Pre-feasibility Study for Establishing Radioisotope and Radiopharmaceutical Production Facilities in Developing Countries

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Abstract: Background: A significant number of developing countries have no facilities to produce medical radioisotopes and radiopharmaceuticals.

Objective: In this paper we show that access to life-saving radioisotopes and radiopharmaceuticals and the geographical distribution of corresponding infrastructure is highly unbalanced worldwide.

Methods: We discuss the main issues which need to be addressed in order to establish the production of radioisotopes and radiopharmaceuticals, which are especially important for developing countries as newcomers in the field. The data was gathered from several sources, including databases maintained by the International Atomic Energy Agency (IAEA), World Health Organization (WHO), and other international organizations; personal interactions with representatives in the nuclear medicine field from different regions of the world; and relevant literature.

Results: Developing radioisotope and radiopharmaceutical production program and installing corresponding infrastructure requires significant investments, both man-power and financial. Support already exists to help developing countries establish their medical radioisotope production installations from several organizations, such as IAEA.

Conclusion: This work clearly shows that access to life-saving radioisotopes and the geographical distribution of corresponding infrastructure is highly unbalanced. Technology transfer is important as it not only immediately benefits patients, but also provides employment, economic activity and general prosperity in the region to where the technology transfer is implemented.

Keywords: Radioisotope production, radiopharmaceuticals, developing countries, nuclear medicine, radioisotopes in medical applications, IAEA.

1. INTRODUCTION

Chronic and noncommunicable diseases, such as cancer and cardiovascular disease continue to be the leading causes of morbidity and mortality worldwide [1]. While there has been a significant improvement in recent years to treat and prevent infectious diseases like tuberculosis, AIDS and malaria, another threat to global health is on the rise: cancer rates are going up in the developing world. The majority of cancer cases, as well as deaths from cancer, now occur in low- and middle-income countries [2, 3], and the number of new cases is expected to rise by about 70% over the next two decades [4]. Bray et al. [5] estimate approximately 18.1 mil-
labeled new cancer cases and 9.6 million cancer deaths in 2018. This report also states that high quality cancer data, which is the basis for planning and implementing evidence-based cancer control programs, are not available in most low- and middle-income countries. Finally, it clearly demonstrates that cancer incidences vary according to the economic development and associated social and life-styles factors.

One of the major reasons for the increasing occurrence of cancer in developing countries is the growth and aging of the population. In addition, limited resources and infrastructure to diagnose and treat cancers cannot keep up with the demographic changes. Specifically, many developing countries demonstrate an extremely limited availability of nuclear medicine, which is vital for both diagnosis and treatment of cancer and cardiovascular diseases [6-8].

The most common type of nuclear medical diagnostics is single photon emission computerized tomography, or SPECT. This procedure has the advantages to be a functional test, meaning that rather than just taking an image of anatomical structures, it reveals biological activity, such as blood flow [9, 10]. This technique uses γ-rays directly emitted by a radioisotope and detected with a gamma camera. One of the most common SPECT isotopes is $^{99m}$Tc, which is used in 30-40 million procedures annually worldwide [11]. It has a half-life of six hours, which is long enough to examine metabolic processes, yet short enough to minimize the radiation dose to the patient [12]. Normally, such a short half-life would make it difficult to transport the radioisotope from a production site to the medical facility. However, in case of $^{99m}$Tc, one can supply its longer-lived precursor $^{99}$Mo ($T_{1/2} = 2.7$ days) in a chemical form that allows one to extract or "milk" the daughter $^{99m}$Tc as needed.

