Radiopharmaceuticals: Evolution and Accomplishments at DAE

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Preamble

The application of ionising radiation for societal benefits is a well-known branch of nuclear science and technology. Among them, the benefits available in the health care sector are very popular and also widely practised. Thanks to the early launch of our national programme of atomic energy soon after independence, India has been able to harness since the 1950s the applications of radiation-based medical practices, for both diagnosis and therapy. The utilization of certain radioisotopes (RI, e.g. ^{131}I) and their formulations, known as radio(active) pharmaceuticals (RPh), in the medical branch called nuclear medicine is unique, as it depends upon the regular availability of the RI of varying half-life, ranging from a few hours to days and which cannot be hence stored for long. There has been an evolutionary growth of products (RI, RPh) and procedures (diagnostic studies, therapy), as well as associated imaging technologies. India, through its Department of Atomic Energy (DAE) has enjoyed the privilege of being a contributor to the evolution of the field and has several accomplishments to highlight. The ensuing article is an attempt to trace the early beginnings, evolutionary growth and vital contributions made by the successive teams of professionals and all other staff of the concerned DAE Units over the past six decades.

1. Introduction

The use of radioisotopes for applications in health care has been one of the very early developments in the field of atomic/nuclear sciences. Thanks to the exemplary vision of Dr. Homi J. Bhabha, India made a very early entry in to the field, including the production and use of radioisotopes (RI). A major outcome of this early founding of Indian atomic energy program - at the then Atomic Energy Establishment - Trombay [AEET, which was later renamed as Bhabha Atomic Research Centre (BARC)] of the Department of Atomic Energy (DAE) - has been the indigenous availability over the past six decades of the benefits of radioisotope products, radiopharmaceuticals in particular, for medical uses in patients of our country. For this accomplishment, our society owes a lot to each and every leader of the program of the past over six decades. In this regard, citing the few early pioneers for records will be much appropriate: the doyen Dr. V. K. Iya for the overall growth of the field; (Late) Dr. R. S. Mani and Dr. N. G. S. Gopal for establishing the specialty of radiopharmaceuticals and their quality control, respectively; (Late) Dr. R. D. Ganatra for the clinical use in patients and sowing the seeds (along with the early pioneer (Late) Dr. S. K. Mazumdar in Delhi) for the birth of nuclear medicine (NM) in India; and (Late) Dr. S. M. Sharma for laying the foundation for radioiodine treatment of thyroid patients. It will be a stupendous task to justifiably describe in a small article all the contributions of the DAE Units in the field of radiopharmaceuticals. The authors have opted for a narration based on their personal and professional knowledge. The coverage is not designed to be exhaustive and apologies for inevitable and inadvertent omissions.

2. Historic Glimpses - Down the Memory Lane

Early years, until 1960

India embarked on pursuing atomic energy program quite early thanks to Dr. Homi J. Bhabha setting up Asia's first nuclear reactor, named 'Apsara' in August 1956. The availability of the reactor helped India to start the program of radioisotope production and supply of radiolabeled products from AEET for research and human healthcare in the late 1950s. Isotope Division was created in 1957 to undertake all the work related to radioisotopes and their applications. Temporary labs set up at Cadell Road in Bombay city were followed by isotope labs built at South Site of Trombay campus. AEET started producing medically useful radioisotopes, such as ^{32}P [$E_{\beta(max)}$ = 1.71 MeV, No γ, $t_{½}$ = 14.26 d] and ^{131}I [$E_{\beta(max)}$ = 606 keV, E_{γ} = 365 keV (81%), $t_{½}$ = 8.01 d], in small quantities, in Apsara reactor, by the end of 1958 and started supplying these products to hospitals for carrying out diagnostic studies.

1960-1980

Radioisotope program received a big boost in the year 1960 with the commissioning of the 40 MW_{th} CIRUS (Canada India Reactor for Utility Services) reactor. This reactor helped in production of a variety of medically useful radioisotopes (^{131}I, ^{32}P, ^{51}Cr, ^{24}Na, ^{82}Br, ^{198}Au, ^{203}Hg, ^{99}Mo, etc.) and in larger quantities. Treatment of patients using AEET/BARC supplies of ^{131}I, ^{32}P, ^{198}Au was a regular feature in many centres, apart from numerous diagnostic procedures performed using AEET/BARC supplies of ^{131}I, ^{51}Cr, ^{203}Hg. Supply of ^{99m}Tc of 6 hour half-life after separation from ^{99}Mo by solvent extraction was started, and in turn led to the launch of indigenous $^{99}Mo/^{99m}Tc$ radionuclide generator, popularly known as 'Trombay ^{99m}Tc cow' to facilitate interested hospitals to avail of ^{99m}Tc [E_{γ} = 140 keV (89%), $t_{½}$ = 6 h] product at the time of need. The hospital radiopharmacy concept was thus born in India in early 1970s! Another generator product ($^{113}Sn/^{113m}In$) of interest at that time was also developed by BARC, as well as

trial runs performed for ^{18}F production (for bone scan) in CIRUS reactor by secondary nuclear reaction on enriched $^{6}Li_2CO_3$ target[1]. ^{131}I-labeled products, ^{57}Co-labeled Vitamn-B12[2], and kits for ^{99m}Tc compounds for liver, bone and kidney studies were the other highlights at that time. Augmented infrastructure, in terms of custom-designed laboratories and allied facilities, for safe-handling of large quantities of radioisotopes were set up during this period at the radiological laboratory (RLG) building at BARC. The radioisotopes produced in the CIRUS reactor helped several million patients of our country over nearly 50 years (until its permanent shutdown at the end of 2010).

In 1963, DAE established a dedicated wing to explore the clinical applications of radioisotope-based products, which was later christened as Radiation Medicine Centre (RMC) [co-located with Tata Memorial Hospital (TMH), Mumbai]. RMC has remained at the forefront of nuclear medicine in our country and contributed significantly for the growth of this medical specialty in India.

1980-2000

The construction and commissioning of a completely indigenous 100 MW_{th} R-5 reactor - later renamed as Dhruva reactor at Trombay enabled further expansion of indigenous radioisotope production and supplies. After the planned permanent shutdown of the CIRUS reactor at the end of 2010, Dhruva reactor has become the sole source of reactor produced radioisotopes in large-scale in our country.

In March 1989, DAE established a new unit carved out of BARC for specifically focusing on supply of products and services to users of radioisotopes, radiopharmaceuticals and radiation technology and allied equipment. This unit, named 'Board of Radiation and Isotope Technology' (BRIT) supplies various radioisotope products including radiochemicals, radionuclide generators, radiopharmaceuticals and freeze-dried kits for the formulation of radiopharmaceuticals to over 350 nuclear medicine centers of India.

