2.13 CURRENT STATUS OF PRODUCTION AND RESEARCH OF RADIOISOTOPES AND RADIOPHARMACEUTICALS IN INDONESIA

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Abstract

The use of radioactive preparation in Indonesia has sharply increased during the past years, indicated by the increase of the number of companies utilizing radioisotopes during 1985 to 1999. It has been clearly stressed in the BATAN's Strategic Plan for 1994 - 2014 that the production of radioisotopes and radiopharmaceuticals is one of five main industrial fields within the platform of the Indonesian nuclear industry. Research programs supporting the production of radioisotopes and radiopharmaceuticals as well as development of production technology are undertaken by the Research Center for Nuclear Techniques (RCNT) in Bandung and by the Radioisotope Production Center (RPC) in Serpong, involving cooperation with other research center within BATAN, universities and hospitals as well as overseas nuclear research institution. The presented paper describes production and research status of radioisotopes and radiopharmaceuticals in Indonesia after the establishment of P.T. Batan Teknologi in 1996, a government company assigned for activities related to the commercial application of nuclear technology. The reviewed status is divided into two short periods, i.e. before and after the Chairman Decree No.73/KA/IV/1999 declaring new BATAN organizational structure. Subsequent to the Decree, all commercial requests for radioisotopes and radiopharmaceuticals are fulfiled by P.T. Batan Teknologi, while demands on *novel* radioactive preparations or new processing technology, as well as research and development activities should be fulfilled by the Center for the Development of Radioisotopes and Radiopharmaceuticals (CDRR) through non-commercial arrangement. The near-future strategic research programs to response to dynamic public demand are also discussed. The status of research cooperation with JAERI (Japan) is also reported.

Keywords : radioisotopes, radiopharmaceuticals, production of, research and development of, BATAN, PT Batan Teknologi

INTRODUCTION

To anticipate increases in radioisotope and radiopharmaceutical applications, the National Atomic Energy Agency, BATAN, in 1989 has established a research reactor and its supporting facilities, including the Radioisotope Production Center (RPC), in Serpong. The RPC since then has produced various radioisotopes and radiopharmaceuticals and has also undertaken programs to improve its ability and capability in developing new products. The production of radioisotopes and radiopharmaceuticals which were formerly performed in the Research Center for Nuclear Technique (RCNT) in Bandung were gradually taken over by the RPC.

Entering the third millenium, BATAN's Strategic Plan (1994 - 2019) [1] clearly stresses that the objective of research and development activities in nuclear technology is public welfare. The Plan indicates that the platform of Indonesian nuclear industry essentially consists of five nuclear industrial fields, i.e. nuclear fuel processing industry, engineering and fabrication of nuclear instrumentation, production of radioisotopes and radiopharmaceuticals, application of radiation and isotopes, and radioactive waste management industry. Therefore, the RPC has an important role in supporting the Indonesian nuclear industry, specifically in radioisotope and radiopharmaceutical production technology.

In May 1996, a government company, PT Batan Teknologi (BT), was established which took over responsibility and function in the production of radioisotopes and radiopharmaceuticals from the RPC, while leaving the research and development function with the RPC. Less than 3 years later however, Presidential Decree No. 197/1998 [2] and BATAN Chairman Decree No.73/KA/IV/1999 [3] have changed many things. According to the Decree, the BATAN organization should be rearranged and its functions should be repositioned and reoriented.

The use of radioactive preparations in Indonesia has sharply increased during the past years, indicated by the increase of the number of companies utilizing radioisotopes. From 36 in 1985, it has increased to approximately twice in 1989, and has become to around 300 in 1999. Specifically, the number of nuclear medicine facilities has increased from 6 in 1985 to 11 in 1990 and has become 18 in 1999.

The presented paper reviews radioisotope and radiopharmaceutical production activities as well as related research and development status in Indonesia since the establishment of P.T. Batan Teknologi in 1996. The review is divided into two short periods, i.e. 1996 - 1998 and 1999 up to now (before and after the Chairman Decree No.73/KA/IV/1999). The mid-term strategic research programs to anticipate dynamic changes on public demands are also presented covering programs performed in the CDRR Serpong as well as in CRDNT Bandung.

R & R STATUS IN 1996 - 1998.