Positron emission tomography, or PET, is similar to SPECT in its use of radioisotopes and detection of γ-rays. However, the isotopes used for PET emit positrons which annihilate with electrons, causing two 511 keV photons to be emitted in opposite directions [13, 14]. $^{18}$F, with a half-life of just under two hours, is one of the most common PET isotopes, and is primarily synthesized into $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG). The FDG is readily incorporated into the cell, and is a good indicator of the cell metabolism and consequently cancer. PET diagnostics technically is more superior than SPECT: it has better resolution and higher sensitivity. At the same time PET is more expensive and less accessible than SPECT [15, 16]. As PET and CT/PET systems become affordable and widespread, there is a strong trend towards using positron emitters such as $^{18}$F. However, short half-life of most positron emitters requires a cyclotron either right at the PET center or in close proximity [17].

Although the use of radioisotopes for therapy is less common, it is nevertheless also widespread. The most recognized type of radiation therapy is external beam therapy (also called teletherapy), which uses radioisotopes, such as $^{60}$Co, to treat cancer. Thousands of cobalt therapy units were installed in hospitals and millions of patients have been treated. Nowadays, electron accelerators (LINACs) capable of producing higher beam energies have replaced many $^{60}$Co machines. However, due to their simplicity and reliability, $^{60}$Co therapy units remain in use worldwide. According to Healy et al. [18] and the IAEA Directory of Radiotherapy Centers [19] there are currently over 2,000 $^{60}$Co machines and over 5,000 LINACs in low- and middle-income countries. Worldwide, over 30,000 patients are treated annually, generally as outpatients [20].

An alternative to teletherapy is brachytherapy, in which a radiation source and is placed inside the patient's body, as close to a tumor as possible. One option is to surgically implant radioactive "seeds" or "wires" in the tumor area, such as $^{192}$Ir and $^{125}$I [21-24]. Another option is to temporarily place seeds, wires, or pellets into a desired site for a determined period of time. This technique is particularly effective for treating localized tumors such as breast or prostate cancers. The last option involves attaching radioisotopes to suitable biological carriers and injecting the obtained radio-pharmaceutical into patients - so called radioimmunotherapy (RIT). Mostly α- or β-emitting radionuclides are used for RIT due to their short mean free path in biological tissues and high linear energy transfer [25-27].

### 2. GEOGRAPHICAL DISTRIBUTION OF RADIOISOTOPE PRODUCTION FACILITIES

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 [4, 5]. 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 healthcare due to a lack of life-saving radioisotopes and corresponding infrastructure. Table 1 and Fig. (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 imported radioisotopes.

Of course, this representation has a number of flaws. First of all, even if a country has a radioisotope production facility, it does not mean that every citizen has access to a radiopharmaceutical. Many countries have only one or just a few installations and often produce only several radioisotopes; thus the demand for radioisotopes might still greatly exceed the supply. For example, until 2012, Qatar had no radioisotope production facilities and its citizens often traveled to neighboring UAE for PET and other nuclear medical procedures. In 2012, Hamad Medical Corporation (HMC) in Doha installed a low energy proton cyclotron and started producing $^{18}$F and making $^{18}$F-FDG. Since then, HMC state-of-the-art PET/CT center, has served thousands of cancer, cardiology and neurology patients. Numerous case studies and reports have been published by the HMC PET/CT center researches, disseminating their findings. Among them are diagnostic and treatment of numerous cancers including lung, sweat gland, Hodgkin lymphoma, granulosa cell tumor, and others as well as the palliative care [28-30]. However, $^{18}$F is the only radioisotope available in Qatar as of today.
Fig. (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 imported radioisotopes.
Thus, even though in this work’s database Qatar is marked as the country labeled as “producing radioisotopes with cyclotrons” and “having a radiopharmacy”, its citizens could have benefited much 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 a recent report on the Current Nuclear Medicine Status of the Asian Member States [31] there are about 1,000 nuclear medical institutes, including hospitals, health care centers, and health monitoring institutions in China. According to a different study [32] there are 240 PET/CTs and 101 medical cyclotrons in China. However, the distribution of these nuclear medicine centers 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 facilities and lack of access for some areas is not reflected in this analysis.

Finally, even though there has been a rapid rise in the number of PET and SPECT centers in China (as well as in many other countries), it is not clear whether their clinical potential is being fully realized, primarily due to a shortage of qualified physicians, which is currently being addressed by organizing nuclear medicine training courses.