India embarked on accelerator-based radioisotope production after the setting up of the Variable Energy Cyclotron (VEC) at Calcutta (now Kolkata). In early 1990s, BRIT and VEC Centre (VECC) used the VEC to produce a few medically useful radioisotopes, such as, ^{67}Ga [decays by Electron Capture, multiple gammas, $t_{½}$ = 3.26 d], ^{111}In [decays by Electron Capture, E_{γ} = 173 (90.5%) & 245 keV (94%), $t_{½}$ = 2.81 d] in limited quantities to cater to certain clinical needs.

Emergence of products beyond ^{131}I and ^{99m}Tc and development *cum* launch of products using reactor-produced ^{153}Sm [$E_{\beta(max)}$ = 0.81 MeV, E_{γ} = 103 keV (28%), $t_{½}$ = 47 h] and ^{177}Lu [$E_{\beta(max)}$ = 0.49 MeV, E_{γ} = 208 keV (11%) & 113 keV (6.4%), $t_{½}$ = 6.73 d] for therapeutic applications started during this period. Also, expansion of the range of ^{99m}Tc products took place for meeting clinically important imaging needs, e.g. of heart, brain and cancer.

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[1]This approach, involving generating tritium by $^{6}Li(n,\alpha)^{3}H$ and using it in-situ for $^{16}O(^{3}H,n))^{18}F$ reaction, could not be pursued to its logical end, due to the inability to procure enriched $^{6}Li_2CO_3$ (strategic material) following the May 18, 1974 Pokhran test by BARC, India!

[2]A historic information pertaining to this period is the prestigious export of ^{57}Co-Vitamn-B12 consignments to Australia and Europe. The preparation of ^{57}Co (as also ^{58}Co)-labeled Vitamin-B12 (cyanocobalamin) required bio-synthesis and extensive purification. The product (capsule or injection) in microcurie level was needed for studies of pernicious anemia (Schilling's test). The exports waned only much later, after product registration related regulatory requirements in the recipient countries made it too expensive to export low-volume products!

Since 2000

In 2002, DAE-BARC established the first medical cyclotron (MC) facility of India at Parel (Mumbai) in the premises of RMC with the support of the Tata Memorial Centre (TMC). Since then, this imported 16.4 MeV MC is being used for production of short-lived positron-emitting radioisotope ^{18}F and several ^{18}F-based radiopharmaceuticals required for PET (Positron Emission Tomography) imaging. Additionally, this also triggered the rapid growth of MC and PET centers in India (clearly reflected by the 24 medical cyclotrons and more than 280 PET-CT units now in India) serving thousands of patients every day.

DAE-BARC further complemented its radioisotope production capability by commissioning Apsara-U (upgraded), a pool-type reactor (like vintage Apsara reactor), on September 10, 2018. This indigenously built reactor has made it possible to produce clinically important radioisotopes, like ^{64}Cu [E_{β^+}: 0.653 MeV (17.4%), E_{β^-}: 0.578 MeV (39%), $t_{½}$ = 12.7 h] making use of its higher fast neutron flux. This reactor is envisaged to be used also for irradiation of ^{235}U targets for production of ^{99}Mo.

Another important milestone was achieved in 2018 with the commissioning of India's largest cyclotron facility, namely Cyclone-30, in Kolkata. This facility has started producing some medically important radioisotopes, such as, ^{18}F, ^{68}Ga and ^{201}Tl. VECC and BRIT have plans for full utilization of Cyclone-30 capabilities in near future.

Another medical cyclotron facility is presently being set up at 'Advanced Centre for Training, Research and Education in Cancer' (ACTREC at Kharghar, Navi Mumbai) to supplement and expand the operations of MC at Parel and to fulfill the demand for many important and emerging radioisotopes, e.g. ^{89}Zr, ^{64}Cu, ^{68}Ga, ^{123}I, etc. for various medical applications.

Since the launch of nuclear medicine imaging using gamma camera, ^{99m}Tc has played a very important role and still more than 70% of all nuclear medicine procedures are based on this radioisotope. BRIT has been supplying ^{99}Mo/^{99m}Tc alumina column generators using imported ^{99}Mo of fission origin. Considering the need to strengthen the self-reliant supply of ^{99m}Tc, DAE-BRIT is in the process of setting-up a fission-moly (^{99}Mo produced through nuclear fission of ^{235}U) plant at Trombay, which is expected to provide a significant boost to the indigenous production of ^{99}Mo/^{99m}Tc generators in future.

The growing importance of radioisotope-based therapy, supported by prior imaging of tumor lesions (by PET/CT), has led to the indigenous development and launch of ^{177}Lu products for treatment of certain cancers (e.g. neuroendocrine, prostate). DAE's unique advantage of access to fission-product isotopes from the reprocessing stream has been harnessed to avail ^{90}Y [$E_{\beta(max)}$ = 2.27 MeV, $t_{½}$ = 64 h] to complement the use of ^{177}Lu in this context.

Radioisotope processing laboratory, in the past (left) and at present (right)

3. Iodine-131 products: Reigning Ever in Nuclear Medicine

Iodine-131 is the one RI reigning all through the past six decades, and continues to be of high relevance for future too. Starting from small-scale production using TeO_2 targets and oxidative dissolution plus wet distillation procedure for isolation of ^{131}I, scaling up of production to a few tens of curies every week in tong-operated lead-shielded plants took place over time. Switch over to dry distillation process - for specific advantages of larger batch size, reduced waste generation, flexibility to avail high radioactive concentration, etc. - took place much later, well beyond 2000. In order to ensure greater reliability and safety of radiochemical process, augmented protection measures of plant ventilation were instituted. In addition, new processing facilities are being set up (in the old CIRUS building) for sustainability of product supplies. Currently the average weekly production of this RI is of the order of 40-45 Ci (1.48-1.67 TBq). In future, there is also scope for availing fission-produced ^{131}I, after setting up appropriately augmented processing facilities, at the Fission Molybdenum Plant (FMP) of BRIT (now in an advanced stage of completion) located near the South Gate of BARC campus.

