INTERNATIONAL NUCLEAR SAFETY JOURNAL
vol.3 issue 2, 2014, pp.43-48

ISSN 2285 – 8717
ISSN–L 2248 – 8717
http://www.insj.info

DEVELOPMENT OF THE RADIOISOTOPE PRODUCTION TECHNOLOGIES AT THE WWR-M RESEARCH REACTOR

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Received: *7 April 2014*; accepted: *20 May 2014*

Abstract
The technological cycle was developed for the ^{99m}Tc-pertechnetate radiopharmaceutical (solution $Na^{99m}TcO_4$) by means of nuclear reactions $^{98}Mo(n,\gamma)^{99}Mo$. The description of the technological line on the WWR-M reactor and the hot-cells for the radionuclide generation and fabrication of the radioisotope production is presented. The scheme of centralized extraction generator is used for the radiopharmaceutical production from the irradiated targets when the methilentilketon is used as the extragent. The pilot lot of ^{99m}Tc-pertechnetate was produced. The results of investigations show the compliance of the radiopharmaceutical parameters with the requirements of normative documents for the treatment preparations. The production of closed radiation sources with ^{192}Ir is presented.

Keywords
research reactor, ^{99}Mo, ^{192}Ir, radiopharmaceuticals

1.Introduction

The radioisotope production making for the satisfaction of needs in the different application areas is a self-supporting well-developed branch of industry in the countries having the nuclear reactors and accelerators; this branch exists more than 50 years. More than 30 millions of medical treatments with radionuclides are carried out in the world annually. The most commonly used radionuclides are ^{99m}Tc (diagnostics) and ^{192}Ir (for brachiotherapy and industrial radiography).

This making is practically absent in Ukraine today since in the past in accordance with the "work distribution" between the nuclear installations in the former USSR such fabrication wasn't foreseen at the territory of Ukraine at all.

The country was provided by the radioisotope production by means of centralized supplies from other republics. Therefore, the sharp need is available in Ukraine now for the organization of domestic fabrication of radioisotope production instead of imported one. There are necessary technical capacities for the practical implementation of such fabrication. In particular, several installations are in operation in the Institute for nuclear research (Kiev), namely, the WWR-M research reactor, the cyclotrons U-240 and U-120, the processing lines of "hot-cells" for the remote treatment of high-active materials as well as the scientific departments equipped by the necessary radiometry and spectrometry devices with the high-skilled scientific and technical staff.

The research reactor WWR-M was designed and constructed in 1957-1960, the first criticality was achieved in February 1960. This is a heterogeneous water-moderated pool type research reactor operating with thermal neutrons at a power level of 10 MW_{th}, giving a maximum neutron flux of 1.5×10^{14} $cm^{-2}s^{-1}$ at the core centre. The reactor is equipped with 9 horizontal experimental channels, a thermal column, and 13 vertical isotope channels inside the beryllium reflector. Today the reactor is the operational installation; the INR is the reactor operator and possesses all necessary licenses and permissions for reactor operation.

The considerable experience of the reactor irradiations and the remote treatment of high-active materials was collected due to many-