Despite these flaws, it is clear that there is a significant discrepancy between the fraction of the population having access to radioisotope diagnostics and treatment in different regions in the world. The goal of this paper is to provide guidance for countries interested in setting up a radioisotope production program.

### 3. CYCLOTRON-PRODUCED MEDICAL ISOTOPES

Proton cyclotrons are the most common types of accelerators used around the world to produce medical radioisotopes [33]. 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 of them are compact 10 - 20 MeV accelerators used to produce $^{18}$F for FDG [34]. Energetic protons can cause various ($p,xn$) and ($p,a$) reactions and typically result in neutron-deficient radioisotopes, many of which are either positron emitters or gamma emitters suitable for imaging and diagnostics [35]. Table 2 shows several imaging radioisotopes most commonly produced with proton cyclotrons.

Modern cyclotrons provide beam power in the kW range which results in heat deposition, radiation damage, and mechanical stress on the targets [36]. All three matter states (gas, liquid, solid) are used as target materials. Gas and liquid are both very suitable due to their low density, high heat dissipation, and easy pipeline transfer of irradiated material into hot cells. Such targets usually consist of a solid target body and a thin foil window to allow penetration of the beam. Aluminum, titanium, and niobium alloys are often used as target body materials due to their high thermal con-
ductivity, good corrosion resistance, high tensile strength, and good machinability.

Beam windows need to be very thin, but strong, and remain strong at high temperatures, so they are often made from hafnium, as well as from the aforementioned alloys. Solid targets are usually thin layers of target material, often electroplated on the target backing, usually copper.

To maximize the imaging quality and minimize the dose to the patient an ideal imaging radioisotope should have the following characteristics:

- Short effective half-life
- Low energy (100-300 keV) gamma or β⁻
- Minimal β⁺ dose to the patient
- Chemical properties suitable for labeling biomolecules
- Stable or very short-lived daughters
- Production in accordance with GMP standards

After the irradiation the target yields an overwhelming amount of activated material and cannot be used directly. The ratio of the atoms of target material to the atoms of produced radioisotope can reach many orders of magnitude. To minimize the amount of impurities and maximize the specific (or molar) activity of the desired radioisotope, miniaturization of targets, equipment, tubing, processing vessels, material selection, radiochemistry purification processes, etc, is mandatory. In addition, the target material often needs to be enriched and thus can be quite expensive. In such a case, recovery of target material is necessary for reuse. As an example, the ¹⁸F production process developed over 50 years ago and described elsewhere [37, 38] is shown in Fig. (2).

The production rate \( R \) of the radioisotope depends on a number of parameters, such as the density of target nuclides that are irradiated \( N_T \), the proton flux density \( \varphi_p(E,r) \), and the reaction cross-section \( \sigma_p(E) \) as shown in Eq. 1:

\[
R = \int_V N_T(r) \varphi_p(E,r) \sigma_p(E) d^3 r
\]

(1)

Assuming the target is so small that the proton flux through it is uniform, the integral shown in Eq. 1 can be simplified to Eq. 2 as:

\[
R = N_T \varphi(E) \sigma(E)
\]

(2)

The yield of the radioisotope produced in the target can be found from the production rate as show in Eq. 3:

\[
A(t) = R(1 - e^{-\lambda t}) = N_T \varphi(E) \cdot \sigma(E) \cdot (1 - e^{-\lambda t})
\]

(3)

where \( \lambda \) is the decay constant of the produced radioisotope and \( t \) is the irradiation time.

The term \((1 - e^{-\lambda t})\) gets close to unity when the irradiation time approaches three half-lives of the radionuclide. At this moment the decay rate becomes nearly equal to the production rate and the yield of the produced radioisotope saturates. As a result, the irradiation time usually does not exceed several half-lives of the radioisotopes.