Apart from formulation of ^{131}I as NaI in solution and capsule form (for treatment of hyperthyroidism and metastatic thyroid cancer), labeled product of meta-iodo-benzylguanidine - ^{131}I-MIBG is another important product launched in response to clinical demands and pursuant to its utility demonstrated by colleagues at RMC, who prepared it in-house (at the hospital radiopharmacy). In recent years, ^{131}I-labeled lipiodol and monoclonal antibodies have been developed and added to the list of ^{131}I products for therapy of certain cancers. Over 80% of all therapy procedures of NM use ^{131}I.

The early generation diagnostic products like Rosebengal-^{131}I (for liver scan), Hippuran-^{131}I (for probe renography) and human serum albumin-^{131}I (for blood pool studies) lost their place due to emergence of superior alternate products and/or techniques. The relatively large use of diagnostic $Na^{131}I$ capsules, well into 1970s for thyroid function studies, was overridden by estimation of thyroid hormones *in-vitro* using radioimmunoassay (RIA)[3] and other forms of immunoassay.

4. Technetium-99m products: The Workhorse of Nuclear Medicine Imaging

The serendipitous discovery of $^{99}Mo/^{99m}Tc$ generator at the Brookhaven National laboratory (BNL), USA in 1957, along with the invention of gamma camera by Dr. Hal Anger around the same time, laid the foundation stone for the field of diagnostic nuclear medicine imaging. Decay of ^{99m}Tc by isomeric transition with the emission of 140 keV gamma radiation [ideal match for imaging with (planar) gamma camera and SPECT (Single Photon Emission Computed Tomography)] and its relatively short half-life of 6 h (long enough for logistics of formulation, quality control tests and administration to patients; and yet adequately short for physical decay and biological excretion) are the significant merits, which drove the research and development to launch organ/lesion-specific products for imaging of patients. The versatility of making ^{99m}Tc complexes at various oxidation states (-1 to +7) and exploitation of a vast range of ligands (both known and innovatively designed ones) have made ^{99m}Tc overwhelmingly popular in nuclear medicine. Thus, of the 40 million diagnostic nuclear medicine scans performed worldwide annually, 70-75% are based on using ^{99m}Tc products. Currently, ^{99m}Tc-based radiopharmaceuticals

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[3] *BARC (RMC, RPhD) and BRIT played a significant role in developing radioimmunoassay programme and launching supply of reagents and kits for estimation of many hormones in-vitro, most notably the thyroid related ones. This area (not being within the domain of radiopharmaceuticals) is not covered in this article.*

are available for imaging every major organ of human body, while the large share of its regular clinical use is in the case of renal studies, myocardial perfusion, infection imaging, cancer metastasis, etc., earning ^{99m}Tc the title of '*work-horse of nuclear medicine*'.

Technetium-99m

By the late 1960s, BARC produced (n,γ)^{99}Mo and used solvent (methyl-ethyl-ketone, MEK) extraction methodology to obtain ^{99m}Tc in the laboratories at Trombay and the separated ^{99m}Tc supplied to RMC in Bombay city, co-located with TMH. The logistics of transport and keenness to get ^{99m}Tc early every day drove the colleagues in RMC to seek to operate the MEK extraction system at their end itself. The practices and procedures prevalent then (early 70s) were permissive to this arrangement and thus was born the Indian MEK extraction generator system for ^{99m}Tc, popularly known as 'Trombay Technetium Cow'. This manually operated system required certain operational facilities at the user end and training of the operators and was in extensive use in India since 1970s with the support from the radiopharmaceutical wing of BARC. Dr. O. P. D. Noronha of RMC, who has the credit of being the first hospital radiopharmacist of India, introduced a number of useful tools and procedures to facilitate the handling of MEK extraction process at the user end. After the creation of BRIT in 1989, there was a time when as many as 60 to 70 centres regularly used up to 40-50 Ci (1.48-1.85 TBq) ^{99}Mo per week.

The growth of nuclear medicine in India owes much to the early indigenous availability of ^{99m}Tc. The downside has been that there was no liberation from the MEK technology of DAE for a very long time. Only from late 1990s (opening up of economy, imports, foreign exchange etc.), nuclear medicine practices in India could shift to (a considerable extent) the use of imported alumina column (user-friendly) generators.

Earlier in 1976, in response to RMC's interest to avail the benefit of alumina column generator, there was an attempt by Radiochemistry Division (RCD) of BARC to produce fission molybdenum using natural uranium target. The method involved addition of mg level Mo carrier for precipitation of ^{99}Mo as its alpha-benzoin-oxime complex followed by many purification steps. This technique has been much cited in the literature. ^{99m}Tc was obtained at RMC from alumina column generator loaded with fission molybdenum produced at RCD, BARC. This demonstration on 'campaign-mode' was not pursued further, probably due to the complexity and issues involved in adopting it for regular/frequent production.

During 1979-80, there was a planned, prolonged shut-down of the CIRUS reactor and in order to sustain supplies to medical users, import of ^{99}Mo (available as fission produced) was necessary. The Radiopharmaceuticals Section quickly resorted to a shift in the methodology, in terms of opting for production of alumina column chromatographic generators. A lead shielding unit meant for another purpose was used along with other required items to produce and deliver column ^{99m}Tc generators to hospitals in Bombay and Delhi for a few months. This was however only a short-lived comfort for users at that time.

The major consideration towards column ^{99m}Tc generator took place much later after the formation of BRIT. The feasibility for taking up regular production of alumina column generators using imported fission-moly was seriously considered and engineering efforts were invested. This resulted in many developments and eventually led to BRIT undertaking, over a period of a few months in 1994, regular production and supply of sterile column generators for ^{99m}Tc, based on weekly import of a small quantity of fission ^{99}Mo from South Africa. The unresolved dilemma was whether to depend on permanent weekly imports of fission product ^{99}Mo!

India has been participating in the IAEA's (International Atomic Energy Agency) efforts towards development of alternate technologies for ^{99m}Tc generators, due to its preference to retain the option of (n,γ)^{99}Mo. The gel generator concept of Australia was one of the keenly pursued routes since mid-80s. The R&D level pursuits in gel generator moved up to technical feasibility studies (upon the closure of alumina column generator trials in 1994). There was consequently steady progress in BRIT pursuits of gel generator option. BRIT's GELTECH generators - based on zirconium molybdate gel column - of capacity 5.55 GBq (150 mCi), 9.25 GBq (250 mCi) and 14.8 GBq (400 mCi) have been supplied on weekly basis starting from 2005. The technology is suitable for supplies to a limited number of NM centres; furthermore, it cannot meet the high-activity generator needs of large NM centres.

