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Guest Editorial

^{99m}Tc-Technetium Shortage: Old Problems Asking for New Solutions

Luis F. Metello, MSc*

Department of Nuclear Medicine, High Institute for Allied Health Technologies, Polytechnic Institute of Porto and Medical Faculty, University of Coimbra, Portugal

Technetium 99-metastable (^{99m}Tc) is the most important radionuclide, responsible for more than 80% of applications in nuclear medicine, with more than 40 million procedures being performed each year, worldwide, in all major clinical fields. It decays with a half-life of 6.01 hours by isomeric transition to ^{99g}Tc, thereby emitting 140 keV gamma photons. This energy almost ideally meets the maximum sensitivity of single photon emission computed tomography (SPECT) camera systems. In addition, the rich complex chemistry of Technetium allows the incorporation of the radioisotope into a wide variety of ligands stabilizing the radionuclide at different oxidation states. Thus, since the early 60s, hundreds of radiopharmaceuticals labeled with ^{99m}Tc have been developed, and some have gained significant market success. However, the main reason for the special role of Technetium in SPECT is probably the cost effectiveness and the on-demand worldwide availability of the isotope through the ^{99}Mo/^{99m}Tc generator systems [1].

It all went smoothly until recently, when "dark clouds" appeared on the nuclear medicine global horizon. Since 2007, there were more than 11 periods of serious disruption of generator supplies, with the two most important in 2009 and 2010, involving the simultaneous (and extemporaneous!) break of the two most important nuclear reactors from the five still active. These were jointly responsible for almost two-thirds of the world's supply: the National Research Universal Reactor, at Chalk River Laboratories, in Ontario, Canada, and the High Flux Reactor, from the Nuclear Research and Consultancy Group, in Petten, The Netherlands.

That was a very critical moment for the whole world, indeed a brutal wake-up call for the reality that is the entire community became strongly dependent on a single product, ^{99m}Tc, which is:

- Being produced in a short number of old nuclear reactors, and so becoming unreliable, because it is getting close to the end of their expectable and/or planned lifetime (circa, 50 years): they were essentially five that moment, while, in this moment, and only for a short period, they are a bit more (nine) even if the new added ones are not as strong and/or powerful and productive as those that will be leaving the production-circuit in a short term;
- Using a process that, being the most used for the last four decades, is nevertheless very inefficient (with less than 0.05% efficiency!);
- Strictly depending on Highly Enriched Uranium (HEU), a very critical product subjected to an increasing number of restrictions and stricter regulations; producing a huge amount of hard, and costly to process, highly radioactive waste;
- Depending on an even shorter number of processing infrastructures, already clearly identified as "at the limit of its processing capacities and unable to cope with near future processing needs," [2];
- Under an overall production system and supply chain that, being almost entirely paid and/or heavily subsidized by governments (the owners of the nuclear reactors), is entirely unsustainable. Final prices into the market are so low that there are no other "new" companies (meaning: distinct from those already involved from the very beginning, all of them already complexly involved at multiple levels with the governments here in question) that might stand for a chance, thus limiting the competition and the evolution, allowing to–slowly, but firmly and inexorably!–create the conditions that bring us to the present crisis scenario.

It became clear in that moment, as in this moment, there were–and there are–no reliable solutions for supplying ^{99m}Tc worldwide. There is no "other solution" appearing in the near horizon, since according to the Canadian Nuclear Safety Commission [3], between others that studied the problem and arrived at the same conclusion, the "niche" ^{99}Mo/^{99m}Tc market has been distorted too much by the direct and/or indirect government subsidies. This has caused the cost of medical isotopes to remain so artificially low–and quite far from the real figures, those expectable when all the normally

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* Corresponding author: Luis F. Metello, MSc, Nuclear Medicine Department, High Institute for Allied Health Technologies of Porto, Polytechnic Institute of Porto, Rua Valente Perfeito, 322, P-4400-330 Vila Nova de Gaia, Portugal.

E-mail address: luis.metello@gmail.com

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applying factors would be present–that it completely undermined the competition and interest of private developers, placing them "out of the game" for quite a number of years–another complicating factor.

This is even more disturbing because it is understood that the demand, essentially based on an overall ageing population and on the development in health systems in developing countries, can only increase. Solutions are urgently needed!

