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Production of Radioisotopes and Radiopharmaceuticals at the Dalat Nuclear Research Reactor

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Abstract: After reconstruction, the Dalat Nuclear Research Reactor (DNRR) was inaugurated on March 20th, 1984 with the nominal power of 500 kW. Since then the production of radioisotopes and labelled compounds for medical use was started. Up to now, DNRR is still the unique one in Vietnam. The reactor has been operated safely and effectively with the total of about 37,800 hrs (approximately 1,300 hours per year). More than 90% of its operation time and over 80% of its irradiation capacity have been exploited for research and production of radioisotopes. This paper gives an outline of the radioisotope production programme using the DNRR. The production laboratory and facilities including the nuclear reactor with its irradiation positions and characteristics, hot cells, production lines and equipment for the production of Kits for labelling with ^{99m}Tc and for quality control, as well as the production rate are mentioned. The methods used for production of ^{131}I, ^{99m}Tc, ^{51}Cr, ^{32}P, etc. and the procedures for preparation of radiopharmaceuticals are described briefly. Status of utilization of domestic radioisotopes and radiopharmaceuticals in Vietnam is also reported.

Keywords: Radioisotope; Radiopharmaceutical; Labelled KIT, Nuclear Medicine.

I. INTRODUCTION

During the last 30 years of operation, the DNRR has been successfully used for producing many kinds of radioisotopes and radiopharmaceuticals used in medicine and other economic and technical fields. Providing about 400Ci per year of radioisotopes including I-131, P-32, Tc-99m generator, Kit in-vivo and in-vitro, Sr-46, Cr-51, etc. Each year, about 300,000 patients have been diagnosed and treated by radioisotopes produced at DNRR that contributed to push forward the development of nuclear medicine in Vietnam.

In a developing country of low economic level, the benefit of establishment of a nuclear research center with a research reactor of low power will be recognized by society only when its contributions to social progress become evident. This point of view has oriented us to put forward a limited radioisotope production programme to support radioisotope application in medicine, agriculture and industry. For this objective the core of the present 500-kW reactor reconstructed from the previous 250-kW TRIGA MARK II reactor is equipped with more neutron irradiation channels and with a neutron trap for improving thermal neutron flux. In addition, the reactor characteristics are more useful as far as radioisotope production is concerned, i.e. of higher excess reactivity, the cadmium ratio in neutron irradiation channels being rather high in the thermal neutron trap and rather low in the fast neutron channels. The establishment of a laboratory for routine production of radioisotopes was carefully

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considered by balancing the investment requirement and the production technology of choice, as well as the radioactive waste treatment problem and radiation protection.

II. PRODUCTION OF RADIOISOTOPE AND RADIOPHARMACEUTICALS

A. Production laboratory and facilities

Construction of neutron irradiation positions

Due to the low power of DNRR we must take into consideration of the irradiation position construction, core management and reactor operation mode in order to improve the neutron flux, to maximize the volume available for target irradiation and to balance the formation-decay of activated radionuclides.

For the purpose of augmentation of thermal neutron flux, the central irradiation channel (so called neutron trap) was surrounded by beryllium metal block of thickness of 1.7 cm and height of 60 cm.

The effect of beryllium gave an improving in flux and quality of thermal neutron. As cited in **Figs. 1 & 2**, this neutron trap has a diameter of 64 mm originally and has only one guiding tube of diameter of 38 mm in the centre for holding the target containers. This construction of neutron trap has been found inconvenient in exhaustive exploitation of irradiation volume. So it has been proposed for reconstruction. The design work is based on the fact of self shielding-effect of targets and cooling water circulation, as an example of this, neutron flux depletion in TeO_2 and MoO_3 target under reactor irradiation was noted in **Fig. 1.**

As shown in the case of target sample of diameter of 2 cm, the neutron flux in its center dropped about 10 percent. This fact leads us to design a neutron trap which is composed of two channels of 24-mm diameter. The sectional cut of old and new neutron trap was shown in **Fig. 2**. With this new construction, effective irradiation volume of trap will increase a factor of 1.5.