As a consequence of the establishment of PT Batan Teknologi, the (then) RPC transfered all of the production facilities, including building, chemicals and materials, and therefore has no more activities in the production of radioisotopes and radiopharmaceuticals. The RPC activities were then concentrated on research and development in production and processing technology of radioisotopes and radiopharmaceuticals. On the other hand, commercial production of radioisotopes and radiopharmaceuticals, as well as distribution to the market, were carried out solely by PT Batan Teknologi.

Table 1 shows radioisotopes and radiopharmaceuticals total production by PT Batan Teknologi in 1997 and 1998. The products were supplied to domestic market except for ^{99}Mo, ^{131}I and ^{32}P which were supplied also to Malaysia and China. Considering that the production and commercial activities have been started from 1989, the company activities should be reevaluated and redirected.

Subsequent to the establishment of PT Batan Teknologi, the RPC with the remaining facilities and manpower has redefined itself towards research programs on radioisotope and radiopharmaceutical processing technology, i.e.

a. Production technology of primary radioisotopes.
b. Recovery technology for enriched target materials.
c. Separation technology of fission radioisotopes from low enriched ^{235}U irradiated target.
d. Improvement in radioanalytical techniques of radioactive preparations.
e. Production technology of radiopharmaceuticals for diagnosis, therapy and radioimmunology.
f. Synthesis of ligand compounds for radiopharmaceutical substrates.

Table 2 shows some developments on radioisotopes and radiopharmaceuticals performed by RPC in 1997-1998. Other related researches performed in the Research Center for Nuclear Techniques (RCNT) are also presented.

R & R STATUS AFTER THE DECREE NO. 1971998

Toward the end of 1998, a new Presidential Decree No. 197/1998 on nuclear energy was declared. Consequently, the BATAN organization should be rearranged and its functions should be repositioned and reoriented. The new BATAN organizational structure was then declared by the Chairman Decree No.73/KA/IV/1999 in April 1999, which also formulated its new functions. In the Decree, the Center for Development of Radioisotopes and Radiopharmaceuticals (CDRR) is established to cover all the remaining facilities, activities, and function of the previously RPC after its commercial activities were reassigned to PT Batan Teknologi. The new BATAN organization has also established Center for Research and Development of Nuclear Techniques (CRDNT, then was RCNT) and reinstall its function in research and development of radioisotopes and radiopharmaceuticals.

At that stage, the CDRR as an institution for the technology development of radioisotope and radiopharmaceutical processing has developed itself to be capable also in performing research and development on preparation and utilization of radioactive compounds. On the other hand, PT. Batan Teknologi has so far be able to produce only old generation (1970-1980s) radioisotopes and radiopharmaceuticals, whereas *new* and better radiopharmaceuticals which have been known by general public were fulfilled by imported products.

Since the PT Batan Teknologi reluctantly supplied non-commercial radioisotopes or radiopharmaceuticals, therefore most public request on such preparation was thus directed to the CDRR. Consequently, production of radioisotopes and radiopharmaceuticals was carried out by both PT Batan Teknologi and the CDRR. The CDRR produces and supplies radioactive preparations for non-commercial applications as in research, clinical test, local science and technology development, etc. Simultaneously, the CDRR has to continue with its original function in technology development of radioisotopes and radiopharmaceuticals.

Table 3 shows some research and developments which are still progressing, while some developments have been delivered to users (mostly to hospitals) which can be commercialized later. Basic research in radioisotopes and radiopharmaceuticals to support these programs are mainly carried out by the CRDNT in Bandung.

Table 4 shows all radioisotopes and radiopharmaceuticals delivered by the CDRR from January to October 1999 for medical and non-medical applications. It can be seen that the CDRR was requested also to supply radioactive preparations which have never been prepared before, such as potassium iodate (^{131}I), dibromo(^{82}Br)-benzene, ^{86}Rb+ and ^{41}Ar gas. The CDRR also has data showing hundreds companies using long half-life radioisotopes for industrial purposes such as in level gauges, thickness gauges, and flow gauges.

MID-TERM RESEARCH PROGRAMS.

Radioisotope and radiopharmaceutical applications in Indonesia are predicted to be growing fast in the near future. An effort to master and to improve production technology is absolutely necessary in order to endeavour the dynamic public demands. On one hand, increase in radioisotope demands should be responded accordingly and should trigger scientists to develop alternative radioisotopes, new radioactive preparations, and new radioisotopes applications. On the other hand, improved technology should also push more application of nuclear technology in the society.

