TECHNOLOGY FOR PRODUCTION OF PORTABLE TC-99M GEL GENERATORS USING NEUTRON ACTIVATED NATURAL MOLYBDENUM ALMATY, REPUBLIC OF KAZAKHSTAN

E. CHAKROVA, V. BANNYKH, P.CHAKROV, V. KUTEPOV, I. FETSSOV
INSTITUTE OF NUCLEAR PHYSICS, ALMATY, REPUBLIC OF KAZAKHSTAN

1. INTRODUCTION

Development of the ^{99m}Tc production technology at the Institute of Nuclear Physics was started in 1998 after re-commissioning of the WWR-K research nuclear reactor. Different types of alternative (non-fission) methods for ^{99m}Tc generator production such as: classic chromatographic, solvent extraction, sublimation and zirconium polymolybdate gel were studied. The gel method was chosen as the most promising for small-scale production both ready to use ^{99m}Tc solution and portable ^{99m}Tc gel-generators [1].

The basic concept of ^{99m}Tc gel generators consists of the direct transfer of ^{99}Mo with low specific activity into an insoluble zirconium molybdate gel that contains app. 25 wt. % of molybdenum and allows retaining the advantages of ease and reliability of column chromatography generators. The zirconium molybdate gel is predominantly a cation exchanger with an open structure which allows free diffusion of pertechnetate anion under simple elution by saline [2, 3].

For production of the central type of ^{99m}Tc gel generators, the irradiated molybdenum oxide is dissolved in 2N sodium hydroxide solution with adding of a few drops hydrogen peroxide, then formed sodium ^{99}Mo-molybdate is converted into sodium ^{99}Mo-polymolybdate by adding 3M nitric acid, pH 4.0- 4.5. Zirconium ^{99}Mo-polymolybdate gel (^{99}Mo-Zr gel) is synthesized by reaction of sodium ^{99}Mo-polymolybdate with $ZrOCl_2*8H_2O$ solution. After adjustment of pH to 4.5 with 2N sodium hydroxide, the solution gel was stirred slowly and precipitated during 30 min. After precipitation, the zirconium polymolybdate gel is filtered, dried, decrepitated by cool water, washed with saline and used as a matrix for elution of ^{99m}Tc by saline.

Both standard and unique specially designed and fabricated equipment were used for production. The standard equipment as peristaltic pumps, air compressor, and vacuum pumps with remote control are used for transferring solutions slurry and supplying compressed air and vacuum. For filtration, drying, disintegration of dried gel, washing and elution was fabricated a special unit that allows avoidance of radioactive dust formation during the process.

^{99}Mo was produced by irradiation of natural molybdenum oxide powder sealed in quartz ampoule in the WWR-K reactor during 120 hours at thermal neutron flux $1.1 \cdot 10^{14}$ $n \cdot cm^{-2} \cdot c^{-1}$. Specific activity was 0.5 – 0.8 Ci/g and about 40% of total ^{99}Mo activity produced due to epithermal neutron.

The main goal of the presented work is development technology for production of portable ^{99m}Tc gel-generators using existing experience in production of the central type of gel generators at the Institute of Nuclear Physics, Almaty and supplying ready to use ^{99m}Tc solution to local hospitals.

2. DEVELOPMENT OF THE DESIGN OF THE PORTABLE TC-99M GEL-GENERATOR SYSTEM

For development of the design of the portable ^{99m}Tc gel-generator system the model of Mo-Zr gel was prepared. For synthesis of gel we use alkaline solution of non-active sodium molybdate with adding of 0.5GBq of ^{99}Mo.

2.1. DETERMINATION OF OPTIMAL DESIGN OF THE GEL COLUMN

As was defined from previous investigations, the gel column for portable gel generators could contain 4 to 6 g of gel. For determination of the optimal design of the gel column, the ^{99m}Tc elution curve was studied using three kinds of model columns. For that purpose the columns with different d/h ratio were prepared. The exact size of columns used for experiments are shown in Table 1.