In order to meet the needs of the large volume NM centres in India, around 2008, DAE-BRIT shifted again to reconsidering production of alumina column generators using imported fission-moly. This led to the setting up of imported processing plant facilities and launch of ^{99}Mo/^{99m}Tc COLTECH generators [capacity 11.1 GBq (300 mCi), 18.5 GBq (500 mCi) and 37 GBq (1000 mCi)]. This was a much welcome step for the NM community in India, although logistic reasons (procurement constraints, return of shielded container, etc.) kept the production and supply at a limited level (40-50/week)[4]. A significant portion of generators used in India is still by imports on regular basis. Since the large demand for ^{99m}Tc has to be sustainably met, it is necessary to secure reliable sourcing of fission-moly.

DAE/BRIT hence took up a project in 2014 for setting-up a FMP (Fission Molybdenum Plant) facility at the south site of Trombay campus. This 300 Ci (11.1 TBq) capacity plant, based on the Argentinian company INVAP technology, is presently in an advanced stage, nearing commissioning and is expected to be in operation later in 2022. Indigenous availability of fission-moly will enhance the share of BRIT's supplies of ^{99m}Tc generators to NM centres.

^{99}Mo/^{99m}Tc Generator Production Facilities at BRIT (Vashi, Navi Mumbai) - GELTECH Generator (left) and COLTECH Generator (right)

Kits for ^{99m}Tc Radiopharmaceuticals

Technetium-99m based radiopharmaceuticals, unlike other ready-to-use finished product drugs, need to be prepared afresh just prior to administration in patients, at the hospital radiopharmacy using the ^{99m}Tc-pertechnetate obtained from the ^{99}Mo/^{99m}Tc generator.

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[4]Brief mention can be made of also the following efforts to use (n,γ)^{99}Mo as source of ^{99m}Tc, though with limitations. BARC worked on high-capacity adsorbents for Mo to suit the low specific activity of (n,γ)^{99}Mo. BRIT team in Kolkata explored post-elution concentration of ^{99m}Tc obtained from large-bed alumina column holding (n,γ)^{99}Mo, and also in collaboration with VECC, launched automated version of MEK extraction system.

Clean room facility corridor (left) and preparation of Freeze-dried kits at BRIT (Vashi, Navi Mumbai) (right)

Table 1: Freeze-dried kits supplied from BRIT for the formulation of various ^{99m}Tc-radiopharmaceuticals

BRIT Code	Kit for	Applications
TCK-5	^{99m}Tc-Sulphur Colloid	Liver imaging
TCK-7	^{99m}Tc-DTPA	Kidney function studies
TCK-15	^{99m}Tc-GHA	Kidney function studies
TCK-16	^{99m}Tc-Phytate	Liver imaging
TCK-30	^{99m}Tc-MDP	Bone imaging
TCK-33	^{99m}Tc(III)-DMSA	Kidney imaging
TCK-35	^{99m}Tc(V)-DMSA	Medullary thyroid carcinoma imaging
TCK-38	Sn-Pyrophosphate	Red Blood Cells labeling
TCK-39	^{99m}Tc-Mebrofenin	Hepatobiliary function studies
TCK-42	^{99m}Tc-ECD	Brain perfusion imaging
TCK-43	^{99m}Tc-EC	Kidney function studies
TCK-50	^{99m}Tc-MIBI	Myocardial perfusion imaging
TCK-52	^{99m}Tc-Tetrofosmin	Myocardial perfusion imaging
TCK-53	^{99m}Tc-HSA Nanocolloid	Sentinel lymph node imaging
TCK-54	^{99m}Tc-HYNIC-TOC	Neuroendocrine tumor imaging
TCK-55	^{99m}Tc-TRODAT	Dopamine transporter imaging
TCK-56	^{99m}Tc-Macro-Aggregated Albumin	Lung perfusion imaging
TCK-57	^{99m}Tc-UBI	Infection imaging
TCK-58	^{99m}Tc-HYNIC-TATE	Neuroendocrine tumor imaging
TCK-59	^{99m}Tc-HYNIC-E[c(RGDfK)]$_2$	Imaging of Tumour Angiogenesis

Freeze-dried (lyophilized) kits are sterile and pyrogen-free formulations containing a mixture of all the non-radioactive pharmaceutical ingredients - ligand, reducing agent, stabilizer, fillers, etc. - in freeze-dried/lyophilized powder form, for use at the hospital radiopharmacy for the formulation of various radiopharmaceuticals. The kits when reconstituted with sterile, pyrogen free sodium-[^{99m}Tc]-pertechnetate solution (obtained from ^{99}Mo/^{99m}Tc generators) following the prescribed procedure, produces the desired injectable ^{99m}Tc radiopharmaceuticals.

BRIT/BARC has made significant contributions in this area matching with the global developments and Indian NM demands. Since the 1970s, scientists working in the radioisotope program in both Isotope Group and RMC have carried out intense research for the development of various freeze-dried kits, demonstrated their utility and deployed such kits in the hospitals for the imaging of patients. Beginning with colloidal products used for liver studies and other products for excretory organs like kidneys and hepato-biliary system, products for imaging the skeletal system (bone being a frequent site of cancer metastasis), blood pool, blood flow to heart and brain, infection, certain tumors, etc. have been developed and launched for regular clinical use. In some cases, the required ligands or precursors have also been synthesized in-house. In light of the injectable nature of the kit products, the production has to be done in clean-air laboratories under GMP (Good Manufacturing Practice) conditions, adopting practices followed in conventional pharma-labs. Such facilities have been evolved and established by DAE-BRIT at Vashi - Navi Mumbai campus.

In the area of kits, the share of BRIT supplies has been around 80%, with direct imports by users much limited (cf. the case of ^{99}Mo/^{99m}Tc generators). Presently, BRIT supplies 20 different types of freeze-dried kits (Table 1) for various radiopharmaceuticals required for diagnostic imaging of organs or diseases or dysfunction of physiological processes. They enable imaging applications pertinent to brain, heart, lungs, liver, kidneys, lymph nodes, thyroid, red-blood cells, dopamine transporters, angiogenesis, tumors, various types of cancers, etc.

5. Cyclotron-based products: High-value Utility for Patient Management

There was a strong case for cyclotron-produced radioisotopes (neutron-deficient ones, decaying by electron capture or positron emission) to complement the reactor-based ones for applications in medicine. When the VEC became available to users, BARC/BRIT team carried out feasibility studies for production of some medical RI of interest at that time. Limited quantity of ^{67}Ga as gallium citrate was regularly produced and used in early 1990s, apart from demonstrating technology for ^{111}In products. Experience was also gained in developing targetry systems, recovery of precious target materials, etc. at the radiopharmaceutical laboratories located at VECC. There were limitations in large-scale RI production due to varying needs of VEC users, availability of projectile and energy, etc.