The total number of cyclotrons producing radionuclides has been gradually growing. In many developed regions, PET/CT scans become a necessity before setting up a treatment protocol for certain diseases. We hope that a significant growth will be observed in developing, low-income countries in the near future.

## 4. REACTOR-PRODUCED MEDICAL ISOTOPES

Even though accelerators generate a variety of radionuclides, many medical radioisotopes are produced in nuclear research reactors [39-41]. 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. Table 3 shows some most common medical isotopes produced in a nuclear reactor.

The yield of the radioisotopes produced in a reactor can be estimated similarly to Eq. 3. One must keep in mind though that while cyclotrons produce a nearly monoenergetic...
beam of protons, neutrons in the reactor core have a broad spectrum of energies, so integrating over the energy is needed as well as shown in Eq.

\[ A(t) = N_T \int \varphi(E, \vec{r}) \sigma_n(E) dE \cdot (1 - e^{-\lambda t}) \]  

(4)

where \( N_T \) is the density of target nuclides, \( \varphi_n(E, r) \) is the proton flux density, \( \sigma_n(E) \) is the reaction cross-section, \( \lambda \) is the decay constant of the produced radioisotope and \( t \) is the irradiation time. Similarly, the irradiation time usually does not exceed few half-lives of the produced radioisotope.

Research reactor outputs reach hundreds of MW and the resulting neutron fluxes can reach \(-10^{15}\) n/cm²s. Historically most of the research reactors were running on highly enriched uranium (HEU) containing up to 90% of \(^{235}\)U. However, as a result of international scientific and political cooperation to reduce the use of HEU \([42]\), most of the research reactors have been converted to low enriched uranium (LEU) containing less than 20% of \(^{235}\)U fuels and targets. One of the key challenges for operating a reactor is access to LEU/HEU and the management of spent fuel.

Neutron capture is the most common reactor-based production method due to high reaction cross-section \( \sigma \), and as a result, high yield. However, it results in neutron-rich isotopes which typically decay by emitting \( \beta^- \) so they are not suitable for imaging. This method, nevertheless, can be used to produce gamma-emitters such as \(^{177}\)Lu and \(^{153}\)Sm \([43, 44]\) commonly used for therapeutic applications. Unlike (p,nx) reactions, neutron capture results in radioisotopes which

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**Fig. (2).** Flowchart showing the main steps of \(^{18}\)F production process. Impurity analysis and Quality Control (QC)/Quality Assurance (QA) steps are not shown.

**Table 3.** Some common medical radioisotopes produced in a reactor and their production methods.

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Half-Life</th>
<th>Application</th>
<th>Production Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{99})Mo/(^{99m})Tc</td>
<td>66 hours/6 hours</td>
<td>SPECT</td>
<td>(^{235})U fission</td>
</tr>
<tr>
<td>(^{131})I</td>
<td>8 days</td>
<td></td>
<td>(^{239})U fission or (^{130})Te(n,(\gamma))(^{131})Te(\rightarrow)(^{131})I</td>
</tr>
<tr>
<td>(^{51})Cr</td>
<td>28 days</td>
<td>Radioisotopes for injectable radiopharmaceuticals</td>
<td>(^{89})Cr(n,(\gamma))(^{89})Cr</td>
</tr>
<tr>
<td>(^{152})Sm</td>
<td>46 hours</td>
<td></td>
<td>(^{152})Sm(n,(\gamma))(^{152})Sm</td>
</tr>
<tr>
<td>(^{177})Lu</td>
<td>7 days</td>
<td>Radioisotopes for brachytherapy</td>
<td>(^{176})Lu(n,(\gamma))(^{177})Lu</td>
</tr>
<tr>
<td>(^{186})Ho</td>
<td>27 hours</td>
<td></td>
<td>(^{166})Ho(n,(\gamma))(^{166})Ho</td>
</tr>
<tr>
<td>(^{96})Y</td>
<td>64 hours</td>
<td></td>
<td>(^{96})Y(n,(\gamma))(^{96})Y</td>
</tr>
<tr>
<td>(^{125})I</td>
<td>60 days</td>
<td></td>
<td>(^{124})Xe(n,(\gamma))(^{125m})Xe(\rightarrow)(^{125})I</td>
</tr>
<tr>
<td>(^{192})Ir</td>
<td>74 days</td>
<td></td>
<td>(^{191})Ir(n,(\gamma))(^{192})Ir</td>
</tr>
</tbody>
</table>
are chemically identical to the target nuclides and thus cannot be easily separated. As a result, the specific activity of such radioisotopes is relatively low, which limits their uses. A flowchart showing $^{153}$Sm production process is shown in Fig. (3).