TABLE 1. DIMENSION OF GEL COLUMNS

№	Column diameter, (d, mm)	Column height, (H, mm)	Gel layer height (5 g of Mo-Zr gel), (h, mm)	Ratio d/h
1	12	30	25±2	0,4
2	15	30	17±2	0,9
3	20	25	10±2	2,0

For all experiments, 5 g of gel with approximately 50 MBq of ^{99}Mo was loaded in each column. Then columns were eluted with 10 ml of saline by 2 ml portions. Activity of ^{99m}Tc was measured on gamma spectrometry system "Eurisys Mesures" with HPGe detector. Elution curves of ^{99m}Tc for column with different d/h ratio are presented in Fig. 1.

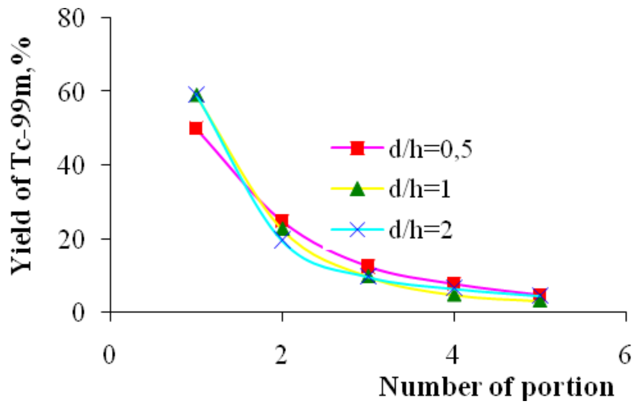

FIG.1. ^{99m}Tc elution curves from gel columns with different d/h ratio.

Elution experiments show that 50 – 60 % of ^{99m}Tc was eluted in the first 2 ml portion and up to 90 % in 5 ml of saline. Besides, the shape of columns doesn't exert significant influence on elution of ^{99m}Tc. It allows choosing a column where the d/h ratio is equal 0,5 to minimize in future the weight of lead shielding of the generator.

2.2. DETERMINATION OF DIMENSIONS FOR ADDITIONAL ALUMINA COLUMN

For purification of eluted ^{99m}Tc solution from ^{99}Mo, non-active molybdenum and other chemical impurities, the portable gel generator should contain in addition to the gel column a safety alumina column. Sufficient amounts of alumina and the dimensions of the additional column were determined experimentally. Sorption of molybdenum was studied with using a model solution (0.1 MBq/ml of ^{99}Mo, 20 μg/ml of Mo^{6+}). The content of non-active molybdenum was measured by ICP atomic-emission spectroscopy and ^{99}Mo - γ-spectrometry system with HPGe detector. Analysis of experimental data shows that column 1.5 g of alumina allows to clean ^{99m}Tc solution eluted from gel column and content of molybdenum is not more than 0,06 μg/ml and ^{99}Mo not more 0,001%. The proposed size for safety column is 8 mm diameter and 40 mm height.

2.3. DETERMINATION OF LEAD THICKNESS FOR PORTABLE GEL GENERATOR SHIELDING

For determination of lead thickness for gel generator shielding the dose rate of gamma emission from a model gel generator with 15 GBq of ^{99}Mo was calculated. Geometry for calculation is presented in Fig. 2.