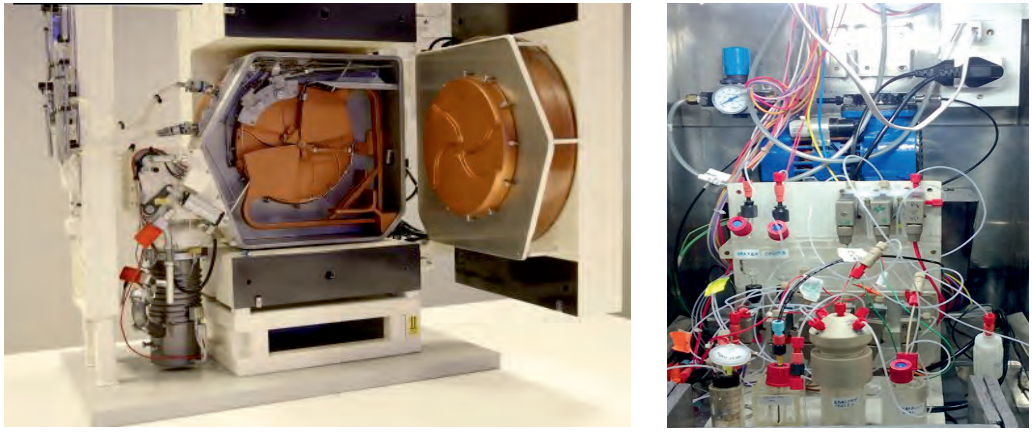
All along, the RI teams of BARC and BRIT have been persuading BARC/DAE management to support establishing a dedicated cyclotron facility for all relevant RI, for both SPECT and PET imaging. ^{201}Tl (69-80 keV X-rays, $t_{½}$ = 73 h,) was then the product of very high interest for myocardial SPECT imaging. Its production involving (p,3n) reaction required use of 28-30 MeV protons as projectile. IBA, the Belgian company, had very successfully launched Cyclone-30 model (30 MeV proton cyclotron, rugged system, high current machine) and several units were in operation in various countries. The same system was much desired by the stakeholders in India. Both BRIT and VECC sought support to set up MC in the plan period 1997-2002.

Thanks to Dr. Bikash Sinha (then Director, VECC and SINP) recognizing the opportunity to foster cyclotron-based RI, available VECC expertise and his keen interest there emerged scope (around 2000-2001) for IBA setting up, along with the participative support of VECC/DAE, a Cyclone-30 facility in Kolkata to meet the Indian needs and also of other countries in the Asian region. However, such a (partnership) venture was not then commonplace and could not get the required support for implementation. This led to the planning and pursuit of VECC/DAE's own project on medical cyclotron at Kolkata. IBA and its already planned supporting entity in Kolkata/India got left out, though their role and support were crucial for the VECC/DAE project. Due to multiple reasons the project ran into considerable delays. The Cyclone-30 system could be finally installed and commissioned in 2018, aided much by the in-house competency strength of VECC. BRIT has made use of the facility and started regular production of ^{18}F, ^{68}Ga and also ^{201}Tl (on demand basis) in the last couple of years.

What was the much-cherished goal of the 5-year plan periods of 1997-2002 and 2002-2007, could thus finally become a reality after 2018 only. The RI scenario and imaging procedures have however undergone much transformation during the intervening period. Some products have become obsolete (e.g. ^{67}Ga), while the high demand for ^{201}Tl has considerably reduced (due to alternate products). Lower energy MC and radiotracers for PET imaging have emerged as the larger interest for medical use. Yet, the 30 MeV proton cyclotron, Cyclone-30, is a powerful addition to the national nuclear infrastructure. It can meet the needs for PET imaging (growing area) and also help in making other medically useful RI in demand, e.g. ^{68}Ge/^{68}Ga, $^{123/124}$I, etc. (apart from meeting also R&D needs beyond RI domain). BRIT and VECC have demonstrated the high utility of Cyclone30 and also cited plans for further enhanced utilization of the Cyclone-30 facility in the coming years.

The other medical cyclotron facility pursued in parallel by DAE in Mumbai (1997-2002 plan project) for the establishment of a 16.4 MeV unit (GE Petrace) at the basement of TMH building in Parel progressed well in time, despite severe constraints of space and other issues (narrated elsewhere, Sl. No. 5 in Bibliography). The MC facility and associated radiopharmacy laboratories, along with a PET system for RMC, were set up by October 2002, ushering in the era of PET tracers and their applications in India. Two dedicated publications in 2012 (Sl. No. 5, 6 in Bibliography) and a thematic issue of IANCAS Bulletin in 2014 (Sl. No. 7 in Bibliography), contain detailed account of the project team's sustained efforts, challenges faced and eventual accomplishments. This facility rendered daily production and use of ^{18}F (97% positron emission, $t_{½}$ =110 min) products a reality. ^{18}F-FDG (2-Fluoro-2-deoxyglucose) in particular is the most widely used product for management of cancer patients, apart from Na^{18}F and other ^{18}F-based radiopharmaceuticals. The advent of the hybrid imaging system PET/CT (CT: Computed Tomography) in 2001 coinciding with the DAE's launch of India's first MC in Mumbai, became an important turning point. The leadership of (Late) Dr. (Mrs.) A. M. Samuel for DAE's MC + PET project deserves to be highlighted, as well as her subsequent role in TMH setting up the first PET/CT-based nuclear medicine services using radiopharmaceutical supplies from the MC at RMC.

Many other institutions followed the BARC model for setting up MC in the subsequent years. They are successfully operating the MC and associated radiopharmacy, including some in commercial mode.



India's first Medical Cyclotron at RMC (BARC, Mumbai) (left) and automated module for the preparation of PET radiopharmaceuticals like ^{18}F-FDG (right)

BARC has also developed kits for the formulation of ^{68}Ga labeled products (e.g. ^{68}Ga-DOTA-TATE, ^{68}Ga-PSMA-11) for PET imaging of cancer metastases to help the centres importing ^{68}Ge/^{68}Ga generator. The kits are also useful for recipients of ^{68}Ga supplies from Cyclone30 facility at Kolkata.

Currently, the MC at RMC, jointly operated by BRIT and BARC, has the following major performance credits (Table-2).