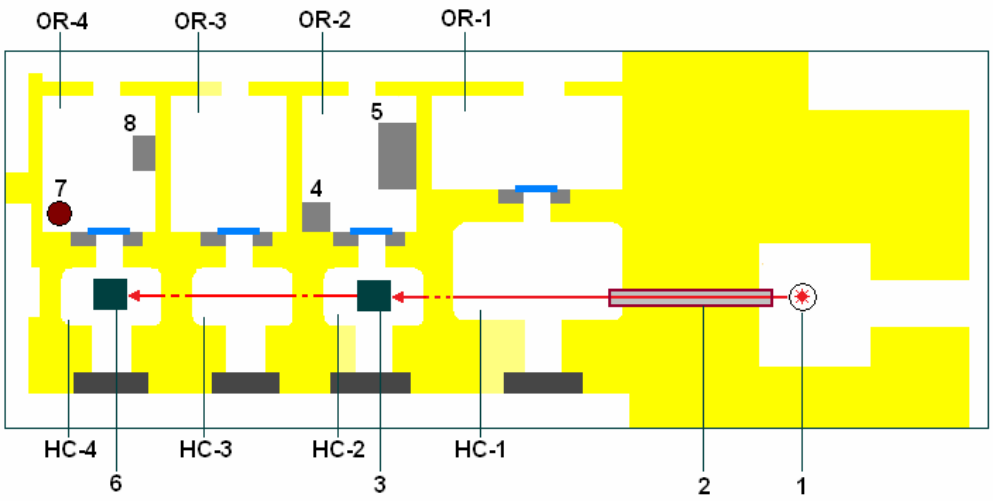

Figure 1. Layout of equipment for the radionuclide making: HC-1÷HC-4 – hot cells No 1÷4; OR-1÷OR-4 - operator room of hot cells No 1÷4; 1- irradiation position in the reactor core; 2 – transportation channel for irradiated samples; 3 - centralized extraction generator; 4 - control board; 5 - pre-packaging glove box; 6 – welding installation; 7 – vessel with inert gas; 8 - control board.

years scientific investigations on neutron physics [1] and radiation material study [2]; the necessary automatic tools and equipment was build. Now, the experience and technological elaboration of the radionuclide production and sample manufacturing [1, 3] are transferred successfully into technologies of experimental-industrial fabrication of the radionuclide products for the practical needs. These products include the closed sources of irradiation both the industrial and medical purposes as well as the preparations for different areas including the radiopharmaceutical for medicine.

This paper presents the development of stationary processing line for the series manufacturing of radiopharmaceutical ^{99m}Tc-pertechnetate (solution of $Na^{99m}TcO_4$) for the medical diagnostics and the radionuclide closed sources with ^{192}Ir for the industrial purposes.

2. Production of radiopharmaceuticals on the base of ^{99m}Tc

The radiopharmaceutical on the base of ^{99m}Tc is one of the most demanded one in the modern nuclear medicine. About 90% of all diagnostic procedures in the world are carried out by means of this radiopharmaceutical. The sort-lived radioisotope ^{99m}Tc ($T_{1/2}$ = 6,02 hours) is the daughter product at the beta-decay of ^{99}Mo ($T_{1/2}$ = 66 hours). The genetic pair ^{99}Mo/^{99m}Tc is the base for production of the sorption radionuclide generators [4], which are transported to the clinics and then the accumulated ^{99m}Tc is extracted by means of chemical methods immediately before the application.

The alternative of the traditional transport variant of the sorption generator was developed at the reactor WWR-M, when the final product for the clinic supplies is not a radioisotope generator, but the solution of $Na^{99m}TcO_4$, namely, the finished radiopharmaceutical prepared for application. The cycle of radiopharmaceutical fabrication is including the following technological stages:

- generation of the mother radionuclide ^{99}Mo in the reactor;
- treatment of irradiated target and extraction of ^{99m}Tc-pertechnetate from the mixture of ^{99}Mo and ^{99m}Tc;
- sterilization and prepackaging of the radiopharmaceutical (solution of $Na^{99m}TcO_4$);
- analysis of radiopharmaceutical (certification and preparation of quality certificate);
- packaging, dosimeter control and supply of ^{99m}Tc-pertechnetate to the clinics.

The relevant technological lines on the base of unified technical complex “Reactor – Hot cells” were constructed (Fig.1). This complex, besides the reactor, is including 4 boxes of the reactor’s “hot-cells” and 8 boxes of the material testing “hot-cells”.