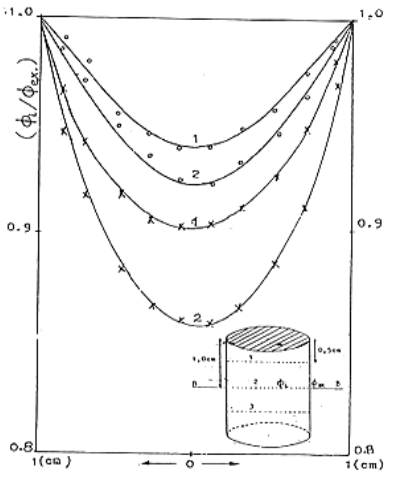
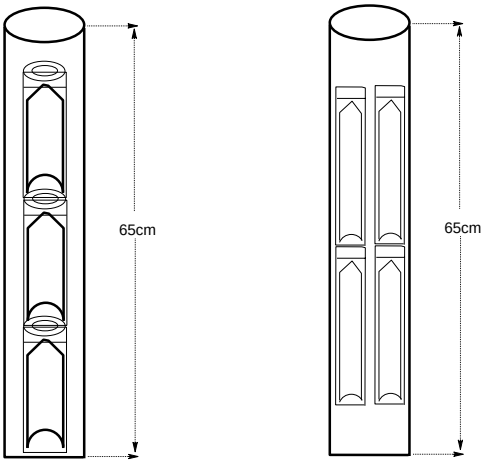


Fig. : Neutron flux depletion in TeO_2 target (o-o-o line) and in MoO_3 target (x-x-x line) at piercing lines 1 and 2 under reactor activation.
- Samples of cylindrical shape of height of 2 cm, diameter of 2 cm:
δ = 2.53 g/cm3 (for TeO_2) and
δ = 1.81 g/cm3 (for MoO_3).

Fig. 1. Neutron plux depletion in target.



Old trap *New trap*

Fig. 2. Neutron trap construction for the optimization of effective irradiation volume exploitation.

Irradiation techniques

The targets held in the quartz ampoule were irradiated with thermal neutron either in the neutron trap at the center of the reactor core or in the rotary specimen rack. For fast neutron irradiation, it was carried out in a dry channel inserted between fuel elements of the reactor

core. Before irradiation, the targets were purified to remove traces of impurities.

Fig. 3. Quartz ampoule and aluminum container for containing target.

Reactor core management for the irradiation of targets

The core management plays an important role in the optimization of research reactor utilization for production of radioisotopes. The core management is based on the nuclear reaction applied to produce a predescribed radionuclides, the neutron activation cross section and/or requested specific radioactivity of a specified radioactive products. Besides, the neutron flux and characteristics of irradiation position such as R_{cd}, neutron flux distribution were also taken into consideration.

At the DNRR, the irradiation channel of lowest cadmium ratio, R_{cd} =1.90 is used for fast neutron irradiation to produce the radionuclide with (n, p) nuclear reaction, such as $^{32}S(n, p)^{32}P$. ^{32}P isotope produced in this channel is of high specific radioactivity and is used for preparation of injectable ^{32}P solution. Meanwhile the rotary specimen rack of highest cadmium ratio, R_{cd} = 4.5 is used for production of ^{32}P of low specific radioactivity with $^{31}P(n, \gamma)^{32}P$ reaction. This ^{32}P product was used to prepare the ^{32}P applicators for skin disease treatment. In the neutron trap of highest thermal neutron flux and of R_{cd} = 2.93, the (n, γ) nuclear reaction was applied to produce the radioisotopes of higher specific radioactivity, such as ^{131}I and ^{99}Mo. ^{99}Mo with high specific radioactivity used for ^{99}Mo-$^{99}Tc^{m}$ generator. ^{99}Mo was produced by neutron irradiation of MoO_3 target at the centre of neutron trap, where thermal neutron flux is of highest value. The distribution of neutron flux in an irradiation position is a very important parameter for the management of target irradiation.

Reactor operation schedule

The schedule of reactor operation mainly depends on the kinds of radionuclide produced and their role. The formation rate of these kinds of radionuclides and the required minimal specific radioactivity of radioisotopes are indispensable factors to decide on the option of reactor operation mode. The DNRR was offered to produce some important radionuclides for nuclear medicine application. Among these radioisotopes, ^{131}I and $^{99}Tc^{m}$ isotopes are most highly evaluated. So the reasonable schedule of reactor operation must be chosen, taking into consideration of the production yield and quality of ^{131}I and ^{99m}Tc radioisotope products. Basing on the formation rate under reactor activation and half life of ^{99}Mo and ^{131}I radionuclides a reactor operation schedule of 130-150 hrs of continuous run every three weeks has been applied.