Table 2: Major Radiopharmaceuticals supplied by BRIT from MCF at RMC, BARC

Radiopharmaceuticals	Application using PET	Production and supply commenced from
^{18}F-FDG	Imaging of cancer mets	2002
^{18}F-NaF	Imaging of bone metastases	2007
^{18}F-FLT	Marker for tumor proliferation	2010
^{18}F-MISO	Imaging of tumor hypoxia	2010

6. Radiopharmaceutical Therapy Products Beyond Iodine-131: Unique Importance for Personalised Treatment

Products for Bone Pain Palliation

The successful use of radioiodine for the treatment of thyroid related disorders way back in 1960s was followed by the potential utility of radiopharmaceutical therapy for palliation of bone pain due to diffused metastasis in cancer patients (for better quality of life for patients in mostly terminal stage). The bone seeker ^{89}Sr [$E_{\beta(max)}$ = 1.49 MeV, $t_{½}$ = 50.5 d], being calcium analog, emerged as the global choice. However, it was difficult to produce ^{89}Sr (involved ^{88}Sr(n,γ) reaction of very low cross-section or ^{89}Y(n,p) reaction using fast neutrons) in those early years. ^{32}P [$E_{\beta(max)}$ = 1.71 MeV, $t_{½}$ = 14.3 d] as sodium phosphate of BARC/BRIT was used in many centres since 1980s as a practical alternate to ^{89}Sr, although with limitations due to inevitable bone marrow toxicity.

The development of ^{153}Sm-EDTMP (ethylenediamine tetramethylene phosphonic acid) with superior radiochemical and biological features (phosphonates were known drugs for pain palliation) in University of Missouri, Columbia (USA) led to BARC-BRIT scientists exploring its formulation and supply for use in India. Concerted efforts and extensive work carried out (including large animal studies in collaboration with Christian Medical College, Vellore) helped in establishing regular production of ^{153}Sm-EDTMP using natural samarium oxide targets, and subsequently with enriched ^{152}Sm targets, by neutron activation in medium flux reactors at BARC. By the end of 1990s, BARC started producing medical grade ^{153}Sm in sufficient quantities and this enabled BRIT to formulate and supply ^{153}Sm-EDTMP injection for palliative care of cancer patients in various medical institutions. The initial monthly production frequency was improved to fortnightly/weekly, depending on the demands of users.

Later on, with the development of ^{177}Lu based products for radiopharmaceutical therapy at BARC, the additional advantage of the relatively longer half-life of ^{177}Lu and similarity of chemistry, ^{177}Lu-EDTMP was developed and clinical studies initiated from 2008 to supplement the use of ^{153}Sm-EDTMP. This was also an important contribution to a Coordinated Research Project (CRP) of IAEA. Thus currently, users have the choice of using both ^{153}Sm-EDTMP and ^{177}Lu-EDTMP. BARC has also developed and evaluated another phosphonate ^{177}Lu-DOTMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid) for bone pain palliation. Kits for formulation of both ^{177}Lu-EDTMP and ^{177}Lu-DOTMP are also available from BARC/BRIT for formulation at hospital radiopharmacy end.

In light of the fast neutron flux available at FBTR (Fast Breeder Test Reactor) and the knowledge of the importance of ^{89}Sr, scientists in IGCAR, Kalpakkam took up considerable efforts to use mono-nuclidic Y in place of a fuel element to produce ^{89}Sr by ^{89}Y(n,p) reaction and its subsequent recovery by radiochemical processing[5].

BARC has also developed and launched kits for formulating ^{188}Re-HEDP (1-hydroxy ethylidene-1,1-diphosphonic acid) at hospital end for similar use in cancer patients for bone pain palliation and enabled the interested NM centres in making more effective use of the imported, expensive ^{188}W/^{188}Re generator (^{188}W is a product of successive neutron capture and its production in useful quantities require reactors having neutron flux of 10^{15} n.cm^{-2}.s^{-1}, which is available only in a very few reactors in the world).

Launch of ^{177}Lu for Targeted Tumor Therapy

Since the beginning of 2000, the Radiopharmaceuticals Division (RPhD) of BARC started exploring the feasibility of producing ^{177}Lu as another therapeutic radionuclide using the medium flux research reactors at BARC. The first irradiation of natural lutetium oxide target was carried out in 2000 and was followed by the production of high specific activity ^{177}Lu from enriched ^{176}Lu target in mid-2001. Extensive studies were carried out to optimize the production of this radionuclide, with maximum achievable specific activity and radionuclidic purity, using the highest available flux positions in the reactor and irradiating the target for an optimum duration. This enabled production of ^{177}Lu with adequately high specific activity for the preparation of target-specific therapeutic radiopharmaceuticals.

^{177}Lu is being produced on a regular basis at BARC since the end of 2006 for carrying out clinical investigations using ^{177}Lu-based radiopharmaceutical product. The most noteworthy development is the successful formulation and translation to clinical use of the new therapeutic

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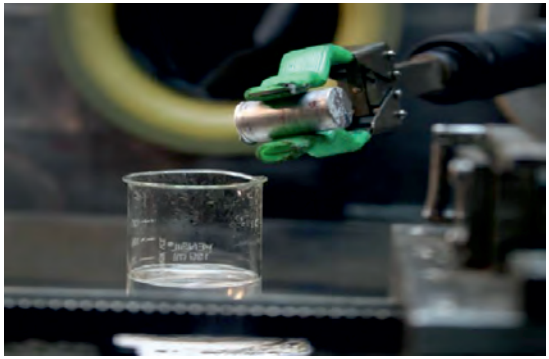
[5] *It may not be necessary to pursue further such demanding efforts on ^{89}Sr production, in light of easy-to-produce, effective alternate products available from BARC/BRIT for clinical use.*



In-cell gadgets inside the lead shielded plants for radiochemical processing of ^{177}Lu (left) and ^{131}I (right)

radiopharmaceutical, ^{177}Lu-DOTA-TATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid coupled Tyr^3-Octreotide), receptor binding peptide-based product used for targeted therapy of neuroendocrine tumours (e.g. pancreatic cancer).

BARC started commercial supply of $^{177}LuCl_3$, as the precursor radiochemical, and along with know-how transfer for the formulation of the finished radiopharmaceutical product, ^{177}Lu-DOTA-TATE (and also ^{177}Lu-EDTMP) at hospital end. This pragmatic approach helped the collaborating nuclear medicine centres to formulate the finished product and perform clinical procedures by the end of the first decade of 2000 onwards. Since then, ^{177}Lu of medium specific activity is being regularly produced at BARC and supplied to various nuclear medicine centres in India through BRIT. The subsequent addition of another important product denoted as ^{177}Lu-PSMA-617 (Prostate Specific Membrane Antigen binder ligand conjugate) by BARC, for treatment of one type of prostate cancer patients, is another significant accomplishment, keeping India at the forefront of targeted radionuclide therapy. This product received US-FDA (Food and Drug Administration of United States of America) approval very recently and is likely to be more extensively used in future.