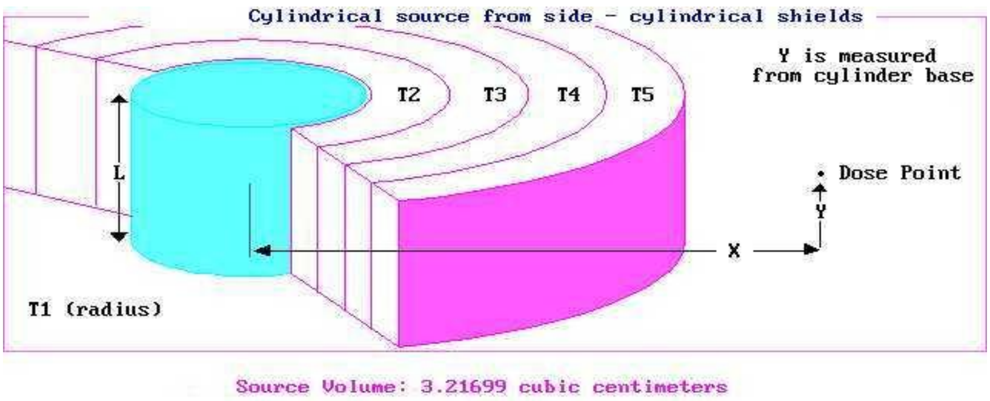

FIG. 2. Geometry for calculation of dose rate from packing surface of 15 GBq gel generator, where L - height of lair of gel in the column; T1 – internal radius of column; T2 – thickness of glass of gel column; T3 –lair of air; T4 - thickness of lead; T5 - thickness of steel packing; X – distance from center of column to point of dose rate calculation.

The calculation results (relation of roentgen-equivalent-man, mRem/h from lead thickness of shielding, sm) are shown in Fig. 3 and 4.

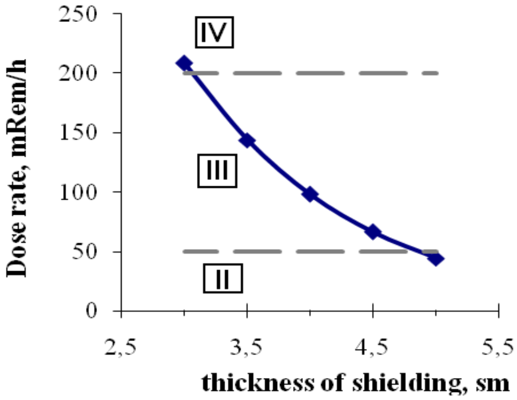

FIG.3. 40 sm from outside surface of packing. II, III, IV - permissible dose rate from packing of radioactive material for different transportation categories according to local requirements.

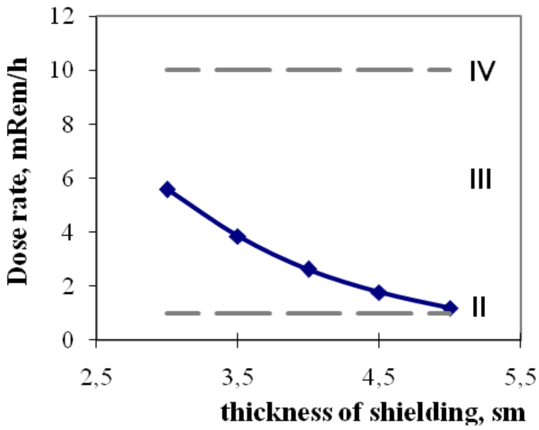

FIG. 4. 1m from outside surface of packing. II, III, IV - permissible dose rate from packing of radioactive material for different transportation categories according to local requirements.

The more reasonable thickness of shielding is between 3.2-4.8 sm of lead. If thickness of shielding is 3 sm or lower, the packing category will be IV and in this case we need specially conditioned transport, and if thickness of shielding is 5 sm or higher the packing will be too heavy.

The calculated dose rate from 15 GBq generators with 4 sm lead shielding are shown in Tables 2 and 3.

TABLE 2. CALCULATED DOSE RATE OF GAMMA EMISSION FOR 15 GBq GEL GENERATOR WITH 4 sm OF LEAD SHIELDING AT THE SURFACE OF PACKING (DIAMETER OF PACKING 40 sm)

Group #	Energy (MeV)	Activity (photons/sec)	Dose point flux MeV/sec/sq. cm	Dose rate (mr/hr)
1	.820	1.997e+07	4.953e+02	9.917e-01
2	.773	6.720e+08	1.382e+04	2.797e+01
3	.742	1.920e+09	3.338e+04	6.801e+01
4	.680	3.876e+07	4.760e+02	9.835e-01
5	.367	2.054e+08	4.431e+00	9.116e-03
6	.180	9.350e+08	3.093e-19	5.557e-22
7	.133	5.683e+08	2.239e-54	3.693e-57
TOTALS:		4.360e+09	4.817e+04	9.796e+01

