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## 2. ESTABLISHING RADIOISOTOPE AND RADIOPHARMACEUTICAL PRODUCTION FACILITIES IN DEVELOPING COUNTRIES

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### INTRODUCTION

The importance of radioisotopes in modern medicine, for both diagnosis and treatment, is hard to overestimate and is described elsewhere. The most common type of nuclear medical diagnostics is single photon emission computerized tomography (SPECT), a functional test, which reveals biological activity, such as blood flow. One of the most common SPECT radioisotopes is <sup>99m</sup>Tc, obtained from its precursor <sup>99</sup>Mo. Positron emission tomography, or PET, is similar to SPECT in its detection of Gamma rays, but uses positron emitters such as <sup>18</sup>F, primarily for cancer diagnostics.

Although the use of radioisotopes for therapy is less common than for diagnosis, it is nevertheless widespread. The most recognized type of radiation therapy is external beam therapy (aka teletherapy), which uses radioisotopes, such as <sup>60</sup>Co, to treat cancer. An alternative to teletherapy is brachytherapy, in which a gamma radiation source (for example <sup>192</sup>Ir or <sup>60</sup>Co) is placed inside the patient's body, as close to a tumor as possible.

### PRODUCTION OF RADIOISOTOPES AND RADIOPHARMACEUTICALS

Proton cyclotrons are the most common types of accelerators used around the world to

produce medical radioisotopes. Hundreds of cyclotrons in the 10 - 70 MeV energy range with extracted currents of up to hundreds of mA are installed worldwide to produce radioisotopes; however, the majority are compact, less than 20 MeV accelerators used to produce  $^{18}\text{F}$  labeled fludeoxyglucose (FDG). Energetic protons can cause various (p,xn) and (p,  $\alpha$ ) reactions and typically result in neutron-deficient radioisotopes, many of which are either positron emitters or gamma emitters suitable for imaging and diagnostics.

Even though accelerators generate a variety of radionuclides, many medical radioisotopes are produced in nuclear research reactors. Reactors offer much larger irradiation volumes than accelerators, and many targets can be irradiated simultaneously. Additionally, reactors usually offer high neutron flux, which results in high isotope yield. Finally, a wide variety of radioisotopes can be produced in reactors by fission, neutron capture, and other neutron-induced reactions.  $^{99}\text{Mo}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ , and many other isotopes are routinely produced in many reactors worldwide for both diagnostics and treatment.

The production of a radionuclide is an important step towards a useful product; however, it must be followed by another important stage - preparation and packaging of a complete radiopharmaceutical – a compound which contains one or more radionuclides. This process is done at a radiopharmacy facility, which often is located right next to the production site, especially in the case of short-lived PET isotopes.

## **ACCESS TO RADIOISOTOPES AND RADIOPHARMACEUTICALS**

A large body of evidence confirms that cancer and cardiovascular diseases are and will continue to be the leading causes of death all over the world. A steady and reliable supply of radioisotopes can tremendously help the early diagnosis and treatment of these diseases. The poor in developing countries are even less likely than the better off to receive effective health care due to a lack of life-saving radioisotopes and corresponding infrastructure. Table 1 and Figure 1 show the percentage of the population in different countries where radioisotope production facilities or radiopharmacies exist. Top stack bars (a) represent the population of the countries where research reactors exist and are used

for medical radioisotope production. Middle stack bars (b) represent the population of the countries where accelerator facilities exist and are used for medical radioisotope production. Bottom stack bars (c) represent the population of countries where radiopharmaceuticals are produced from either domestically produced or exported radioisotopes.

Table 1. Population of different countries (grouped by continents or regions) where radioisotope production facilities or radiopharmacies exist. The data for radioisotope production facilities or radiopharmacies in individual countries were obtained from various references and from numerous private communications.

Continent or region	Population (million people)			
	All the countries	Countries producing isotopes with reactors	Countries producing isotopes with accelerators	Countries producing radiopharmaceuticals
North America	361.08	361.08	361.08	361.08
		100 %	100 %	100 %
Central and South America	630.46	407.48	537.10	590.22
		64.6 %	85.2 %	93.6 %
Europe	734.42	508.88	697.32	702.34
		69.2 %	94.9 %	95.6 %
Asia	4,503.70	3,447.21	3,953.15	3,950.15
		76.5 %	87.8 %	87.7 %
Africa	1,247.92	347.88	231.33	319.04
		27.9 %	18.5 %	25.56 %
Australia and Oceania	39.82	24.45	29.16	29.16
		61.4 %	73.2 %	73.2 %
<b>Total</b>	<b>7,436.16</b>	<b>5,096.98</b>	<b>5,727.90</b>	<b>5,870.76</b>

