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REVIEW ARTICLE

An Increasing Role for ^{68}Ga PET Imaging: A Perspective on the Availability of Parent ^{68}Ge Material for Generator Manufacturing in an Expanding Market

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ABSTRACT

The use of gallium-68 for molecular imaging is gaining momentum world-wide. While our understanding of ^{68}Ga chemistry, generators, and associated synthesis modules appear to have advanced to a clinically-reliable stage, uncertainty in the supply of radiopharmaceutically-suitable parent is of significant concern. In this work, we examine the current supply of ^{68}Ge in an effort to better understand the potential for expansion of manufacturing to meet an increasing demand for ^{68}Ga. Although specific information on sales and demand of ^{68}Ge is highly business sensitive and thus guarded, our examination finds no shortage in the current supply of ^{68}Ge. On the other hand, increases in the use of ^{68}Ge generators for clinical applications in the United States point to the need for continued support for production at DOE laboratories in the United States to ensure a reliable supply and suggests that new commercial facilities may be needed to meet the increasing demand.

Keywords: Gallium-68, Germanium-68, Generators, PET imaging, Molecular imaging.

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INTRODUCTION

The use of gallium-68 (^{68}Ga) for molecular imaging of disease has seen a marked increase over the last several years.[1-6] Applications for ^{68}Ga positron emission tomography (PET) are emerging across a broad spectrum of diagnostic imaging challenges including cancer, cardiovascular disease, infection and inflammation.[7-18] The increase in enthusiasm for ^{68}Ga use can be ascribed to several factors, including: Superiority in achievable image quality compared to other gamma-emitting radionuclides (e.g. indium-111);[19] nuclear decay characteristics (i.e. half life and positron emission branching ratio) that are considered favorable for clinical molecular imaging; and the potential for on-demand production via the introduction of maturing-competitive generator and fluid handling technologies that are now capable of providing reliable, high-purity, on-demand ^{68}Ga precursor in sufficient quantities for routine radiopharmaceutical production in the absence of cyclotron operations.[2,3,5,6,14,20] These characteristics promise an increasing role for ^{68}Ga PET imaging that has great potential to expand in the United States and throughout the world. The advances of generator technology for ^{68}Ga production, chemistry of gallium within the context of radiopharmaceuticals, and emerging applications for ^{68}Ga radiopharmaceuticals have been reviewed in detail by several authors recently.[2,3,5,6,21] The observations of these authors provide evidence that the future for ^{68}Ga appears bright. However, to accelerate the use of these exciting new diagnostic agents for clinical applications, concerted effort will be required to promote the 'promising' status of gallium-68, as alluded to by Breeman and Verbruggen,[22] to widespread routine clinical use in the United States.

One area of development that has the potential to significantly impact the trajectory of ^{68}Ga for clinical imaging in the United States revolves around uncertainty as to the supply of generators and parent radionuclide germanium-68 (^{68}Ge). A parallel can be made, in this context, to recent challenges to the use of the long-time dominant radionuclide technetium-99m (^{99m}Tc) with the loss of a single supplier of parent molybdenum-99 (^{99}Mo).[23,24] While the potential advantages of ^{68}Ga relative to ^{99m}Tc can be debated,[2] the need for a reliable source of parent radionuclide is critical to success. Thus, while ^{68}Ga chemistries and associated synthesis modules appear to have advanced to a clinically-reliable stage, uncertainty in the supply of radiopharmaceutically suitable parent is of significant concern. In this work, we examine the current supply of ^{68}Ge in an effort to better understand the potential for expansion of manufacturing to meet an increasing demand for ^{68}Ga.