Since the first set of official reports published in 2009 and distinct international analysis assuming the primary ^{99}Mo-producing reactors are becoming less reliable, it became obvious that new or replacement technologies were/are needed; albeit under a sustainable economic structure that is consensual and globally mentioned as a "full-cost recovery" model. But, it is evident, as mentioned clearly by Zakzouk from the Canadian Government [4], that "international progress is slower-than-desired." In its most recent forecast of future ^{99}Mo/^{99m}Tc supply [2], the Organization for Economic Co-operation and Development (OECD) Nuclear Energy Agency (NEA) predicts that the current global irradiation and processing capacity will likely be insufficient over the 2015–2020 period, a reason why the agency stresses the need to establish an economically sustainable supply chain as quickly and efficiently as possible, since this will most certainly be the most efficient way to avoid further disruptions of important diagnostic tests.

In June 2011, the High Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) prepared an international policy approach, endorsed slightly later in a joint declaration [5] by the ministers and representatives of the 13 countries most involved with this international issue (agreeing to implement it by June 2014), urging governments and industry to work toward:

- The implementation of full-cost recovery for all new and replacement technologies;
- The establishment of a reserve capacity that is sourced and paid for by the supply chain;
- Fostering market-driven investment through a business and regulatory environment that promotes safe and efficient market operation;
- Promotion of nuclear nonproliferation by favouring low-enriched uranium (LEU) technologies or other approaches not based on highly enriched uranium (HEU);
- The international collaboration toward a globally consistent approach to secure ^{99}Mo/^{99m}Tc supplies;
- The periodic reviewing of the supply chain to verify the implementation of full-cost recovery by the ^{99}Mo/^{99m}Tc producers, the remaining approaches agreed by the HLG-MR are being implemented, and that the overall operational activities have no negative effects on market operations.

As a direct action to implement the last principle, the OECD-NEA conducted an assessment of the ^{99}Mo/^{99m}Tc supply chain in February 2014 to evaluate the progress made by supply chain participants since the last assessment in 2012 [6]. A higher number of questionnaires were sent to key supply-chain participants: reactor operators, processors, generator manufacturers, nuclear medicine associations–representing the end-users of ^{99}Mo/^{99m}Tc generators–and governments. For the first time–an important point and a potential added value–waste management costs were included when assessing progress toward full-cost recovery. This is a particularly important issue because the bulk of waste management costs are currently being paid by governments, except in Australia, South Africa, and Belgium. Nevertheless, one might wonder about the reliability of the analysis since the clear sensitivity of data and the fact (clearly mentioned) that it is "entirely based on information provided directly by the supply chain participants and have not been verified independently." [6].

Briefly, the main findings were that progress toward full-cost recovery (the first agreed principle) has been slow, and government subsidies continue to be a barrier, sending a negative signal to the rest of the market and slowing down full implementation. Similarly, planned reactor and processor infrastructure is being built with public funds, which further undermines the process toward economic sustainability [6]. At another level, generator manufacturers, as all commercial entities, are expected to fully recover their costs of producing ^{99m}Tc generators plus a profit. However, to the extent that below-full-cost-recovery prices are passed down the supply chain from subsidized reactors, generator manufacturers do not pay the "true" cost of ^{99}Mo.

In this self-assessment, end-users reported higher prices from their suppliers over the last two years without a corresponding increase in reimbursement, except for the additional payment of 10 USD in the United States for non-HEU ^{99}Mo. This has put pressure on hospital budgets and may lead to a noticeable substitution of ^{99m}Tc-based radiopharmaceuticals by other less costly eventual options–even if less efficient–in the future. However, despite the higher prices, many end-users reported that they have been able to absorb the higher costs, even if this is not consensual [6].

Concerning the Outage Reserve Capacity (the second agreed policy principle), despite noticing some progress, it is far from being universally accepted and used by the market. Reported figures are much lower than what it is actually accepted as adequate–around 50% of reserve–for both cases: irradiation capacity and processing capacity [2, 6], and this is indeed a great risk because it has been observed that the reserve capacity is in fact almost always being used, so demonstrating that anterior forecasts were in fact "underevaluated."

Concerning the supposed diminished governments' role in the market (the third agreed policy principle), in fact it all happens at both ends of the global supply chain–at the reactor and end-user levels. Although governments have been reducing their support for ^{99}Mo irradiations at reactors, much is yet to be done before attaining the implementation of full-cost recovery …and there are "worrying sign of intentions to continue government subsidization" [6], meaning that there is no reason to expect huge changes in the short term. Downstream, very few governments intend to or are already reviewing their reimbursement rates for medical isotopes, with only two exceptions: the Belgian government that had implemented a separate reimbursement for ^{99m}Tc at the beginning of 2015 and the US government that has added the supplementary payment of 10 USD to reimburse hospitals for the higher cost of non-HEU–produced ^{99m}Tc, clearly motivated by the desire to encourage conversion to LEU, as well as to help cover the costs of moving to full-cost recovery [6]. At the same time, some responders agreed with the supplementary payment amount, while others thought that amounts should be higher, with values proposed at a threefold range (30–35 USD).