As has been known that many radioisotopes can be produced also by particle bombardment in the cyclotron, and the demands for radiopharmaceuticals are not limited to radiodiagnostic agents, but also to radiotherapeutic compounds. With the availability of the reactor and cyclotron, it is understandable that expectation to meet various demands are very high. The GA Siwabessy Reactor is known as a multi-purpose reactor suitable for producing radioisotopes by neutron activation or by fission of ^{235}U. Having a thermal neutron flux of 2.4×10^{14} n. cm^{-2}. sec^{-1} in the central irradiation position (CIP) and 1.4×10^{14} n. cm^{-2}. sec^{-1} in the beryllium reflector irradiation positions, the reactor is able to produce high quality radioisotopes by short-time and efficient irradiation.

To exploit the cyclotron better, BATAN has modified the cyclotron from initially a positive ion cyclotron to a negative ion cyclotron [5]. With the modification, the operational proton-beam performance for radioisotope production purpose is better than before. Installation of a beam profile viewing system has also succeeded as to facilite a better and stable irradiation efficiency. Installation of gas target irradiation facility is now progressing which could add alternative radioisotope available for labelling, such as ^{123}I.

Considering all the facts, the CDRR mid-term program has been reoriented towards strategic programs on the development of radioisotopes and radiopharmaceuticals. Execution of the programs will be improved involving other research units within BATAN, domestic hospitals or universities, and even overseas research institutions such as JAERI (Japan) and ANL (United States) and IAEA. Some of these strategic programs which are carried out in cooperation with other institution are presented in Table 5.

The development of ^{99}Mo production technology from LEUin cooperation with the ANL has almost completed. Utilization of the technology is now under careful consideration to yield a meaningful impact. Along with the CDRR, the revitalized CRDNT is expected to add more resources for development in radioisotopes and radiopharmaceuticals. Some of the mid term research program now are progressing in CRDNT are : preparation of $^{188}W/^{188}Re$-generator ; formulation of DMSA (basic) and EC radiopharmaceutical kits; preparation of ^{165}Dy for therapy, Glucose-6-(^{32}P) phosphate; and $^{186}Re^{V}$-DMSA.

Achievement of all these programs will hopefully support the availability of radioisotopes and radiopharmaceuticals in Indonesia and subsequently will serve for the improvement in the welfare of the Indonesian society.

It is important to mention that cooperation with JAERI in research programs between the CDRR and the Department of Radioisotopes has flourished for the last 2 years, particularly in the development of ^{192}Ir-hair pin and ^{192}Ir-needles production technology, synthesis of tetrofosmine and separation of HMPAO isomers.

The ^{192}Ir-needles program is temporarily canceled due to a problem in the purchase of laser welder, although the radiocalorimeter for the program has been installed and calibrated in a newly furnished room. The first target irradiation will be carried out soon after the reactor yearly maintenance in Dec 1999 - Jan 2000. Preliminary studies on dose calculation and application test are simultaneously performed with the participation of scientist from the CRDNT and radiotherapists in Hasan Sadikin Hospital Bandung. The programs are expected can be finalized and followed by clinical trials in three hospitals, i.e. Hasan Sadikin Hospital for the ^{192}Ir-hairpin, Dharmais and Cipto Mangunkusumo Hospitals in Jakarta for the ^{192}Ir-needles.

Other cooperation with JAERI in the synthesis of tetrofosmine has reached the first synthetic step producing an intermediate compound which was characterized and confirmed as 1,2-bis-(phosphino)-ethane by IR-spectrophotometric, elemental analysis and GC-Mass Spectrometric methods. Cooperation in the separation of HMPAO stereoisomers is progressing using modified crystallization method. The isolated compounds are analyzed using HPLC and compared with the HMPAO standard received from the IAEA (Vienna). Some isolated compounds evidently have similar chromatographic pattern with that of the HMPAO standard. Further investigation will be proceeded.

The CPZ cooperative program was rather unfortunately delayed due to the shipment of the compound. The compound was just recently used in experiment, and a preliminary report indicated that the absorption of the CPZ for molibdenum is very high, but the yield of technetium-99m was very low in 4 day observations (below 10%).

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Table 1. Production of Radioisotopes and Radiopharmaceuticals in 1997 and 1998. (By P.T. Batan Teknologi).