TABLE 3. CALCULATED DOSE RATE OF GAMMA EMISSION FOR 15 GBq GEL GENERATOR WITH 4 sm OF LEAD SHIELDING AT THE 1 m DISTANCE FROM SURFACE OF PACKING

Group #	Energy (MeV)	Activity (photons/sec)	Dose point flux MeV/sec/sq. cm	Dose rate (mr/hr)
1	.820	1.997e+07	1.329e+01	2.661e-02
2	.773	6.720e+08	3.708e+02	7.503e-01
3	.742	1.920e+09	8.953e+02	1.825e+00
4	.680	3.876e+07	1.276e+01	2.638e-02
5	.367	2.054e+08	1.186e-01	2.441e-04
6	.180	9.350e+08	8.328e-21	1.497e-23
7	.133	5.683e+08	6.139e-56	1.013e-58
TOTALS:		4.360e+09	1.292e+03	2.628e+00

The calculated dose rate at the packing surface is 100 mP/h and at the 1 m distance from surface of packing - 2.6mP/h.

3. MODERNISATION OF THE EXISTING PROCESS INSTALLATION FOR ^{99}MO-ZR GEL PREPARATION

Estimated batch size of the portable gel generators is 20 generators. For loading 20 generators with gel we plan to produce 100 g of dry ^{99}Mo-Zr gel. For developing synthesis technique we used existing pilot installation for production of gel in laboratory conditions. The technological scheme of it is presented in Fig. 5. Vessels for gel synthesis (pos.1, Fig. 5) and filtering-drying (pos.2, Fig. 5) were prepared anew.

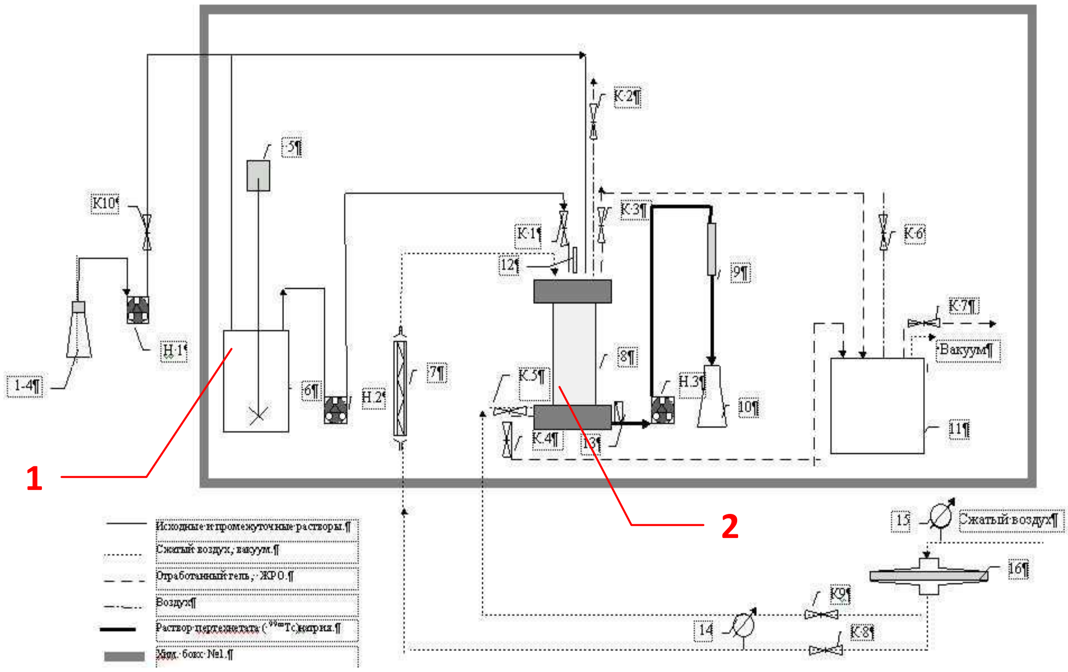

FIG. 5 Technological scheme.

