can dramatically mitigate the effects of the shortage. Despite the disruptions, drug supplies are eventually restored. Until supplies are restored, demand can be moderated by adjusting patient schedules. If they have their own pharmacies, critical patients can be scheduled earlier by eluting the generators sooner. Less critical patients can be rescheduled to a later date. Depending on the individual patient history and the diagnostic tests available, alternative tests may be used. These decisions are medical, and will depend on the patient's medical status, the patient's individual history, and the alternative tests available. Bottomline, with such flexibility, the shortage can be managed.

Reimbursement and Full Cost recovery

The confusion over costs and reimbursement have often dominated some of the dialogue, so let me discuss them briefly, and make my own recommendations.

There have been dramatic changes in how health care is delivered and paid for, these are ongoing. I will spare you the details, but one major, undeniable trend is toward bundled payments. Hospitals are receiving bundled payments for patients, often a fixed amount for managing that patient. It will be up to the hospital as to how it distributes that money. The cost of the ^{99m}Tc may be a few dollars, but add the cost of the drug, the cost of professional staff and services, and capital costs such as facility and the nuclear medicine cameras, and the final cost may be thousands of dollars. Hospitals are reimbursed for the sum total of "full costs", but how the reimbursement trickles down the supply chain to the pharmacies, generator companies, producers, reactors, and suppliers of the uranium is simply difficult to track. The solution, vendors need to be more business smart, and negotiate fair prices with their suppliers and customers, and let the marketplace regulate itself. This actually is what seems to have happened.

Full Cost Recovery, is actually similar to the reimbursement issue. It is too complex to resolve. If a reactor was built 50 years ago by the government dedicated to research, how do you compare capital costs with a new reactor dedicated to ^{99}Mo production? What proportion of production is for ^{99}Mo production? If the new reactor is built by the private sector, did they receive grants, government guaranteed loans, or private bank loans. If a loan is in default, who pays for the full cost of the loan? So estimating full costs is simply too complex. The practical solution, is to simply let the market sort itself out.

6. Summary of Important Observations

Global demand for ^{99}Mo has decreased from about 12,000 6 day Curies/week to 9,000 6 day Curies/week in 2017.

The total capacity of ^{99}Mo is 24,800 6-day Curies/week, about 2.75 times the estimated demand of 9,000 6-day Curies/week.

There are more reactors in 2017 producing ^{99}Mo than in 2009, including the loss of OSIRIS and Chalk River. This reduces the risk of any single reactor causing a shortage. However the mean operating age went from 47 years old (n=5) to 54 years old (n=6).

The older reactors have generally undergone major refurbishment, and have also increased their individual reserve capacities, an improvement over 2009.

There is an intrinsic 35% additional reserve capacity built into the models.

AIEPES routine assessment of irradiator schedules has been an important action. Knowledge of maintenance and production schedules of ^{99}Mo producers have enabled adjustments to these schedules to minimize risks.

There are many new potential domestic and global entrants as exporters such as Argentina, Brazil, Canada, China, India, and Kazakhstan. These may be traditional reactors, or commercially unproven alternative technologies.

Although there are many U.S. domestic alternative technologies, none of which have yet to be approved by FDA for marketing. They are in various stages of development or approval.

There is concern about the economic viability of some of the participants in an environment where all of the current and future producers of ^{99}Mo were active participants.

7. Conclusion

The Global Shortage of Mo-99 is over. The ^{99}Mo capacity is 2.75 times the estimated demand of 9,000 6-day Curies/week. Producing it, and getting it to market efficiently are common problems that have been overcome in many other industries.

It is highly unlikely all of the future potential aspirants to commercially produce ^{99m}Tc will succeed.

8. References

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