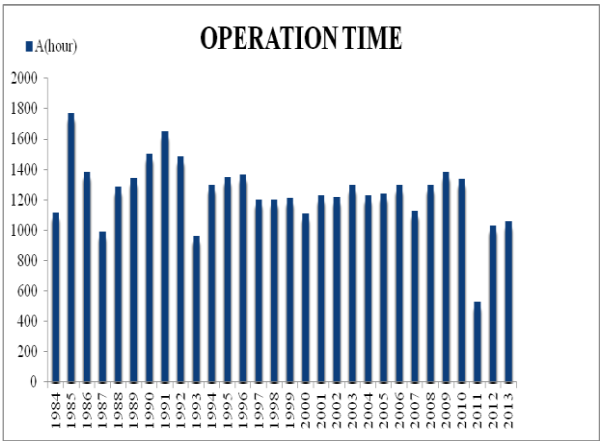


Fig. 4. Annual operation time at DNRR since 1984 to 2013.

B. Production laboratory

The main utilization of the DNRR is the production of radioisotopes for nuclear medicine, agriculture, sedimentology and other scientific research. About 90 percent of time is used for radioisotope production.

An area of 200 sq.m is reserved for a rather limited programme of isotope production. The facilities available for the isotope production consist of one hot cell with master slave manipulator (**Fig. 5**).

Fig. 5. Hot cell with master slave manipulator

One ^{131}I isotope production line equipped by the IAEA TC Project VIE/0/002 in 1987 with 4 shielded cells, one ^{131}I isotope production line equipped in 2008 by the National Project with 2 shielded cells ball-joint manipulators (**Fig. 6**), and five shielded fume hoods for isotope labelling and γ-emitted isotope processing.

One ^{99m}Tc generator production line (using fission ^{99}Mo solution) equipped under the IAEA TC Project No. VIE/6/016 in 1990 with 2 shielded cells ball-joint manipulators (**Fig. 7**).

Fig. 6. ^{131}I isotope production line equipped in 2008 with 2 shielded cells.

Fig. 7. ^{99m}Tc generator production line.

All these facilities are connected with the existing ventilation system of the reactor.

Equipment for the production of Kits to be labeled with ^{99m}Tc isotope and for the quality control of radioisotopes and radiopharmaceuticals was also supplied by the National Projects (**Figs. 8 and 9**).

Fig. 8. Sterile hot cell.

Fig. 9. Clean room**.**

Since the beginning of 1984 (the year of reactor inauguration) up to now the radioisotope production at the DNRR has concentrated on the following radionuclides:

- ^{32}P in injectable orthophosphate solution and ^{32}P applicator for skin disease therapeutics.

- ^{131}I in NaI solution.

- ^{99}Mo-$^{99}Tc^{m}$ generator.

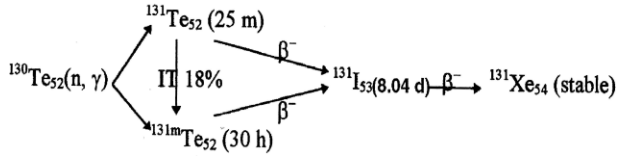
- ^{51}Cr in injectable sodium chromate solution and Cr-EDTA.

- Other radioisotopes such as ^{60}Co, ^{65}Zn, ^{64}Cu, ^{24}Na, ^{86}Rb, ^{46}Sc, ^{71}Ge, ^{55}Fe, etc., were also produced in a small amount when requested.

C. Radiochemical processing of activated targets

Iodine-131:

Iodine-131 is produced from the irradiated tellurium dioxide in neutron trap. The target of tellurium dioxide contained in a welded aluminum capsule, according to the nuclear reaction as follows:



The irradiated tellurium dioxide powder is transferred to a Vycor distillation vessel and connected to the iodine-131 tellurium processing system. The processing furnace is heated up to 750^{o}C in order to distill the iodine-131 over to a charcoal column trap connected in-line of the distillation system. The charcoal column trap is rinsed with the de-ionized water then eluted with sodium hydroxide 0.05N to form the final product of iodine-131 solution. The scheme in **Fig. 10** shows the flow chart of the operation and procedures.