NO	PRODUCTS	TOTAL PRODUCTION		USERS
		1997	1998	
1	Mo-99 bulk	1.835 Ci	2.002 Ci	Domestic, Malaysia
2	I-131 bulk	368 Ci	307 Ci	Domestic, Malaysia
3	Ir-192 bulk	27.129 Ci	39.355 Ci	Domestic
4	Ir-192 sealed source	126 pcs [a)]	181 pcs [a)]	Domestic
5	Tc-99m Generator	449 pcs [b)]	333 pcs [b)]	Domestic
6	NaI-131 oral	106 Ci	75 Ci	Domestic
7	NaI-131 injection	2.85Ci	2.97Ci	Domestic
8	NaI-131 capsules	22 mCi	74 pcs @ 100 uCi	Domestic
9	I-131-Hippuran	3.8 Ci	5.5 Ci	Domestic
10	MDP Kit	524 single dose vials	1041 single dose vials	Domestic
11	DTPA Kit	264 single dose vials	775 single dose vials	Domestic
12	Zn-65-Piptag	100 pcs [c)]	500 pcs [c)]	Domestic
13	P-32 bulk	7.5 Ci	---	Domestic, China

Remarks : a). alternatively 70-80 Ci, 80-90 Ci or 90-100 Ci ^{192}Ir per piece
b). nominal of 200 mCi ^{99}Mo per generator.
c). 6 - 8 mCi ^{65}Zn per piece.

Table 2. Research topics on radioisotopes and radiopharmaceuticals carried out by RPC and RCNT during 1996 - 1998 *).

NO	RESEARCH TOPICS	REMARKS
1	^{125}I Production Technology	Preparation of ^{125}I from enriched ^{124}Xe
2	Development of 2-Steps-AFP IRMA Kit	Technology improvement
3	Preparation of HBsAg-^{125}I Tracer	Technology improvement
4	Preparation of Hepatitis C-RIA Kit	Technology improvement
5	Determination of Thallium in ^{201}Tl-Processing Waste	Recovery of enriched ^{203}Tl target from ^{201}Tl processing waste
6	Analysis of ^{89}Sr and ^{90}Sr in Fission-^{99}Mo Product by Cerenkov Method	Quality Control Improvement on Fission-^{99}Mo Product
7	Development and Manufacturing of Cyclotron Critical Components	Improvement in Cyclotron Technology
8	Effect of Co-ligands on the Quality of MDP Kit.	Alternative in Radiopharmaceutical Kit
9	Preparation of Immunoglobulin Kit and Labeling with ^{99m}Tc.	Alternative in Radiopharmaceutical Kit
10	Synthesis and Characterization of 3-Bromo-2,4,6-Trimethylacetanilido-imminodiacetic Acid	Alternative in Radiopharmaceutical Kit
11	In Vitro Test on the Biochemical Behaviour of ^{153}Sm-EDTMP Produced by RPC	Improvement of Radiopharmaceutical Preparations
12	Separation of Fission Produced ^{131}I and Its Utilization for Preparation of ^{131}I-Labelled Molecule	Improvement of Radioisotope and Radiopharmaceutical Preparations
13	Production of ^{99}Mo Using Low Enriched Uranium	Separation of fission produced radioisotopes using low enriched ^{235}U.
14	Synthesis and Characterization of MIBI and MAG-3 and Formulation as Radiopharmaceutical Kits	Alternative in Radiopharmaceutical Kit
15	Synthesis and Characterization of PETS, ESD and Pn(AO)$_2$ Ligand Compounds	Improvement of ligand compounds for Radiopharmaceutical Kits.
16	Synthesis and Characterization of Wolfram-Phtalocyanine	Target compound for primary radioisotope of ^{188}W.

Note : *). No. 1 to No. 14 were resumed from Annual Research Report of the Development Project on Radioisotope and Radiopharmaceutical Production Technology, RPC, BATAN, Fiscal Year of 1996/1997 to 1998/1999 [6]. No. 15 and No. 16 were performed in the RCNT, Bandung.

Table 3. Research and Development of Radioisotopes and Radiopharmaceuticals by CDRR and CRDNT in 1998-1999.