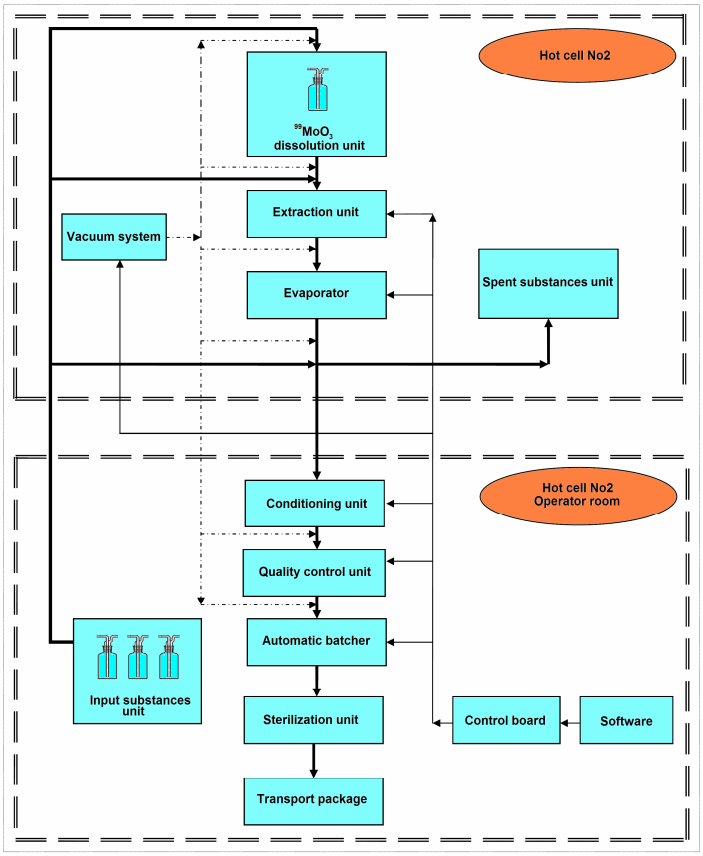

Figure 2. Scheme of centralized extraction generator

The accumulation in the reactor of ^{99}Mo, which will be used as the output radionuclide for the fabrication of radiopharmaceutical, is carried out by means of nuclear reaction ^{98}Mo(n,γ)^{99}Mo→^{99m}Tc in the irradiated $^{98}MoO_3$ target having the enrichment on ^{98}Mo up to 98.5% (target ^{99}Mo). This method has several advantages in comparison with the prevalent one, which is based on the ^{99}Mo extraction from the mixture of fission fragments from ^{235}U (fragment ^{99}Mo) after irradiation of uranium target. First of all, the target ^{99}Mo provides the high radionuclide purity of the prepared ^{99m}Tc-pertechnetate since the possibility of contamination of the radiopharmaceutical by the radiotoxic admixtures (such as ^{131}I, ^{103}Ru, ^{95}Zr etc.) is excluded. Moreover, the technology of fragment ^{99}Mo production creates the big amount of high-active waste (including the alpha-emitters) and this waste should be immobilized. This leads to the significant complication and cost growth of this part of technological cycle taking into account the modern requirements to the solution of ecological problems. At the same time, the production of the target ^{99}Mo allows to organize the practically wasteless technology.

The most suitable scheme of centralized extraction generator, in which the methilentilketon (MEK) is used as the extragent, was selected for the radiopharmaceutical production from the irradiated molybdenum targets. The extraction of ^{99m}Tc-pertechnetate from the solution of ^{99}Mo/^{99m}Tc is carried out by means of MEK with the subsequent evaporation and dissolution of solid residual in the 9% solution of sodium chloride (NaCl). The scheme of technological cycle for the production of ^{99m}Tc-pertechnetate radiopharmaceutical is shown on Figure 2.

The target irradiation (reactor area) is carried out in the vertical experimental channels inside the reactor core [5, 6]. All operations with the irradiated targets are executed by means of remote tools; the container-opener machine is located in the hot cell No 1. The fully automated process is carried out by means of special software under a management of com-

puter. This allows avoiding an unnecessary exposure of the staff during the radiation-dangerous works. In accordance with the results of individual dosimetry control, the dose load is a minimal and doesn't exceed the established control levels [7].

Main equipment of the centralized extraction generator (the extraction column, the evaporator, the refrigerator, the electromagnetic valves etc) and the detector of radiometer installation for the measurements of ^{99m}Tc activity inside the evaporator are assembled directly in the protective box of the hot cell No2.