The target used in the production is an analytical grade material of natural tellurium as tellurium dioxide obtained from Fluka Inc. The chemical purity of the target as TeO_2 is >95%. The specification of the target before being fired in a muffle furnace through analysis by emission spectrograph should contain of selenium less than 0.05% and heavy metals less than 0.1%. After being fired in the muffle furnace the analysis should give selenium less than 0.005% and heavy metal less than 0.1%.

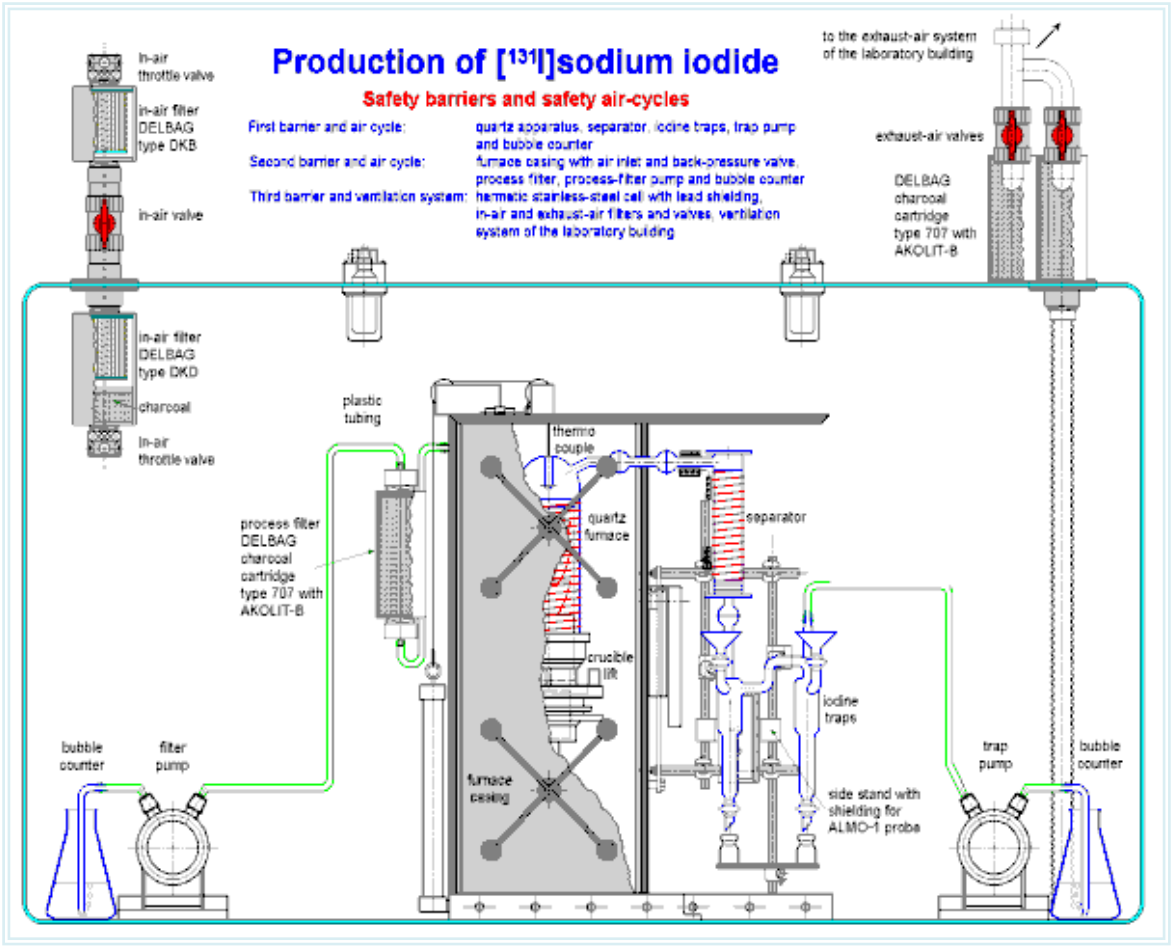


Fig. 10. The flow chart of the operation and procedures of I-131.

Final product specification for use

The final product as sodium iodide, ^{131}I solution in NaOH, without reducing agents will be used as ^{131}I bulk solution for radiopharmaceuticals production. The specification of the final product is as follows:

Physical appearance: Colorless solution.

Radioactivity of ^{131}I: more than 11.1 GBq (300 mCi) I-131/mL.