It is noteworthy to mention that the production and use of ^{177}Lu have seen a phenomenal growth in the last two decades all over the world and the Indian contribution is acknowledged in several citations. Presently the use of ^{177}Lu is second to ^{131}I among all the therapeutic applications. Currently, BRIT supplies ^{177}Lu, both as precursor radiochemical and as ^{177}Lu-labeled radiopharmaceuticals, to more than 50 nuclear medicine centres of India.

In view of the need for no-carrier-added ^{177}Lu, for formulations involving very small quantities of targeting binder (vector) moiety, the production of ^{177}Lu by isolation from its precursor ^{177}Yb (produced by irradiation of enriched ^{176}Yb targets) is also being developed at BARC and BRIT.

There are also other products of ^{177}Lu in use, mostly due to favourable radionuclide features, for bone pain palliation (covered in the earlier sub-section) and treatment of inflammatory joint pain (covered later in this section).

Leveraging the Closed Fuel Cycle Pursuit of India to Deliver ^{90}Sr/^{90}Y

High-level radioactive liquid waste of the back-end of the fuel cycle stream contains various useful fission products, such as ^{137}Cs, ^{90}Sr, ^{106}Ru, etc. The Nuclear Recycle Group (NRG) of BARC has been striving to make available these products for applications in human healthcare.

The very long-lived ^{90}Sr ($t_{½}$ = 28.79 y) decays to ^{90}Y ($t_{½}$ = 64 h), which has a high energy beta emission of 2.27 MeV. It is thus useful for therapy of large tumors or where deeper penetration is required to reach target lesions. ^{90}Y is an ideal complement to therapy products of ^{177}Lu for clinical use.

NRG has developed in-house a strontium-selective extractant and successfully deployed for separation - recovery of ^{90}Sr from high-level radioactive liquid waste and converting into $^{90}Sr/^{90}Y$ radionuclide generator system. Two systems for separation of ^{90}Y from ^{90}Sr have been developed at BARC - the first involving 2-stage liquid membrane technology (by NRG), and the other using electrochemical means (by RPhD). The latter has been adopted and converted into an automated, commercial unit (named *Kamadhenu*) by a company in Europe.

During the recent past, ^{90}Y is periodically recovered (*milked*) from purified ^{90}Sr and supplied by NRG to RMC for the preparation of therapeutic radiopharmaceutical, ^{90}Y-DOTA-TATE. Building up an adequate stock of a few curies of ^{90}Sr and delivering ^{90}Y in several hundreds of mCi on weekly basis will be needed for regular clinical use in India.

Other products for targeted therapy

Radiolabeled monoclonal antibody (MoAb) to tumor-associated antigen as vector for targeted tumor therapy was explored by many leading centers including BARC, but could not yield satisfactory results, mostly due to unfavorable pharmaco-kinetics. With advances in immunotherapy of cancer patients (as part of systemic therapy), an altered approach for using RI - as additional *pay-load* - along with the specific antibody administered (as drug) in large quantities for immunotherapy of cancer was proposed by Dr. R. A. Badwe, Director, TMC. Reduced dose of MoAb quantity, combined with suitable particulate radiation of RI, can render this therapy more affordable and efficacious. In this connection, the collaborative pursuit between BARC and TMC and the ongoing clinical evaluation of three radiolabeled antibodies, namely, ^{131}I-Rituximab, ^{177}Lu-Rituximab (both for the treatment of non-Hodgkin's lymphoma, a type of blood cancer) and ^{177}Lu-Trastuzumab (for the treatment of metastatic breast cancer), are noteworthy.

The emerging area of targeted tumor therapy requires alpha emitters due to the known merits of the high LET (Linear Energy Transfer) radiation for efficacious delivery of radiation dose to the tumors. In the recent years, ^{225}Ac ($t_{½}$ = 10 d, multiple alphas) has been attracting the global attention, as its use has shown promising results in patients of prostate cancer. BARC has made a beginning by locating old legacy stock of ^{229}Th for separation of ^{225}Ac in very limited quantities for initial studies. BRIT and BARC are also looking at options and strategies for planning the production of this RI of envisaged high demand in future. Other potential alpha emitter RIs are also being explored by BARC.

Products for Therapeutic Applications Involving Loco-Regional Instillation

***Rph for treatment of hepatocellular carcinoma*:** Apart from the targeted therapy approach using ^{90}Y obtained from ^{90}Sr, ^{90}Y-labeled hard-microspheres have been in use for treatment of a certain type of liver cancer (unresectable (non-operable) hepatocellular carcinoma, HCC). This is based on intra-arterial delivery of the product to the tumor (loco-regional delivery of the therapeutic product). The product (TheraSpheres®, glass microspheres containing ^{90}Y) is imported from commercial sources in Europe at very high cost and used in limited cases on patients who can afford to pay the high cost of import. The multi-disciplinary expertise of BARC has been harnessed recently to develop an import substitution. Scientists of RPhD, in collaboration with the researchers of the Materials Group, BARC have been successful in developing ^{90}Y-incorporated glass microspheres (fondly named as BhabhaSpheres). Here ^{90}Y is produced by neutron irradiation

of the said spheres, which contain yttrium as one of its constituents. This has been used for the treatment of a limited number of liver cancer patients at TMH, Mumbai. Many other centers have also shown interest in using the product. This development, when completed, is expected to increase the accessibility to such therapy of HCC and also at significantly reduced cost.

There are also other alternate products to the hard-particulate based agents in use for HCC therapy. Viscous formulations of lipiodol labeled with ^{131}I and ^{188}Re have been in use. BARC has developed and made available these products for such therapy. BRIT has subsequently taken up regular production and supply of ^{131}I-lipiodol. BARC developed kits for use with imported ^{188}W/^{188}Re generator and formulation of ^{188}Re-lipiodol have also been helpful in this context. The recent demonstration of the utility and technology capability in terms of BhabhaSpheres may render some of the above products redundant in future.