A special case of reactor-based radioisotope production is uranium fission. The highest yields are achieved by fissioning $^{235}$U with thermal neutrons ($\sigma = 580$ barn). Each fission process results in two isotopes and their mass distribution has a characteristic double hump shape (Fig. 4). The most important fission product for the medical community is $^{99}$Mo (precursor for $^{99m}$Tc, used in over 80% of all nuclear medical procedures), even though $^{191}$Ir and $^{133}$Xe are often extracted from irradiated uranium.

Recently, alternative $^{99}$Mo/$^{99m}$Tc production methods have been suggested and investigated [54, 55] including:
- neutron capture on $^{99}$Mo (using a reactor)
- photon-induced transmutation of $^{100}$Mo (using an electron accelerator)
- direct production of $^{99m}$Tc from $^{100}$Mo via (p, 2n) reaction (using a proton accelerator)
- proton spallation of $^{238}$U (using an electron accelerator)
- photofission of $^{238}$U (using an electron accelerator)

Despite some promising results, neither of the aforementioned paths can at present compete with $^{235}$U fission to produce $^{99}$Mo (and some other fission fragments) for medical use. As of today, reactors remain the main source of $^{99}$Mo, as well as many other essential radioisotopes for nuclear medicine.

A comprehensive publication on a feasibility study preparation for new research reactor programs including justification for a new research reactor, an assessment of national nuclear infrastructure, cost and benefit analysis, including associated risks for implementation can be found in the IAEA publication [56].

5. RADIOPHARMACIES

The production of the radionuclide is an important step towards a useful product; however, it must be followed by another important stage: the preparation and packaging of the 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. Radiopharmacies are designed to produce radiopharmaceuticals according to good manufacturing, aseptic dispensing, and radiation protection practices [57]. The radiopharmaceutical production process can be impaired by contamination by dust and viable particulates, poor hygiene and lack of resistance to microbiological and sanitizing agents; thus, certain requirements (also called Good Manufacturing Practice - GMP requirements) exist to keep the facility as clean as possible. Additionally, there exist regulations to protect the environment, the radiopharmacy personnel, the product and finally the patient. All those rules and requirements are specific to each country and are regulated nationally.

![Flowchart showing the main steps of $^{153}$Sm production process. Impurity analysis and QC/QA steps are not shown.](image)

**Fig. (3).** Flowchart showing the main steps of $^{153}$Sm production process. Impurity analysis and QC/QA steps are not shown.

![Mass-distribution of $^{235}$U fission fragments.](image)

**Fig. (4).** Mass-distribution of $^{235}$U fission fragments.
Radiopharmaceuticals must be prepared in well-controlled rooms with appropriate HVAC (Heating, Ventilation, and Air Conditioning) systems and lead shielding for handling radioactive materials. Such rooms, often called hot laboratories, are also clean rooms and must follow the ISO 14644 [58] standards requirements. To keep radiation exposure as low as reasonably achievable shielded hot cells are installed inside these hot laboratories for the radiopharmaceutical handling, production, fractionating and packaging. Automatization and minimization of human intervention in the processes result in both a significant decrease in the risk of microbiological contamination of the radiopharmaceutical and radioprotection of radiopharmacy personnel [59, 60]. Details on standard radiopharmacy installation and equipment can be found elsewhere [61-63].