The auxiliary equipment for the transportation of solutions and operation of whole system (the micro-pump, the thermostat, the power supply unit of electromagnetic valves, and the control panel of auxiliary equipment) is assembled in the operator room (outside the box) with the aim of maintenance simplicity.

The sterilization and pre-packing area is located in the operator room too inside the glove box. This box contains the germicidal lamp and the packing block. The sterilization of obtained solution is carried out by the bacterial filtration in the aseptic conditions using the membrane filters. The solution is pre-packaged into the medical rolled sterile vacuum-processed flasks by means of the special syringe (Fig.3).

Figure 3. Delivery set of the ^{99m}Tc-pertechnetate: the flask with the solution of $Na^{99m}TcO_4$ and the transport container (encasement and cover).

The centralized extraction generator with the centrifugal extractor has provided to realize a following:

- the possibility to use ^{99}Mo in the broad range of activity both the "fission" and "activated" Molybdenum;
- the absence of complicated operations at the reloading;
- the obtaining of high-purity ^{99m}Tc without an inorganic admixtures;
- the obtaining of the ^{99m}Tc solution with the pre-arranged high volume activity;
- the absence of the Molybdenum loss, which is especially important at the work with enriched ^{98}Mo.

The sample of MoO_3 (98% enrichment on ^{98}Mo) is irradiated during 100 hours. The activation method for the obtaining of ^{99}Mo as well as the preliminary preparation of initial stable Molybdenum sample leads to the complete exception of possibility for the origin of ^{90}Sr, ^{95}Zr, ^{131}I and α-emitters, which are presented necessarily in the "fission" ^{99m}Tc. This provides the radionuclide purity of the eventual product. The content of non-active admixtures is practically negligible; the content of organic admixtures is minimized due to use of the centrifugal extractor, where the total time of contact between phases doesn't exceed a few minutes. The quality parameters of eventual product are presented in Table 1.

Table 1. The quality parameters

Parameter	Value
Volume activity (GBq/ml)	0.74÷2.96
Radiochemical purity (%)	≥ 99.2
Radionuclide admixtures (in % to ^{99m} Tc activity)	≤ 0.001
Other γ-emitters (%)	≤ 0.00003
pH	5÷ 7
Concentration of NaCl (g/l)	8.9
Concentration of MEK (mg/ml)	≤ 0.01

The pilot lot of the ^{99m}Tc-pertechnetate was produced. This radiopharmaceutical (the solution of $Na^{99m}TcO_4$ in the rolled sterile flasks with the activity of 96.0 MBq for 5 ml) was tested in the pre-clinical investigations on the animals in the Institute of oncology of Academy of Medical Sciences of Ukraine [8]. The results of investigations show the compliance of the radiopharmaceutical parameters with the requirements of normative documents for the treatment preparations.

The use of radiopharmaceutical from the centralized extraction generator leads to the absence of any kinds of radioactive waste in the clinics. All inevitable high-active waste is remaining on the reactor, which is equipped by the special technical base for the radwaste collection and storage. This allows avoiding the

problems in the clinics with the storage of residual activity after the utilization of the sorption generator and additional expenditures for the return of spent generator to the producer.

The unutilized stable molybdenum is remaining at the reactor after the treatment of irradiated target. This provides the possibility of its regeneration from the used solutions for the repeated irradiations. The regeneration allows a significant decreasing of the final product cost, especially, in the case of the enriched molybdenum targets.

Currently it is planned that the stationary technological line for the production of sterile $Na^{99m}TcO_4$ solution, which is in operation at the WWR-M reactor, will provide by the ready radiopharmaceutical all medical institutions (clinics) in Kiev and neighbor regions. It is important that the $Na^{99m}TcO_4$ solution, which was obtained from the target ^{99}Mo on the centralized extraction generator, has a higher quality in comparison with the similar solution, which was obtained from the fragment ^{99}Mo on the sorption generator [9]. Moreover, each set of the fresh radiopharmaceutical from the centralized extraction generator is certified before the supply, while the eluate, which is washed periodically from the sorption generators directly in the clinics, isn't a subject of daily control. Furthermore, the time of the sorption generator loading has an important mean, since the generator useful life is limited by two weeks when the washing of ^{99}Mo to the eluate begins. Finally, the use of fresh radiopharmaceutical from the centralized extraction generator decreases the dose load on the patients and medical staff.