***Rph for therapy of inflammatory joint pain (Radiosynovectomy)*:** Therapeutic RI labeled non-dispersible particulate formulations have been proposed for treatment of joint pain due to inflammatory processes (e.g. Rheumatoid arthritis, bleeding joints in patients of hemophilia). Depending upon the size of the joint, low or medium or high energy beta emitter RI formulations are in use. Since the late 1990s, BARC has developed and evaluated a number of products for this purpose, e.g. ^{166}Ho-labeled hydroxyapatite (HA) was used for large joints. Later, BRIT launched ^{32}P-labeled colloidal formulation of samarium phosphate for similar use. Currently, ^{90}Y obtained by direct irradiation of the mono-nuclidic ^{89}Y target is used for preparing ^{90}Y-HA for similar treatment of pain in large-joints. The product ^{90}Y-HA is supplied through BRIT. ^{177}Lu-labeled HA particulate formulations are similarly useful for medium and small joints and are made available by BARC/BRIT.

7. Technology and Other Core Capabilities Underpinning DAE's Radiopharmaceutical Program

The foregoing contributions of the various types of products and their indigenous availability would not have been a reality without the support of the large, competent teams of DAE Units and the variety of technology and other core capabilities that they could pool together as well as augment when needed (e.g. pharmacy and pharmacology expertise). It will be difficult to describe in detail all the underpinning strengths in the development and launch of the vast range of RI and radiopharmaceutical products covered in the previous sections. The following bullet points will give glimpses of the range and diversity of competences deployed/harnessed.

- Radioisotope production systems and facilities in nuclear reactor and cyclotron - targets, handling systems, cooling, radiological safety, etc.
- Radiochemical processing: Separation systems; Rapid synthesis/formulation & purification; Amenability to remote handling and automation.
- Chemical synthesis of ligands, precursors, other reagents including peptides.
- Radioanalytical, pharmacological & biochemical methods for evaluation (including animal studies) and QC tests for rapid certification.
- Automation of high-activity processes and production modules.

The multi-disciplinary expertise in BARC, BRIT, VECC and other Units of DAE have been the backbone for leveraging most of the above capabilities and allied competences. An additional initiative was launched in May 1999 (continued until 2019), in terms of identified senior

professionals in the radiopharmaceuticals program being given concurrent roles and responsibilities in both BARC and BRIT (Adjunct Post holders), to strengthen synergies and deliverables.

An internal peer review scheme for the self-regulatory functions of DAE-produced radiopharmaceuticals, called the Radiopharmaceuticals Committee (RPC) of BARC/DAE, has been an important mechanism in place since 1968. This has helped in relevant experts' (including from non-DAE entities) reviewing and facilitating the transfer of the products from the laboratory stage to clinical use in patients, by taking care of the quality standards and ascertaining the product's safety and efficacy. The scientists of DAE Units have also been involved with the Indian Pharmacopoeia Commission (IPC) in getting many of the regularly used products incorporated in the Indian Pharmacopoeia (IP 2014 onwards).

8. Future perspectives: Keeping an Eye on the Horizon

Two major emerging areas in radiopharmaceutical are: MC-based product developments and targeted therapy of tumors. For the first, enriched targets of many elements are essential for RI production and for the latter, alpha emitter ^{225}Ac is an urgent and important need. In addition, increasing longevity of the population is leading to increasing number of patients burdened with neuro-disorders (and also cancer). The role of radiopharmaceuticals for management of patients of neurology is envisaged to be very high (especially PET tracers for neuro-receptor imaging as well as in aiding new drug development) and due attention in this direction will be a key future need. DAE is also advantageously placed (due to its multi-disciplinary ambience) to similarly leverage the on-going efforts for development of novel targeting molecules for imaging the cardiac plaques, amyloid, angiogenesis, etc. Based on objective identification along with clinical experts, DAE Units can contribute to development and launch of such products of clinical relevance.

Most enriched targets for RI production are based on electro-magnetic enrichment process (in calutrons). Such targets are invariably difficult to access or expensive to procure and building indigenous capability for enriched targets is much needed. The recently reported initiative of BARC to develop indigenous facility for this technology is very crucial to address future needs. The Heavy Water Board of DAE has set up a facility to produce oxygen-18 enriched water to be used as target for ^{18}F production. When fully established, this will be a much-needed addition to serve the MC facilities in India as well as for exploring exports.

The importance of high-LET based alpha radiation for targeted tumor therapy has been known since long, while the recent success of ^{225}Ac in treating one type of prostate cancer patients, and the earlier initial success in the use of ^{223}Ra for treating bone metastases, have led to growing interest in alpha therapy. Projects with huge investments are underway in some countries in building up large-scale production capacity for ^{225}Ac. DAE/BARC is uniquely placed with its all-round expertise in handling alpha emitters. DAE Units may choose any of the three methods of production of ^{225}Ac and position itself to serve the NM users in India with ^{225}Ac and/or other similar alpha emitters of potential high utility.

Towards sustaining the DAE Units' crucial role in supporting the availability of indigenous RI and radiopharmaceutical products for NM practices, it is necessary to consider further strengthening *cum* expanding the larger infrastructure required. This will be by way of planning for an additional reactor, dedicated to RI production (likely to be met by the proposed new research reactor under Public-Private-Partnership mode), and a high-current (proton) cyclotron of 60-70 MeV. With 350+ NM centers in operation and continuing overall growth in medical

facilities in India, the additions proposed are vital for meeting the future needs of NM practices and sustaining affordable clinical benefits to patients.

9. Concluding remarks

The development and utilization of radiopharmaceuticals for nuclear medicine practices have gone through a series of 'continual change for the better' over the past five to six decades. Thanks to the multi-disciplinary teams of the DAE Units, BARC and BRIT in particular, and strong support of the Units' leaders for sustained pursuits - both R&D and production-supply services, availability of most radiopharmaceutical products has been ensured for NM practices in India, and in turn, leading to nearly half a million procedures performed every year for the benefit of patients. There are over 350 NM centers (85+ % in private sector), 250+ SPECT-gamma cameras, 24 MC, more than 280 PET/CT units, and 3 PET/MR units in India. Almost all the NM centers depend on BARC-BRIT for most of the reactor-based RI and radiopharmaceutical products. In addition, there is further scope, as well as need, for BARC and BRIT to plan and address some of the emerging needs of products for NM applications, e.g. alpha emitter radioisotopes, as well as augmentation of infrastructure for RI production. As India is celebrating its 75th year of independence - *Azadi Ka Amrit Mahotsav* - it is highly appropriate to recall the past creditable achievements and record them, being worthy of special mention, and also serve as motivation for the current leaders and professionals in the field to continue to strive for sustainable delivery of products and services for patient benefits in future.

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