Most radiopharmaceuticals are a combination of a radioisotope and a biologically active molecule that acts as a radioisotope carrier to the desired organ or tissue. Some radioisotopes do not require a carrier as they can themselves confer the desired localization properties. These radiopharmaceuticals are usually administered intravenously or orally in form of a simple salt. Iodine, which is absorbed directly by the thyroid gland, and thallium, which is absorbed directly by the heart muscle, are most common examples of radioisotopes used “as is” (Table 4 and references [64-71]). However, most radioactive nuclides are bound to a carrier molecule which has an affinity for a certain type of cell or receptor. Nowadays, numerous classes of carriers exist which include metabolic substrates, neurotransmitters, and drugs that exploit the distinctive metabolism of normal and pathologic tissue function to monoclonal antibodies, peptides, and molecules that have an exquisite specificity for detecting molecules expressed in various disease processes.

Development of new radiopharmaceuticals continues especially the development of theranostic agents which integrate diagnostic information with pharmaceuticals to increase effectiveness and safety of cancer treatment [72, 73]. Theranostic agents typically involve a pair (or a trio) of isotopes, one of which is suitable for imaging and the other one for therapy, for example, 89Y/90Y or 125I/131I [74-76]. The diagnostic radiopharmaceutical verifies the state of the disease for an individual patient and the uptake of the radioisotopes by different organs essentially turning the diagnostic imaging into quantitative dosimetric information. This individualized approach significantly improves the effectiveness of the treatment and increases the survival rate.

Using different carriers allows significant enhancement of the applications of the same radioisotope. For example, technetium injected into a human body by itself will be absorbed by the thyroid gland due to its similarity to iodine in radius and charge. However, the chemistry of technetium allows it to form stable complexes with a wide range of chelators, including MIBI, DTPA, HEDP, MDP, and others. These numerous chelators for the use with 99mTc allow for a number of highly sensitive functional studies of the brain, heart, thyroid, lungs, liver, kidneys, gallbladder, bones, and blood [77, 78].

A special type of radiopharmaceutical preparation can be done using a generator: a device loaded with a parent radionuclide so that its radioactive daughter can be eluted or “milked”. The most common example of the generator is 99Mo/99mTc (Fig. 6), which allows to extract 99mTc in the form of sodium pertechnetate (Na99mTcO4). Using generators makes it possible for radiopharmacies to receive relatively long-lived 99Mo from distant producers (often from abroad), load the generators, and distribute them to local hospitals or clinics for use. In some cases, generator-type radiopharmaceuticals can be imported as a ready-to-use product directly to hospitals.

The 99Mo/99mTc generator production starts with the manufacturing planning for the 99Mo activity amount that needs to be imported from the 99Mo supplier. All the generator manufacturing steps are carried out in hot cells. After
bulk $^{99}$Mo is received, it needs to be fractioned, autoclaved, and dispensed into the generator columns. Then the columns are loaded into the generator shielding containers and subsequently the generator assembling workstations. The flowchart in Fig. (7) shows the main steps for the generator manufacturing and assembling until the final step - shipping the generator to a hospital. After the decay period, the generator is sent back (by reverse logistics) to the radiopharmacy manufacturer and the system is disposable following the waste treatment procedures. While $^{99m}$Tc is the most common generator, other radioisotopes are also prepared in the form of the generator. Among them are $^{68}$Ga, $^{81}$Rb, $^{82}$Sr [79-81].