The OECD-NEA, concluding the results of the second self-assessment of the global ^{99}Mo/^{99m}Tc supply chain, mention that they were, globally, quite similar to the first one. They showed a slower progression, missing the deadline of June 2014 agreed by the governments, and the remaining participants have not taken sufficient action [6] …and that is the reason behind the fact that the market remains unsustainable today and the risk of shortages in the 2015–2017 period, as clearly shown in *Medical Isotope Supply in the Future: Production Capacity and Demand Forecast for the ^{99}Mo/^{99m}Tc Market, 2015-2020 (NEA, 2014)* [2], even if it is admitted that "timely and coordinated actions by the supply chain could minimize this risk" [6].

The expert panels seem to believe that most of the difficulties relate directly to the simultaneous transition to full-cost recovery and the conversion to the use of LEU targets for ^{99}Mo production. Strangely, the OCDE-NEA defend the position that, "since the LEU conversion is an externality, government support to these supply chain participants (eg, through financial incentives) would be consistent with the HLG-MR principles." Other external players do not think that way…and wonder about who is going to support the radioactive waste management. The use of LEU implicates even lower production yields–from 20%, the minimum reduction, to five times less; as well as the production of much higher amounts–between five and 20 times more as predictable figures!–of very highly contaminated, dangerous, and costly-to-handle radioactive waste. If the answer is, most probably, "the usual suspects" …then the full-cost recovery model might be definitely compromised.

The OECD-NEA, via the HLG-MR, thinks that "short-term commercial considerations (eg, increasing or retaining market shares) continue to trump long-term sustainability, resulting in unhealthy competition and inefficient market outcomes. Furthermore, some governments are still subsidizing ^{99}Mo production, despite their commitment to the HLG-MR principles, which is sending negative signals to potential investors in future commercially based production, jeopardizing the long-term security of supply by potentially perpetuating below-full-cost-recovery prices." [6]. Others might entirely agree with the causing considerations, while sharing distinct opinions about how to address it and what could be identified as possible solutions.

It is immediately apparent, from the OCDE-NEA full range of documents that one "kind of" bias; that is, to always admit that "THE good solution," will be the one that will "be based on a network of research reactors" [6] as it is stated, both directly and indirectly, on many occasions in the aforementioned documents. They affirm that "despite the promise of alternative ^{99}Mo/^{99m}Tc production technologies, such as linear accelerators and cyclotrons, whether they will be widely deployed on a commercial basis remains to be seen. Given the current reliance on ageing reactors for most of the global ^{99}Mo supply, plans for their replacement or building new reactors are important developments for ensuring the security of supply" [6].

In another document, the lack of confidence with "the fact that alternative technologies have yet to be proven on a large scale in the ^{99}Mo/^{99m}Tc market" is justified, and adds that it is not clear whether the alternative production technologies (which are to be commercially based, to be sustainable) will be priced competitively in the market. This is essentially because not all (most of the) current ^{99}Mo producers, many of whom are subsidized, will have implemented full-cost recovery in the near future, so assuming that it "would present future challenges for producers who have or will have implemented full-cost recovery by then, and other new projects that are being planned to operate on full-cost recovery. In the limit, those producers could be forced to exit the market because of a lack of ability to compete on price" [2]. All this is happening because the countries that have agreed and jointly signed the Declaration assuming the Six HLG-MR Policy Principles did not implement them in a timely and/or consistent manner and the situation can only become more critical while this is not done efficiently. Until that happens, there will be a huge risk that projects that could become part of the solution will never be able to develop enough to prove it, because the unfair market conditions they are obliged to compete with might make it an "impossible mission." If there is any consensus between the involved experts, it is the urgent and/or imperative need to establish an economically sustainable ^{99}Mo/^{99m}Tc supply chain as quickly and efficiently as possible because this "would be the way to enable investment in new and/or replacement, non-HEU–based production capacity and its timely entry in operation, providing sufficient amounts of funded outage reserve capacity to the market" [2].

Even assuming that not all the proposed alternative technologies are at the desired level of maturity, there are considerable differences at this level as well as the distinct options being advanced. In this case, it might not be the best approach to consider them all the same way, because while some of them are steadily and globally implemented, and almost immediately functional, well proved and reliable, others still have a long way to get there …but we will come back to this point. What can be less obvious is the reason for insisting on going in a direction that creates almost the same problems (if not bigger, as in the case of radioactive waste being produced when using LEU targets) that brought us all where we are now: in deep trouble!