As a row materials for pilot gel production, 40 g of non-irradiated molybdenum oxide (MoO_3) and 112 g of zirconium oxychloride ($ZrOCl_2$*$8H_2O$) were used. After dissolution the molybdenum oxide in 2N sodium hydroxide, the spike of 200 MBq ^{99}Mo was added.

The formed sodium ^{99}Mo-molybdate was converted into sodium ^{99}Mo-polymolybdate by adding 3M HNO_3 up to pH 4.0- 4.5. Zirconium ^{99}Mo-polymolybdate gel is synthesized by reaction of sodium ^{99}Mo-polymolybdate with $ZrOCl_2$*$8H_2O$ solution. After adjustment of pH to 4.5±0.2 with 2N NaOH, the gel was stirred slowly and precipitated during 40 min.

After precipitation, the zirconium ^{99}Mo-polymolybdate gel was transferred by peristaltic pump to the "filtration-drying" vessel for filtration and drying by hot air flow. After drying, the gel was washed and crushed by cool water. Washing is repeated three times with 0.9 % saline.
Chemicals needed for production of 100 g ^{99}Mo-Zr gel:

- 40 g MoO_3 irradiated in sealed quartz ampoule during 72 -200 hours at the thermal neutron flux of $1.1x10^{14}$ $n{\cdot}cm^{-2}{\cdot}s^{-1}$.
- 112 g $ZrOCl_2$*$8H_2O$ (water solution with pH 1.5 adjusted by sodium carbonate), 2N NaOH, 3N HNO_3, H_2O_2, DD water, 0.9 % NaCl.

Drying of gel was carried out during 4 hours at a temperature not higher 100ºC.
Full synthesis time from Mo dissolution to washing of dried gel was ~12 hours. The most critical step for synthesis is drying (~4 hours) of the gel.

4. DEVELOPMENT TECHNIQUE FOR FILLING OF GEL-GENERATOR COLUMNS WITH ^{99}MO-ZR GEL

Procedure of loading of gel generators consist of the next steps: remote transportation of ^{99}Mo-Zr gel from production to filling unit, filling of column with ^{99}Mo-Zr gel, washing, sealing and sterilization of filled columns.

To select optimal transportation and filling techniques two experimental installations were made and a study of “dry” and “wet” filling was done.
For “dry” filling of ^{99}Mo-Zr gel to portable generator columns we used installation shown on Fig. 6.

Dry ^{99}Mo-Zr gel from production unit (1) was transferred by compressed air (overpressure of air was changed from 0.1 to 0.8 atm.) to the dispensing vessel (2). Excess of air after passing filter (3) and safety water vessel (4) is released through ventilations system. Proportioning valve of filling unit allowed filling column with gel by portions with exact volume. Then mass of gel in each column was checked by weight and uncertainty of filling came to 5-8%.

The results of 3 series of experiments show that gel was transferred fully and quickly using compressed air; however, loss of dry gel on filter was 15-40%.

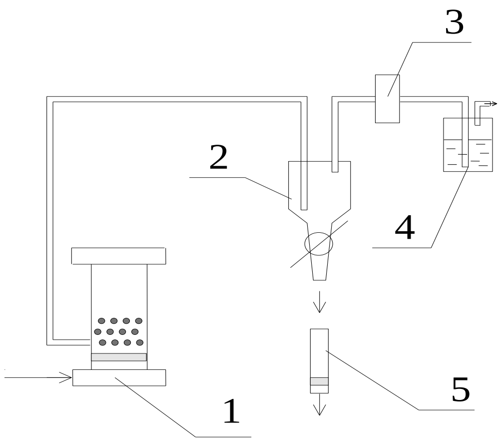

FIG.6. Installation for “dry” column filling with ^{99}Mo-Zr gel, where: 1. ^{99}Mo-Zr gel production unit;2. Dispensing vessel; 3. Dust filter; 4. Safety water vessel; 5. Column of portable gel generator.

For “wet” filling of ^{99}Mo-Zr gel to portable generator columns we used installations shown on Fig.7.