MEETING AN INCREASED DEMAND FOR ^{68}Ga

As the potential for ^{68}Ga-labeled compounds has become evident, several commercial companies have advanced generator technologies to meet the demand for reliable production of ^{68}Ga on a routine basis.[6] Several promising technological platforms have been applied for the development of these generators,[5] based on TiO_2,[2] SnO_2,[25] nano-zirconia,[26] and organic- or silica-based solid-phase materials.[27-29] The first generators documented in the literature were developed as early as the 1960s,[2,30,31] while the commercial alternatives available today were initially introduced in the early 1980s. The technology improvements of these commercial alternatives have played a large role in advancing the potential of ^{68}Ga. Significant advances included removing the need for complexing agents to selectively remove ^{68}Ga from the generator-column and reducing the acid concentration from as high as 1 M hydrochloric acid (HCl) to as low as 0.1 M HCl eluate concentration to remove ^{68}Ga as a cationic species. These improvements facilitated more reliable pH adjustments for the radiolabeling reaction with most chelator-modified peptides and small molecules. Importantly for smooth transition to routine clinical use, recently introduced commercial generators are demonstrating excellent elution yields (65-80%) and low initial breakthrough levels of ^{68}Ge parent on generator elution.[2,5,6]

While these findings and observations point to a maturing technology, which is increasingly recognized around the world as suitable for routine clinical operations,[6] one area of concern for expanding operations in the United States (US) is the availability of parent ^{68}Ge for manufacturing of generators and the potential for a shortfall. Specific information on the capability and capacity of current production of ^{68}Ge parent material is not entirely transparent. However, there is documented capacity from at least three major sources that lend confidence to the ability of current manufacturing to maintain a stable inventory of ^{68}Ge that can meet near-term projected demand. Four major centers which produce parent ^{68}Ge for generator manufacturing currently are: iThemba laboratories (South Africa), Brookhaven and Los Alamos National Laboratories (USA) and Cyclotron Co Ltd (Obninsk, Russia). According to a recent IAEA report, these facilities have production capacities of approximately 0.5 to 2 Ci per run.[32]

iThemba LABS (South Africa) has been producing chemically processed ^{68}Ge commercially for many years. The company reports production of unprocessed ^{68}Ge by standard irradiation of stable Ga targets (encapsuled in Nb) via a cyclotron proton irradiation (iThemba-provided communication). The raw ^{68}Ge material is then purified by way of volatilization and ion-exchange chemical processing techniques to produce radiochemically pure ^{68}Ge that is suitable for incorporation in $^{68}Ge/^{68}Ga$ generators. The manufacturing capacity under current capability at iThemba Labs is estimated to be approximately 4-5 Ci (148-185 GBq) ^{68}Ge per year, with the ability using current facilities to increase production to nearly 8 to 10 Ci (296-370 GBq) of process-purified ^{68}Ge per year.

The second major source of ^{68}Ge parent material is the United States, Department of Energy (DOE), which operates production facilities at Los Alamos National Laboratory (LANL; Los Alamos, NM) and Brookhaven National Laboratory (BNL; Brookhaven, NY), in the United States. Production facilities in the DOE have operated since 1954 with the inception of the US Atomic Energy Act, which specified a role for the US government in isotope production and distribution.[33] This program has grown to provide domestic supply of about 300 different isotopes (stable and radioactive), which the DOE sells for medical, commercial, research and national security applications. In fiscal year 2009, the DOE reports programmatic repositioning of isotope production to the Office of Science and revision of the program's mission to include maintenance of the infrastructure required to produce and supply isotopes (including ^{68}Ge) and related services. The revised mission of the program further included investigation and development of improved isotope production and processing techniques that can make new isotopes available. The DOE Isotope Program relies on appropriations and revenues from isotope sales to fund its operations. Yearly appropriations and sales revenues are deposited in a revolving fund that has flexibility for carryover from fiscal year to operate facilities, pay salaries, produce isotopes and fund other activities. The value of this flexibility to maintain operations in an unconstrained manner was evidenced recently with a steep decline in the use of strontium-82 (^{82}Sr) in 2010, which had accounted for over one-third of the programs total revenues.[34] The decrease in orders for ^{82}Sr declined steeply and unexpectedly as a result of a recall of the cardiac imaging device that represented the majority of the isotopes use. Through use of the revolving fund, the program demonstrated the ability to maintain continuous operations in spite of significant loss of current revenues. Further flexibility for production of ^{68}Ge by the DOE is related to the ability to produce at two independently operated sites (i.e. Brookhaven and Los Alamos).