In fact, continuing to defend the nuclear reactor route as an option (or even further: advising in the construction of new–dedicated?–units, with economical resources to be spent and the time needed to become effective–when their own studies demonstrate clearly that the most critical period is fast approaching…–and when there are already more than 450 nuclear reactors installed worldwide, most probably and/or certainly including some that could be more or less easily adapted…) is the same as admitting that the best option is to continue to use a process with such a lousy inefficiency becomes even worse when considering the use of LEU and producing such huge amounts of highly radioactive (and proportionally dangerous and costly to manage and/or process) waste…is something seemingly difficult to advocate. Even when that is exactly what is indeed happening.

Could it be that some alternative possibility has not been explored adequately? Some authors believe that could be the case for the direct production of ^{99m}Tc using low-energy, the so called "medical," cyclotrons. I'm one of them.

Even if it is not yet completely established in a definitive way (essentially for industrialization, optimization and/or regulatory issues yet to be closed definitively), ^{99m}Tc has been directly produced via cyclotrons, in several reliable manners, in sufficient quantities to deserve to be considered as, at least, "a serious option for a solution." Even more so with the knowledge that there are more than 500 units installed globally and working daily, each one potentially able to enter to the supply chain and have a direct impact, creating security and reliability in the ^{99m}Tc supply in their own region (meaning anything with an approximate radius of 400 km when travelling by road or 3 hours of flight when travelling by plane). These figures correspond to about the double admitted as "comfortable" for fluoro-2-deoxy-2-D-glucose labeled with fluorine-18 (^{18}F-FDG), despite the fact that ^{99m}Tc has three times longer half-life and one third of the energy emitted.

^{18}F-FDG production and distribution is already the core activity of those cyclotron-related radiopharmaceutical centres, so it would be considered as "another radiopharmaceutical product" in their portfolio of products, to be distributed to the same clients or a bit more than those they are already busy with …so just "business as usual"! In fact, for well-established and efficient companies–most of them with years of experience in producing, handling, and distributing essentially ^{18}F-based radiopharmaceuticals (with 110-minutes half-life and 511 keV energy)–adding ^{99m}Tc-based radiopharmaceuticals (with 6.01 hours half-life and 140 keV energy) would be considered a very easy thing, fully compatible with all the remaining activities–just another product and/or family of products!

When considering the costs of the investment needed to build the "new capacity," they are probably quite reasonable, essentially consisting of an "entry-fee" at the contract signature, giving access to all documents, and the acquisition of some hardware; all the rest would be production costs concerning all the consumables, so directly proportional to the amount of ^{99m}Tc being produced …and billed.

A very important aspect, eventually to be considered as "THE" most important aspect, depending on the severity of the shortage of supply at the moment of the decision, would be the time frame needed for the dissemination of the methodology and the full implementation of this alternative route, place by place and/or worldwide. And there is good news here, as it is potentially very short: in fact, nothing compares with this possibility, because the cyclotron centres are already actively in place, most of them firmly installed in the market, fully equipped from the point of view of specialized human resources, already benefiting from proven efficient solutions for local and/or regional distribution (as perfectly tailored for and strictly adapted to its own region of influence), having built expertise on the daily operation with radiopharmaceutical products, which are much more stringent regarding physical conditions and time limitations.

Of course, economic conditions and related implementation time frames would be distinct for the new cyclotron-based centres, but this is something else; and, essentially, those are not significantly different from those that a new company wishing to install and become active in this particular field would have to face. In fact, as enlarging considerably the portfolio of products available for the same market (the nuclear medicine departments–NM), it increases the range of potential clients that can be served because the classical nuclear medicine departments (SPECT only) would apply for potential clients as well, while before and/or currently only the positron emission tomography (PET) scanners-equipped NM departments were or are concerned. An even further advantage becomes evident when considering the obvious trend, for a developing an NM department, to start with SPECT scanners before evolving to PET. They are already involved as a supplier of ^{99m}Tc-based radiopharmaceuticals, so having the opportunity to build a relationship with the client, knowing and adapting to his own specificity, while getting known and being exposed to the opportunity to win his confidence, can only be identified as a great opportunity to become their future PET tracers supplier. This clearly constitutes a highly interesting competitive advantage regarding the other suppliers in the same region, those that only have positron emitters in their portfolio. Moreover, it is of upmost importance to clarify that, despite what has been announced "here and there," repeatedly, even in seemingly responsible official documents and "final reports," there is absolutely no reason why the ^{99m}Tc direct production method should not be compatible with the remaining "classical" radiopharmaceutical products (^{18}F-FDG in more than 98% of the cases): it is a very simple and easy-to-handle logistic issue, nothing else!