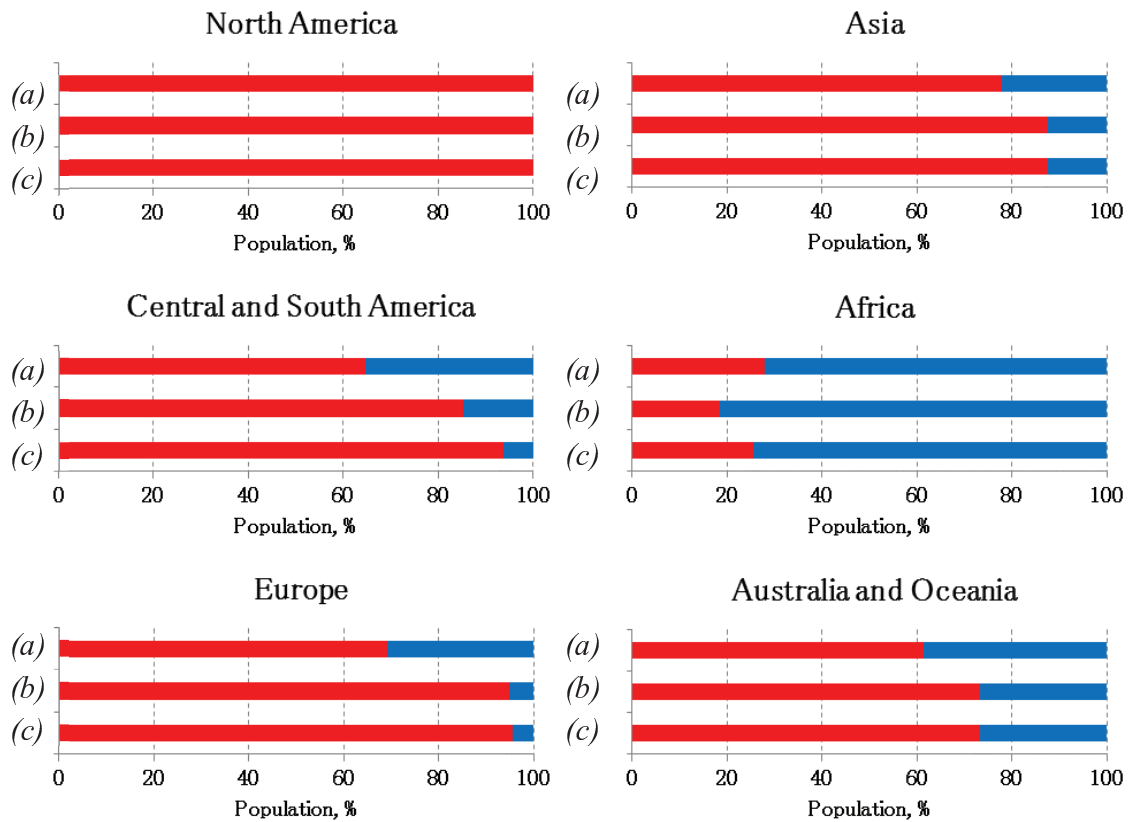
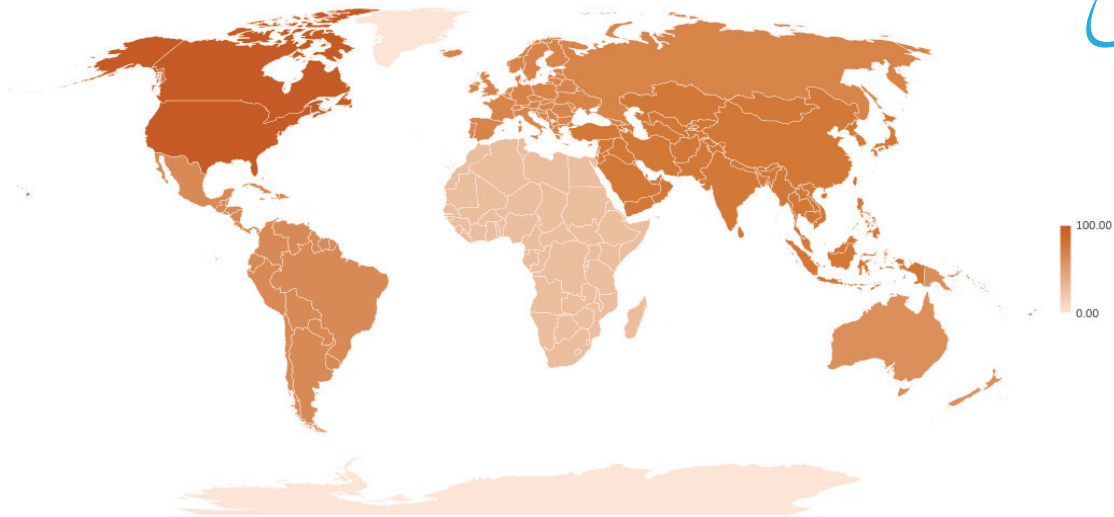


Figure 1. Fraction of the population with access to medical radioisotopes. Top stack bars (a) represent the population of the countries where research reactors exist and are used for medical radioisotope production. Middle stack bars (b) represent the population of the countries where accelerator facilities exist and are used for medical radioisotope production. Bottom stack bars (c) represent the population of the countries where radiopharmaceuticals are produced from either domestically produced or exported radioisotopes.