Suspension of ^{99}Mo-Zr gel in saline solution formed by compressed air was transferred by peristaltic pump from production unit (1) to the dispensing vessel (2). Excess of air after passing filter (3) and safe water vessel (4) is released through ventilations system. Proportioning valve of filling unit allowed filling column with gel consecutively by portions with exact volume. Excess of saline after filling of column was evacuated by vacuum.

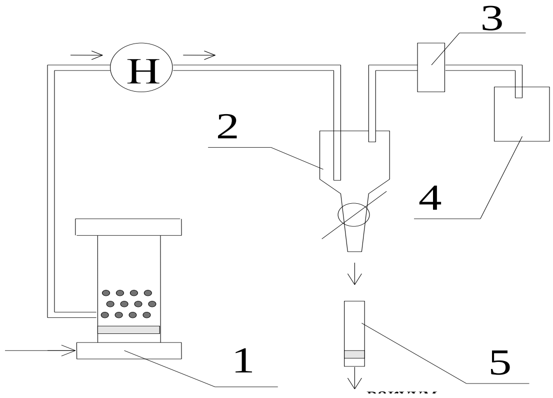

FIG.7. Installation for "wet" column filling with ^{99}Mo-Zr gel, where: 1. ^{99}Mo-Zr gel production unit; 2. Dispensing vessel; 3. Dust filter; 4. Safety water vessel; 5. Column of portable gel generator; H - Peristaltic pump.

Besides consecutive filling of the columns, we studied the possibility to fill sets of 5 columns simultaneously through a special dispenser. The results of these experiments show that suspension of gel was not fully transferred by peristaltic pump and losses of the gel in production unit and on filter were 20%. After drying of gel in the columns, as before the mass of gel in each column was checked by weight and uncertainty of consecutively filling came to 10% and of simultaneous filling came up to 40%.

After comparison data from "dry" and "wet" filling, we designed and made a working model of new equipment that combines the process of final preparation of ^{99}Mo-Zr gel (filtration, drying, washing) and column filling. That technical solution allowed avoiding the process of transferring gel from the production unit to the filling unit. Design drawing and working model of new "production-filling" unit is shown in Fig. 8. Besides equipment for ^{99}Mo-Zr gel preparation (Fig. 9), columns filling, crimping and sterilisation were done.

Equipment shown on Fig. 8 was used for:

- filtration (0.5 hour, pressure, vacuum);
- the first drying (compressed air, 4 hours, ≤100ºC);
- washing/disintegration (cool water, 150 ml, 3-10ºC, saline 150 ml);
- the second drying (compressed air, 0,5 hour, ≤100ºC).

For filling of the gel generator columns with dried ^{99}Mo-Zr gel, the same module after rotation on 180°.

Equipment shown on Fig. 9 was used for following technological steps:

- dissolution of irradiated MoO_3 (2M NaOH, H_2O_2; heating);
- synthesis of sodium polymolybdate (3M HNO3; pH 4-5; stirring);
- synthesis of zirconium polymolybdate (ZrOCl2, 5-7% solution; pH 4,5; stirring);
- precipitation (30 min, without stirring).

FIG.8. Beaker for synthesis of ^{99}*Mo-Zr gel.*

FIG.9. Equipment for filtration, drying and filling of dried gel granules.

5. PRODUCTION AND QUALITY CONTROL OF COLD PILOT BATCHES OF GEL-GENERATOR

Pilot ^{99m}Tc gel-generator assemblies (lead shielding, set of needles and columns) were designed and manufactured. A general view of an experimental gel-generator is shown in Fig. 10. A pilot batch of ^{99m}Tc gel-generators was produced in hot laboratory conditions using natural molybdenum oxide spiked with 3 MBq ^{99}Mo.

FIG.10. General view of experimental ^{99m}Tc *gel-generator.*

Each generator was eluted with 10 ml saline and the ^{99m}Tc solution was examined according to quality control flow chart.

Quality parameters of the ^{99m}Tc solution from the experimental ^{99m}Tc gel-generators are shown in Table 4.