The published funding appropriation for the DOE Isotope Program activities totaled nearly \$20M US in fiscal year (FY) 2011, with total revenues exceeding \$26M.[34] The program sold isotopes and provided related services to over 100 customers in FY 2011 domestically and internationally. Six of these customers account for more than 80% of sales in FY 2011. More than 95% of the program revenues were attributed to eight isotopes: Strontium-82, californium-252, helium-3, nickel-63, strontium-90, actinium-225, lithium-6 and germanium-68. According to these reports, of total isotope sales, revenues for the DOE Isotope Program associated with ^{68}Ge production were nearly $2M US for FY 2011. Similar to the production route at iThemba LABS, the DOE has been irradiating Ga targets at its accelerator sites at BNL and LANL to produce and purify raw ^{68}Ge material. Published values for ^{68}Ge sales in radioactivity units from the US DOE were over 10 Ci (370 GBq) and 11 Ci (407 GBq) in FY 2009 and FY 2010 respectively. Interestingly, the modest increase in total ^{68}Ge revenues in radioactivity units contrasts the total number of shipments, which more than doubled from 26 in 2009 to 58 shipments of ^{68}Ge reported by the DOE in FY 2010. These sales are attributed, in these reports, to PET calibration sources, reflecting increased demand and economic dominance of solid ^{68}Ge/^{68}Ga calibration sources (in terms of total market need for ^{68}Ge), relative to generators for ^{68}Ga PET imaging applications. No documented shortages of ^{68}Ge could be found through our examination.[34] These observations suggest that the DOE has adopted strategies to increase production of ^{68}Ge in response to an growing market demand.

The third major source of parent ^{68}Ge material for generator production is the Cyclotron Co Ltd (Obninsk, Russia), which has operated production facilities for many years. Recent reports by the IAEA suggest that high specific activity material is routinely made available with capacity of approximately 2 Ci per run.[32,35] The company reports similar production methodologies, and produced over 6 Ci (222 GBq) in the calendar years 2010 and 2011. The company further reported a significant increase (up to 11 Ci or 407 GBq) in shipments for the calendar year 2012 (Cyclotron provided communication). The company reports that products were destined for generator manufacturing and calibration sources, although further breakdown of the use of the produced ^{68}Ge was not available at the time of this writing. The company further reports that in response to increased demand, the manufacturing facilities are currently capable of producing up to 15 Ci (555 GBq) per year, suggesting that the Obninsk operations are poised to respond to an increased market demand.

SUMMARY AND CONCLUSION

Gallium-68 generators are a promising, maturing technology, which is increasingly recognized around the world as suitable for routine clinical applications. In this brief perspective, the current production and availability of parent ^{68}Ge for manufacturing of generators has been examined. Currently, the vast majority of ^{68}Ge is produced in the Unites States, South Africa and Russia. In the United States, the Department of Energy has been using their accelerators at Brookhaven (BNL) and Los Alamos National Laboratories (LANL) for the production and distribution of ^{68}Ge for many years. The operating cycles at these facilities complement each other to enable continuous production and distribution of ^{68}Ge, with a current production level of approximately 11 Ci (407 GBq). In South Africa, iThemba LABS has been producing chemically processed ^{68}Ge for many years. The company reports current manufacturing capacity to be approximately 4 to 5 Ci (148-185 GBq) ^{68}Ge per annum, with ability using current facilities to increase production to nearly 8 to 10 Ci (296-370 GBq) of process-purified ^{68}Ge per year. Current production capacity of the third major supplier of ^{68}Ge (Cyclotron Co, Obninsk, Russia) is reported to be up to 15 Ci (555 GBq) per year, for a total estimated production capacity for the three major manufacturers of approximately 37 Ci (1369 GBq) per year. Although specific information on sales and demand of ^{68}Ge is highly business sensitive and thus guarded, currently there is no shortage in the supply of ^{68}Ge. On the other hand, increases in the use of ^{68}Ge generators for clinical applications in the United States point to the need for continued support for production at DOE laboratories in the United States to ensure a reliable supply and suggests that new commercial facilities may be needed to meet the increasing demand.

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