3. Production of radioactive sources with ^{192}Ir

Another important radionuclide for the nuclear medicine and industry is ^{192}Ir ($T_{1/2}$ = 74 days). The power sources with the activity in the range 3÷9 TBq are required for the industrial defectoscopy. The production of ^{192}I is realized by means of irradiation of the Iridium target in the reactor core as a result of reaction $^{191}Ir(n,\gamma)^{192}Ir$. The container for irradiation of Iridium samples is shown on Fig.4.

An essential problem at the manufacturing of such sources is the provision of reliable sealing of ^{192}Ir (operating part), which prevent the contact with environment during the operation life of source. For this goal it was constructed and assembled the automatic installation for the encapsulating of radioactive substance. This installation provides the remote welding of capsules made from the stainless steel (diameter of 5÷6 mm; height of 6÷7 mm) destined for utilization in the industrial serial defectoscope of "Gammarid" type.

Figure 4. Container for irradiation.

The technology of TIG- welding (TIG – Tungsten Inert Gas) is applied in the installation, when the welding is performed by the infusible tungsten electrode in the atmosphere of protective inert gas (argon). The general view of installation is shown on Figure 5 and technical parameters are presented in Table 2.

Figure 5. Welding installation.

Table 2. Technical parameters

Parameter	Value
diameter of juncture, mm	4 - 20
welding position	bottom
lowering/lifting	pneumatic
hold	mechanical clip
welding current, A	8 - 160
welding rate, mm/s	0 - 10
welding tool cooling	air
compressed air pressure	>0,4

The remote operation of the installation mechanisms is carried out be means of pneumatic unit. The sequence of welding operations is a following: 1) the assembling of capsule with the radioactive substance on the rotating face-plate; 2) the welding tool lowering to the juncture starting position; 3) the electric arc kindling at the nonmoving capsule; 4) the capsule rotation with the established speed; 5) the juncture covering; 6) the crater welding; 7) the welding tool lifting; 8) the rotating face-plate return into initial position.

- the welding installation provides the following:
- the automatic control of all mechanisms and tools together with their diagnostics;
- the readiness cheackout, the control of welding tool position and the air pressure measurements;
- the execution of welding operations;
- the setup of welding regimes and the modulating regulation of the face-plate rotation.

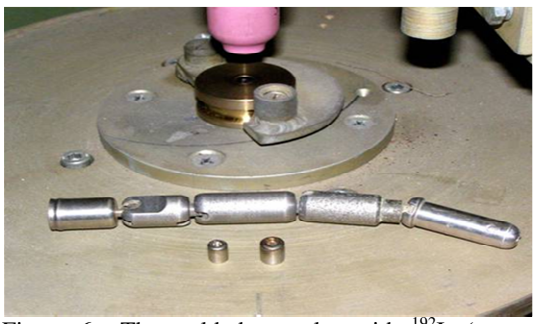

Figure 6. The welded capsules with ^{192}Ir (on a foreground) and technological chain of the "Gammarid" defectoscope.

The welded capsules with ^{192} Ir are shown on Figure 6. The trial runs have confirmed the automatic TIG- welding capabilities, when the welding is possible without any adding materials.

4. Conclusion

The stationary technological line for the production of sterile solution of $Na^{99m}TcO_4$ was commissioned at the reactor. This radiopharmaceutical will be supply to the medical institutions (clinics) in Kiev and neighbor regions. The selected scheme of centralized extraction generator provides advantages in comparison with the sorption scheme.

The technology for the closed radiation sources with ^{192}Ir production was tested. The remote welding of capsules is used for the manufacturing of operating parts of the industrial defectoscopes.

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