This analysis is not completely accurate. First, even if a country has a radioisotope production facility, the demand for radiopharmaceuticals can still exceed supply. Many countries have only one or just a few installations and often produce only several radioisotopes. For example, until 2012, Qatar had no radioisotope production facilities and its citizens had to travel abroad for PET and other nuclear medical procedures. In 2012 Hamad Medical Corporation (HMC) in Doha installed a low energy proton cyclotron and started producing  $^{18}\text{F}$  and making  $^{18}\text{F}$ -FDG. Since then, HMC state-of-the-art PET/CT center, has served thousands of cancer, cardiology and neurology patients. However,  $^{18}\text{F}$  is the only radioisotope produced in Qatar as of today. Thus, even though in our table Qatar is marked as the country “producing radioisotopes with cyclotrons” and “having a radiopharmacy”, its citizens could have benefited more from a wider portfolio of radioisotopes.

Another example would be a big country, such as China, which produces a huge variety of radioisotopes using both cyclotrons and research reactors. According to recent studies there are more than 200 PET/CT centers and more than 100 medical cyclotrons in mainland China. However, their distribution is far from being uniform: about two thirds of all systems are located in four regions (Shanghai, Shandong, Guangdong, and Beijing), which contain less than 20% of the country's population. The unbalanced regional development of PET/CT facilities and lack of access for some areas is not reflected in our analysis.

### **ESTABLISHING MEDICAL ISOTOPE PRODUCTION PROGRAM**

Even such simple analysis shows a significant discrepancy between the fractions of the population having access to radioisotope diagnostics and treatment in different regions in the world. Measures need to be taken to increase access to radiopharmaceuticals in the developing countries. However, this is a complex and demanding process. Design, licensing, and construction of the radioisotope production facility often takes millions of dollars and years of work of highly skilled professionals. Operating such a facility is also costly, both financially and in terms of manpower. As low energy cyclotrons become more common, reliable, and less expensive, more and more hospitals around the world

can afford SPECT and PET centers. High energy cyclotrons while capable of producing a wider portfolio of isotopes remain quite expensive to install and operate. Installing a research reactor for radioisotope production is an even more expensive alternative.

Once it's established that radioisotope production is a clear goal, one of the first steps for a country who is a novice in radioisotope production would be to establish either a PET center (including a low energy cyclotron for  $^{18}\text{F}$  production) or a SPECT center if there is a possibility of buying  $^{99}\text{Mo}$  generators elsewhere. Even such a small step would require a lot of work including choosing the site, facility design, licensing and regulatory issues, actual construction and commissioning of the facility, and training personnel.

The first phase in the planning process is to create a facility needs assessment. This step will verify whether a new site is required or if the need can be satisfied in some other way, such as using an already existing facility. For example, in December 2017, an 18 MeV IBA Cyclone®18 cyclotron was successfully rigged at the Centro de Investigaciones Médico Quirúrgicas (CIMEQ) hospital in Havana, Cuba. If a cyclotron is installed in an already existing hospital it is necessary to estimate modifications for the future nuclear medicine department including additional areas, shielding, and security of the facility. In case of research reactors this step requires even more consideration and efforts. Reactors require significant infrastructure and are usually built on university or national laboratory campuses.

Once the site is chosen, a conceptual design of the radioisotope production facility must be followed with a detailed design. Proper layout of the facility greatly impacts production efficiency and uptime. It is important to remember that the design of radioisotope production facilities is governed by various nuclear regulatory agencies, including radiation monitoring and aseptic processing. Once the detailed design is completed, the construction phase begins.

Only highly qualified personnel can ensure the safe and efficient operation of a radioisotope production facility; it is therefore necessary to train the local labor force, ranging from service technicians to the managers of various levels. Many consulting

companies provide training for personnel as a part of the facility design and construction management package. Additionally, numerous training programs are offered by the IAEA for its Member States. IAEA technical cooperation projects especially focus on the needs and priorities of less developed countries and support fellowships and scientific visits. Short-term leadership development programs also exist, for example the World Nuclear University offers a two-week long School on Radiation Technologies, focused on medical and industrial applications of nuclear radiation and radioisotopes.

## **CONCLUSIONS**

Access to life-saving radioisotopes and the geographical distribution of corresponding infrastructure is highly unbalanced. A significant number of developing countries have either none or very few facilities producing medical radioisotopes and radiopharmaceuticals. As a result, a significant fraction of the population in these countries cannot receive effective health care.

As of today, hundreds of radioisotope production facilities have been built and are operational worldwide. Fortunately, this experience can be used to minimize both construction and operational costs for a new installation. A developing country establishing a medical radioisotope program could start by installing a simple low energy cyclotron producing  $^{18}\text{F}$  and a PET center. Alternatively, a radiopharmacy making  $^{99}\text{Mo}$  generators can be set up.  $^{99\text{m}}\text{Tc}$  generators can be shipped to local hospitals equipped with SPECT cameras.

Various support already exists to help developing countries establish their medical radioisotope production installations. The international community should continue to encourage scientists, engineers, medical doctors, and regulators from developing countries to participate in these training programs.

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