^{133}I content: less than 0.80% of the ^{131}I content at assay time.

pH: more than 11

Radionuclidic purity: ^{131}I content more than 99.9%.

Radiochemical purity: Iodide more than 95%.

^{99m}Tc generator:

Among the two reactions of choice for production of ^{99}Mo parent isotope, the large investment for use of $^{235}U(n, fission)^{99}Mo$ reaction let us to opt for the $^{98}Mo(n, \gamma)\ ^{99}Mo$ reaction to produce ^{99m}Tc generator.

In order to separate ^{99m}Tc from its parent ^{99}Mo we first used the MEK extraction method.

The inherent disadvantages of this method compelled us to start our studies on the preparation of gel type generators in late 1984 in the framework of the IAEA-CRP on the "Development of ^{99m}Tc generators using low power research reactor". This represents the state-of-the-art for generator technology and promises opportunities for both developed and

developing countries particularly with respect to eliminating the need for fission ^{99}Mo. Two directions of preparation of gel type generators were studied:

- Preparation of chromatographic generators using zirconium molybdate (ZrMo) or titanium molybdate (TiMo) column packing materials synthesized from the neutron irradiated molybdenum trioxide and the zirconium chloride and/or titanium chloride, respectively.

- Preparation of chromatographic generators using TiMo column packing material (preformed TiMo) synthesized from the inactive molybdenum compound and $TiCl_4$ and subsequently neutron activated in the reactor.

In both modes of preparation we have carried out studies on three different options of generators:

- The chromatographic generator using 0.9% NaCl solution as eluant.

- The chromatographic generator using organic solvent as eluant Solid-Solvent-extraction).

- The chromatographic generator using dilute saline as eluant and ^{99m}Tc concentration column.

In the other hand, under the framework of Forum for Nuclear Cooperation in Asia (FNCA) program, the PZC based technology for production of ^{99m}Tc- generator has been studied at DNRI as well as FNCA member countries in the past several years.

PZC adsorbent of high performance for ^{99}Mo adsorption was easy to synthesize from isopropyl alcohol (iPrOH) and $ZrCl_4$.

The procedures and relevant ^{99m}Tc-generator designs for the preparation of PZC based ^{99m}Tc- generators were successfully set up. The columns of from 1.0 gram to 4.0 gram weight of PZC and from 100 mCi to 500 mCi ^{99}Mo could be used to produce portable, chromatographic type ^{99m}Tc- generators which have a good performance for application in clinical investigations. Among the established procedures the column loading procedure was highly evaluated, because it proved to be prominent figures for easy and safe operation, for low cost of technology facilities, equipment and for the capability to match the traditional technology of the fission ^{99}Mo based ^{99m}Tc-generator production.

DNRI had been proposed attending in these studies program. The commercial production of PZC generator through the establishment of national project stage 2006-2008 for the routine production of ^{99}Mo/^{99m}Tc generator. In this project the ^{99m}Tc-generator used PZC coming locally synthesis and from KAKEN - Japan as the column material, ^{99}Mo formed from MoO_3 irradiated at DNRR, the semi-automatic loading and adsorption machine had studied, designed and installed in the hot cells available. The generator assembly had also been designed and fabricated, (**Figs. 11, and 12**).

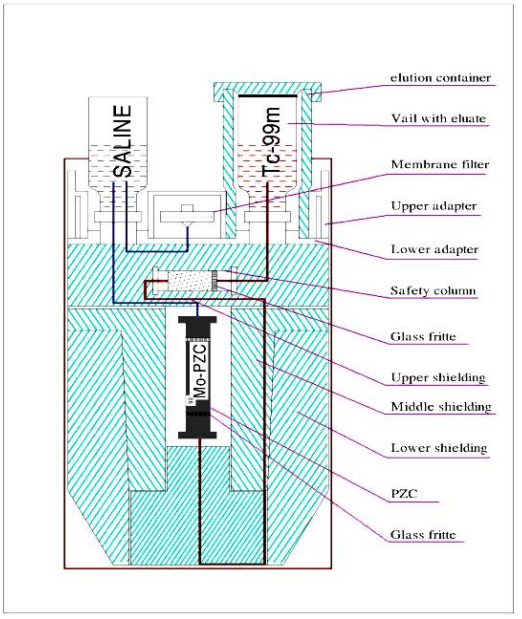


Fig. 11. Schema of ^{99m}Tc – Generator

Design of commercial PZC-^{99m}Tc generator

Fig. 12. The semi-automatic loading machine

In conclusion, it is strongly believed that ZrMo, TiMo and PZC based generator play an importance role as alternative technology for production of ^{99}Mo/^{99m}Tc generator from reaction ^{98}Mo(n, γ)^{99}Mo. However these methods were not very appropriate for the low power research reactor as DNRR. Because of those reasons, it is necessary to build a new research reactor with power at least of 10 MW, and the neutron flux is high enough to research and produce radioisotopes.