NO	PRODUCT OR RESEARCH TOPICS	APPLICATION OR PURPOSE	PRESENT STATUS
1	^{201}Tl-Chloride chemical aspects [7,8]	Diagnosis of cardiovascular disease	Produced on request
2	^{153}Sm-EDTMP various formulations [9]	Therapy of bone metastatic cancer	Produced on request
3	^{153}Sm-Hydroxyapatite/FHMA	Therapy of rheumatoid arthritis	Clinical test
4	Cerebroscan (HMPAO) Kit	Diagnosis of brain blood perfusion	Reproducibility of synthetic procedure
5	Renoscan (MAG_3) Kit [10,11]	Diagnosis of kidney filtration function	On stock
6	Cardioscan (MIBI) Kit [12]	Diagnosis of cardiac blood perfusion	On stock
7	Hepatitis C RIA Kit (^{125}I)	In-vitro diagnosis of Hepatitis C	Validation test
8	CEA and AFP RIA Kits (^{125}I)	In-vitro diagnosis of soft-tissue tumors	Validation test
9	HBsAg and Anti HBs RIA/ IRMA Kit (^{125}I).	In-vitro diagnosis of hepatitis B	Production and assay services on request
10	T3 / T4 /TSH RIA Kit (^{125}I)	In-vitro diagnosis of thyroid function	Produced on request
11	^{131}I-Lipiodol	Synergic therapy of hepatomas	Produced on request
12	^{111}In production technology	Primary radioisotope for medical purposes	Early experiment
13	^{188}Re production technology	Primary radioisotope for medical purposes	Early experiment
14	Recovery of ^{203}Tl and ^{235}U from post-production waste	Recovery of enriched target material	Reproducibility of process procedure
15	^{186}Re-HEDP/EDTMP	Therapy of bone metastatic cancer	Preliminary experiment
16	Synthesis, characterization and biological distribution of ^{99m}Tc-TADT	Radiopharmaceutical for brain imaging	Preliminary experiment
17	DMSA Kit (^{99m}Tc and ^{186}Re)	Diagnosis of medullar thyroid carcinoma	Biological distribution and clinical test

Table 4. Radioisotopes and Radiopharmaceuticals supplied by the CDRR in 1999 (January to October 1999).

NO	PRODUCT	TOTAL	USER		REMARKS
			MEDICAL	OTHERS	
1	$K^{131}IO_3$	72 mCi		X	Incidental
2	$K^{82}Br$	2.772 mCi		X	Incidental
3	^{198}Au foil	1.759 mCi		X	Incidental
4	$^{89}Sr(NO_3)_2$	47 mCi		X	Incidental
5	^{153}Sm-EDTMP	595 mCi	X		Frequently
6	^{131}I-Lipiodol	53 mCi	X		Incidental
7	$Na^{131}I$ oral solution	15 mCi	X		Incidental
8	Cardioscan (MIBI) Kit	101 vials	X		single dose vials, frequently
9	Renoscan (MAG_3) Kit	29 vials	X		single dose vials, frequently
10	^{86}Rb	12 mCi		X	incidental
11	^{41}Ar	10 Ci		X	incidental

Table 5. Strategic research programs anticipating the dynamics of demands on radioisotopes and radiopharmaceuticals.

NO	PROGRAMS	APPLICATIONS	COLLABORATION WITH	REMARKS
1	^{192}Ir-hair pin technology	Internal radiation cancer therapy	JAERI, Hasan Sadikin Hospital (Bandung)	Low Dose *in situ* therapy
2	^{111}In-production technology	Radionuclide for various tumors detection	University, Hospitals	Alternative radioisotope for ^{99m}Tc
3	^{166}Ho-production technology	Radionuclide for cancer therapy	GA Siwabessy Reactor	Alternative radioisotope for cancer therapy
4	$^{32}PCl_3$ production technology	Labeling of phosphor-containing biochemicals	University	Specific labeling of ATP, peptide
5	^{186}Re-Labeled Compounds (testosterone, MoAb, somatostatine, DMSA)	Mammae and prostate cancer therapy, early detection of cancer, neuroreceptor study	University, Hospitals, CRDNT (Bandung)	Alternative Radiopharmaceuticals
6	^{32}P-glass microsphere	Radiotherapeutic agent	JAERI	Hepatoma therapy
7	^{99}Tc-Tetrofosmine	Blood brain perfusion	JAERI	Synthesis and formulation
8	Synthesis of HMPAO	Ligand for brain-imaging radiopharmaceutical	JAERI	Separation of HMPAO isomers
9	^{123}I production technology	Medical radioisotope in neuroscience	--	Cyclotron product, better than ^{131}I
10	^{99}Mo production technology from LEU (^{235}U)	Production of fission-^{99}Mo	ANL ,USA	Replacement of HEU ^{235}U
11	^{32}P-labeled nucleotides	Biochemical studies	CRDNT (Bandung)	Specific labeling of biochemical compounds