### 6. ESTABLISHING MEDICAL ISOTYPE PRODUCTION PROGRAM

Providing access to radiopharmaceuticals is a complex and demanding process. Design, licensing, and construction of the radioisotope production facility often take millions of dollars and years of work of highly skilled professionals [56]. Operating such a facility is also costly, both financially and in terms of manpower. As low energy cyclotrons (up to 18 MeV) become more common, reliable, and less expensive, more and more hospitals around the world can afford SPECT and PET centers, including stand-alone SPECT and PET systems, as well as hybrid systems (SPECT-CT, PET-CT, PET-MRI, etc.). High energy cyclotrons (up to 70 MeV) 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 is established that radioisotope production is a clear goal, one of the first steps for a low-income country would be to evaluate different options. The least expensive option would be to build a SPECT-center and a radiopharmacy to produce SPECT-radioisotopes from generators

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**Table 4. Some primary radiopharmaceuticals.**

<table>
<thead>
<tr>
<th>Radio-isotope</th>
<th>Radiopharmaceutical</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I (oral solution and capsules)</td>
<td>$^{131}$I - sodium iodine oral solution and capsules</td>
<td>Thyroid diagnosis and therapy</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>$^{125}$I - sodium iodine solution (intravenous)</td>
<td>SPECT studies of thyroid physiology and morphology</td>
</tr>
<tr>
<td>$^{68}$Ga</td>
<td>$^{68}$Ga - gallium citrate solution (intravenous)</td>
<td>SPECT imaging for inflammatory process and soft tissues tumors</td>
</tr>
<tr>
<td>$^{201}$Tl</td>
<td>$^{201}$Tl - thallium chloride solution (intravenous)</td>
<td>SPECT imaging for myocardial perfusion and brain tumors</td>
</tr>
</tbody>
</table>

**Without a carrier (salt solutions)**

<table>
<thead>
<tr>
<th>Radio-isotope</th>
<th>Radiopharmaceutical</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99m}$Tc</td>
<td>Numerous radiopharmaceuticals based on various chelators</td>
<td>Several applications accordingly to the lyophilized kit such as bones, lungs, liver, heart, kidneys SPECT imaging</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>MIBG-$^{131}$I (intravenous)</td>
<td>SPECT imaging of pheochromocytomas, neuroblastomas and other tumors</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>MIBG-$^{125}$I (intravenous)</td>
<td>SPECT imaging of pheochromocytomas, neuroblastomas and other myocardial tumors</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>FDG-$^{18}$F (intravenous)</td>
<td>PET imaging for cardiology, oncology and neurology</td>
</tr>
<tr>
<td>$^{153}$Sm</td>
<td>EDTMP-$^{153}$Sm</td>
<td>Palliative care of bone metastases</td>
</tr>
</tbody>
</table>

**With a carrier**

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**Fig. (6).** $^{99}$Mo-$^{99m}$Tc generator (IPEN-TEC®). This generator is manufactured by the Nuclear and Energy Research Institute (IPEN, Brazil) with $^{99}$Mo imported from abroad.
(such as $^{99}$Mo/$^{99m}$Tc or $^{68}$Ga/$^{68}$Ge) purchased from foreign suppliers. Alternatively, it is possible to manufacture their own generators from radioactive material received from abroad. A more expensive choice would be to build a PET-center including a low energy cyclotron for $^{18}$F production. Even the simplest and least expensive option would require a lot of work, such as choosing the site, designing the facility, addressing licensing and regulatory issues, actual construction and commissioning, and training personnel. The following few paragraphs outline the major steps necessary to establish a radioisotope production facility.

The first phase in the planning process is to create a feasibility study report, which should include the following key elements:

- The feasibility study itself: preliminary strategic plan, self-assessment of national nuclear infrastructure, selection of preliminary candidate site(s), consulting services and sub-contracting of external experts;
- Human resources: staff costs including administrative, technical and managerial personnel for both construction and future operation;
- Site: costs associated with surveys, characterization and procurement, as well as maintenance of the facility;
- External technical support;
- Construction work: people, materials and equipment costs for the construction;
- Future operation and maintenance: ongoing costs for the purchase of equipment and consumables need to be established on a yearly basis;
• Security and security assessments and arrangements including radioactive waste management and decommissioning;
• Risk assessment and management plan.