Phosphorus-32:

^{32}P isotope was produced according to two nuclear reactions: ^{32}S(n, p)^{32}P and ^{31}P(n, γ)^{32}P.

The first reaction was used for the production of injectable carrier-free ^{32}P solution, the second for that of ^{32}P –isotope applicators for skin disease treatment.

First the injectable ^{32}P solution of radioactivity of ten mCi scale was produced from irradiated $MgSO_4$ target using magnesia as absorbent to separate ^{32}P isotope from $MgSO_4$ solution. In the case of Ci scale production, the large amount of waste produced from this technology caused storage problems. Recently, we have introduced the distillation technique to separate ^{32}P from reactor irradiated elemental sulfur. Our glass apparatus for this production process is shown in **Fig. 13.** It can be used for distillation either in the vacuum or in the N_2 gas flow by changing the upper stopper of the distillation vessel. The distillation parameters and post-distillation purification of ^{32}P solution were adopted as described in literature.

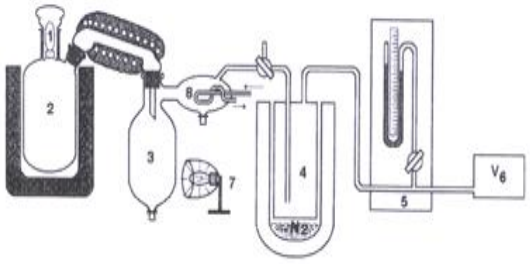


Fig. 13. The glass apparatus for ^{32}P production process using nuclear reaction ^{32}S(n, p)^{32}P

The ^{32}P applicators for skin disease treatment were produced by neutron irradiation of a soft plate preformed from cloth binder and a covering mixture of red phosphorus and glue. After irradiation in the reactor, the radioactive plate was impregnated with plastic and covered with Scotch adhesive. The mechanical strength of the preformed plate was not lost under 75-hour irradiation in a thermal neutron flux of $5x10^{12}$ n.cm^{-2}.s^{-1}. Under this irradiation a plate containing 65 mg P per square centimeter gives a radioactivity of 15 mCi ^{32}P. The absorbed dose rate on the surface of the plate of size 50 x 40 mm^2 was measured as 110 Rad.min^{-1} at the center and 75 Rad.min^{-1} on the edge. Medical doctors' experience over ten years showed that with repeated treatment of three or five 15-minute applications the following diseases will be cured: Eczema, skin cancer, bump scar, etc. At present more than

75 Ci ^{32}P in applicator form are used annually in the country.

Cr-51 isotope:

The production of ^{51}Cr isotope was carried out based on the Szilard-Charmel reaction using reagent grade K_2CrO_4 target. The chemical separation of recoiled ^{51}Cr nuclide was based on the selective adsorption of this isotope on an inorganic ion exchanger Si-ZrP (Silica gel supported zirconium - phosphate) synthesized by us.

Other isotopes were also produced when requested in small amounts for industrial and agricultural applications. The methods for production of these isotopes were selected from investigation results or different reference sources.

D. Production of Kits for labelling with ^{99m}Tc:

In furthering the application of ^{99m}Tc isotope, the local availability of Kits for labelling with ^{99m}Tc plays an important role. With IAEA support the basic equipment for the production of Kits has been installed in our laboratory. At present many kinds of in-vivo Kits have been successfully prepared and put to use in the country, they are Phytate, Gluconate, Pyrophosphate, Citrate, DMSA, HIDA, DTPA, Maccroaggregated HSA and EHDP (1-hydroxy ethylidene-1, 1-disodium-phosphate).

The studies on the preparation of Radioimmuno-assay Kits and therapeutic agents and/or radionuclides were also carried out. The future production of the above mentioned items is foreseen and planned.