In fact, once completely stabilized and optimized–including not only the production and/or distribution issues but those related with the obvious need for strictly complying with all the regulatory aspects (that, in the meantime, need to be clearly defined and solved–…and this is yet to be done, at the regulators' level!)–the entrepreneurial decision to include the "^{99m}Tc direct production method using low-energy cyclotrons" in its daily activities (so adding ^{99m}Tc and ^{99m}Tc-based radiopharmaceuticals portfolio) should be seriously considered by:

- The radiopharmaceutical companies already present in the worldwide market that still have (or want to build) reserve production capacity. In fact, most of them have it, created by the increased worldwide competition observed in the last years in the positron tracers production and distribution market field, with the entry of new players that makes competition and sharing the market as omnipresent conditioning factors… and there should be no doubt that being present in the SPECT market will always signify a competitive advantage over the competitors who do not;
- The "newcomer" companies, because it will help to "build their own place," as they will be entering the market via new clients: the NM departments that are not yet active in the PET field (so are not in relation with the classical radiopharmaceutical companies) facilitating entry in the field, reducing the inherent risk to the creation of a new business, while creating a favourable positioning for the future, when (some of) those NM departments will move to PET as well. At the same time, they will become more attractive for the remaining NM departments (although not all the classical NM departments are–yet–active in PET, all the NM departments active in PET are as well active in SPECT). Thus, in an eventual shortage of ^{99m}Tc supply, they will be more than prone to switch between suppliers, moving to one that could solve ALL the radiopharmaceutical issues …and not just a part of it;
- All those investors potentially interested in becoming present in a field that does not stop to evolve, and that might consider this potentially competitive advantage that will be the capability to directly produce and supply ^{99m}Tc as "THE" good reason and the trigger to make the decision to invest in the field, considering the high potential of the opportunity that might be inherent: once this movement starts, things will never be the same again, and there might be interesting windows of opportunities opening here and there, where the critical mass of the number (and dimension) of NM departments available in a certain specific region of influence would justify it.

This potential for attraction of new actors might be easily assumed as a new factor with a very interesting potential for further promotion of the global growth of the nuclear medicine field … this time in a correctly sustainable way, since fully complying with the inherent full-cost recovery model, naturally ruled by the market, even always duly controlled by the regulators, at all levels, from local to global.

Motivated by the correct aims and goals (namely to serve the best interest of the medical global community and–essentially!—the best interest of an ever growing community of patients worldwide, that already amounts in excess of 40 million subjects per year) there should not be any problem or critical issue: it is just a matter of applying the already existing rules concerning quality, security, and safety, following the inherent procedures and using a bit of common sense to introduce the eventual adaptations, deemed to be adequate to better serve the global society interests …and nothing else.

It is well known that recent (and less recent) studies demonstrate that radiochemical purity and stability of distinct ^{99m}Tc-based radiopharmaceutical kits–with the entirety of the most used included–are not being affected up to a ^{99g}Tc/^{99m}Tc ratio of almost 12 [7] (with ^{99g}Tc standing for Technetium 99 "ground" state, that is the result from the decay of ^{99m}Tc and/or the result from almost 13% of direct decay of ^{99}Mo being used in the "classical" ^{99}Mo/^{99m}Tc generators …as well as directly produced on the irradiation process of ^{100}Mo that produces directly ^{99m}Tc using accelerator-based techniques) and, in a recent interview [8] E. Turcotte, from Sherbrook, Canada, mentioned that in the worst case scenario an irrelevant added exposure dose of (maximum!) 3% could be associated to the differential of contaminants due to the alternative route for ^{99m}Tc production using accelerator-based techniques. Considering this, is it reasonable to create new rules, like those related with contaminants deemed as relevant now–so with the potential to become critical issues from the regulatory point of view, eventually creating obstacles to the acceptance of this alternative route–if they were already present, and in practical terms, with amounts essentially within the same range, in the case of the ^{99}Mo/^{99m}Tc generators …and we all had lived in peace and tranquility with it, with the obvious results, as there were no problems related being noticed during all those years of worldwide use?

Indeed, what could be the justification for, at the same place and moment, in the same marketplace, exactly at the same conditions of application, for the same purposes, one product being refused because of its ^{99g}Tc content when the reference product, the one produced via the ^{99}Mo/^{99m}Tc generator, has it as well, within essentially the same relative amounts, has always had it, and will always continue to have it …and it never has been identified until now as a critical issue?

…but that is what some (more or less) "occult powers" are trying to promote.

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