As soon as the feasibility study report is prepared, activities to design and construct a facility can begin. Once the site is chosen and the infrastructure assessment is done, a conceptual design of the radioisotopes production facility must be followed with a detailed design. Once the detailed design is completed, the construction phase begins. Bringing experienced consultants and advisors to a new site to manage the design and construction steps, as well as facility startup and operation is very common and can prevent costly mistakes.

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

7. THE ROLE OF THE IAEA ON HUMAN DEVELOPMENT FOR NUCLEAR SCIENCE

The IAEA has established several agreements and programs to develop and enhance capabilities of nuclear techniques and human resources development within Member States, such as the Regional Cooperative Agreements for Research, Development and Training Related to Nuclear Science and Technology for Asia and the Pacific (RCA) which was first established in 1972; for Africa (AFRA) which entered into force in April 1990, for the Latin America (ARCAL) since 1984; and for the Arab States in Asia (ARASIA) since 2002 [82]. All those Regional and Cooperative Agreements are addressed to strengthen and enlarge the contribution of nuclear science and technology to socioeconomic development in different regions of the world. For example, an annual course on radioisotopes and radiopharmaceuticals production and application, which is jointly organized by the IAEA, World Council on Isotopes (WCI), and Korea Atomic Energy Research Institute (KAERI), a distance assisted training program, and a human health campus - an educational website provided by the IAEA [83]. The IAEA also promotes Coordinate Research Activities focused on the needs and priorities of less developed countries and supports fellowships and scientific visits in the fields of nuclear applications, nuclear energy, safety and security, safeguards and technical cooperation.

One of the major mechanisms of implementing the IAEA’s programs in promoting education and knowledge transfer in nuclear medicine communities of developing countries has been through coordinated research projects. In addition, the IAEA has developed various mechanisms to collaborate with individual experts to promote radiopharmaceutical science. Among them are advices on commissioning, quality control, and usage; guidance on production, regulatory aspects, and GMP in radiopharmacy; assistance in creating specific radiopharmaceutical monographs for the International Pharmacopoeia; and development of radiopharmacy-related human resource capabilities in member states through regional training and education programs. Short-term leadership development programs focused on radioisotope production also exist, for example, the World Nuclear University [84] offers a biennial two-week long School on Radiation Technologies, focused on medical and industrial applications of nuclear radiation and radioisotopes.

CONCLUSION

This work clearly shows that access to life-saving radioisotopes and the geographical distribution of the corresponding infrastructure is highly unbalanced. According to Fig. (1) and Table 1, Africa remains to be the continent with the lowest availability for medical radioisotopes. A significant number of developing countries in Asia and Latin and South America also have either none or very few facilities producing medical radioisotopes. As a result, a significant fraction of the population in these countries cannot receive effective health care. In 2015, the UN has established 17 Sustainable Development Goals (SDGs) as a part of a wider 2030 Agenda for Sustainable Development. Developing radioisotope and radiopharmaceutical production program and infrastructure in low- and middle-income countries will help address at least two of the goals, namely “To ensure healthy lives and promote well-being for all at all ages” and “To reduce inequality within and among countries”.

Despite the current imbalances, the number of radioisotope production facilities is gradually growing. As of today, hundreds of radioisotope production facilities have been built and are operational worldwide. Fortunately, this experience can be used to minimize the costs of design and construction of new centers. It can also reduce operational costs and increase the radioisotope production efficiency. Still, the design, licensing, and construction of the radioisotope production facility often cost millions of dollars and take years of work of highly skilled professionals. A developing country establishing a medical radioisotope program could start by installing a simple low energy cyclotron producing $^{18}$F and a PET center. Alternatively, a radiopharmacy making $^{99}$Mo generators can be set up. Such 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. Technology transfer is important as it not only immediate benefits patients but also provides employment, economic activity and general prosperity in the region to where the technology transfer is implemented.

Knowledge transfer is even more important due to a shortage of physicians, radiopharmacists, radiochemists and medical physicists in developing countries. To address this problem, a number of training programs including fellowships, research visits, schools, and workshops are available for developing countries. 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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