E. Quality control

Radioisotope and radiopharmaceutical quality control was carried out for all batches of our products. The gamma spectrum analysis using Ge-Li detector coupled with a multichannel analyser is used for radionuclide purity control, the TLC, HPLC and gel-chromatography techniques for chemical purity, and the spectrometry and neutron activation analysis for chemical purity. Biodistribution assay, biological tests (apyrogenity, sterility, toxicity) and physicochemical tests (pH, turbidity) are also carried out regularly.

Fig. 14. HPLC system for QC.

III. LOCAL PRODUCTION VOLUME AND DEMAND

These types of radioisotopes have regularly been supplied to more than 25 hospitals in Vietnam two times per month. The $^{131}1$ radioisotope labelled radiopharmaceuticals such as ^{131}I-Hippuran; $^{131}IMIBG$ have also been regularly supplied to hospitals. Radioisotope production rate is shown in **Fig. 15** and **Table I**.

In order to support the application of ^{99m}Tc, ^{113m}In, ^{177}Lu and ^{153}Sm radioisotopes in clinical diagnosis and therapeutics, the preparation of radiopharmaceuticals in Kit forms has been carried out. The following Kits have regularly been manufactured in DNRI:

Phytate, Gluconate, Pyrophosphate, Citrate, DMSA, EHIDA, DTPA, HSA macroaggregated, HEDP, HmPAO, MIBI, MDP.

Radioimmunoassay Kits: The RIA Kit production and distribution programme have also started. T3 and T4 Kits have been selected locally by end-users with a share of 50% of domestic market. Other RIA and IRMA Kits can be supplied to end-users by dispensing process based on the contract.

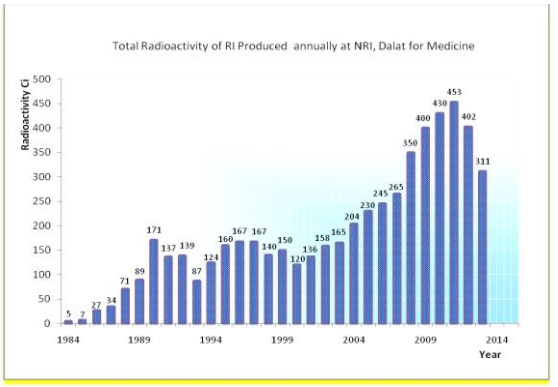


Fig. 15. Total activity of radioisotopes produced at DNRI

Fig. 16. Radioisotopes and Radiopharmaceuticals produced at the DNRI

Table I. The supply/demand for radioisotopes and diagnostic Kits in Vietnam.

Product	**Supply**	**Demand at present**
^{131}I- Diagnostic and therapeutic capsule/solution	20-30 Ci/month	40-50 Ci/month
^{99m}Tc-Generator	10 generators (200-500mCi/each)/month	40 generators (200-500mCi/each)/month
^{32}P-Solution/ Applicator	50 Ci/month	50 Ci/month
Kits for ^{99m}Tc-Labelling		
MDP	400 Kit/ month	500 Kit/ month
DTPA	200 Kit/ month	300 Kit/ month
DMSA	200 Kit/ month	300 Kit/ month
PHYTATE	200 Kit/ month	300 Kit/ month
Orther	200 Kit/ month	300 Kit/ month

IV. THE APPLICATION OF LOCAL PRODUCTS IN THE COUNTRY

- Number of nuclear medicine departments in Vietnam: 25

These departments almost are located in the big cities of the country (**Fig. 17**).

- Number of gamma cameras (planar and SPECT): 22

- There are six centres of PET-CT and cyclotron in Hanoi Capital and Ho Chi Minh City.

- Radiopharmaceuticals used in these centres: $Na^{131}I$ solution and capsule, Sodium-(^{99m}Tc) pertechnetate (^{99m}Tc-Generator) ^{131}I-Hippuran, Sodium-(^{32}P) orthophosphate, ^{131}I-MIBG, In-vivo Kits (MDP, DTPA, DMSA, Phosphon, Glucon, Phytate, MAHSA, EHIDA, HMPAO, MIBI, MAG-3, etc.).

- Locally manufactured products take about 50% of total market. In order to get a higher market share now we increase the production by loading generations with importing raw materials such as ^{99}Mo and ^{131}I solutions.

Fig. 17. Location of Nuclear Medicine Departments in Vietnam.

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