TABLE 4. QUALITY PARAMETERS OF THE TC-99M SOLUTION

N	Quality parameter	^{99m}Tc solution
1.	Radioactivity concentration, kBq/ml	3-3,3
2.	Radionuclide impurities, %:	
	^{99}Mo	≤0,01
	other gamma emitters	≤0,001
3.	Radiochemical purity, %	99,3 - 99,9
4.	pH	5,4 ÷ 6,6
5.	Concentration of NaCl, μg/ml	8,5-9,2
6.	Major chemical impurities, μg/ml:	
	Mo	0,03-0,1
	Al	0,02-0,06
	Zr	≤0,1
7.	Other chemical impurities, As, Hg, Ba, Sn, Be, Cr, Cd, Sb, Ni, Te, Zn, Bi, Cu, Fe, Mn, Pb	Below the detection limits

6. DESIGN, PRODUCTION AND INSTALLATION EQUIPMENT FOR INDUSTRIAL PRODUCTION OF PORTABLE TC-99M GEL-GENERATORS

Generators were received from India's Board of Radiation and Isotope Technology. Each generator was checked and prepared for further work. All generator assemblies were high-quality and worked properly. General view of "Geltech" generator assembly is shown in Fig. 11.

FIG. 11 "Geltech" generator assembly.

Loading/unloading system of hot cells doesn't allow moving "Geltech" generators into the hot cell for loading columns with ^{99}Mo activity into the generator. Therefore, the reloading containers with 40 mm lead for transportation of ^{99}Mo-Zr gel columns from hot cell to the gel-generator containers and lifting mechanism to move the reloading container were designed and fabricated. Besides the "Laminar clean module" for assembly of the ^{99m}Tc gel-generators was installed near the production hot cells.

A gel-generator column filled with ^{99}Mo-Zr gel and reloading containers for filled columns are shown in Fig.12-13.

FIG.12. Column of ^{99m}Tc gel-generator with ^{99}Mo-Zr gel.

FIG. 13. Reloading container for transport of column with ^{99}Mo-Zr gel.

More than 10 experimental batches of ^{99m}Tc gel-generators were produced using new equipment and "Geltech" generator assemblies as well as quality of ^{99m}Tc solution was checked during two weeks. The 1uality of the ^{99m}Tc solutions meets the requirements of the Kazakh Pharmacopeia.

The photo of the experimental assembling of ^{99m}Tc gel-generators in the "Laminar clean module" and ^{99m}Tc gel-generators with a set of evacuated vials and vials with saline are shown in Fig.14 and 15.

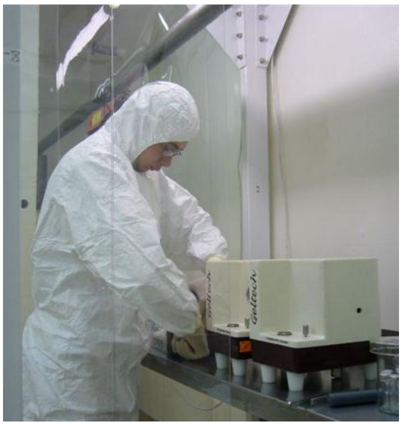

FIG. 14. Experimental assembling of ^{99m}Tc gel-generators in "Laminar clean module".

FIG. 15. ^{99m}Tc gel-generator with set of evacuated and saline vials.

Quality parameters of the radiopharmaceutical "Sodium pertechnetate ^{99m}Tc, solution for injections" from experimental portable generators are presented in comparison with the quality parameters of the radiopharmaceutical "Sodium pertechnetate ^{99m}Tc, solution for injections" from the central type generator in Tables 5 and 6.

TABLE 5. QUALITY PARAMETERS OF RADIOPHARMACEUTICAL «SODIUM PERTECHNETATE TC-99M, SOLUTION FOR INJECTIONS» FROM PORTABLE AND CENTRAL TYPE OF TC-99M GEL-GENERATOR

Quality parameter	Pharmacopoeia Monograph (42- 930-2006)	Central type of ^{99m}Tc gel-generator (2001-2010)	Portable generator (12 batches)
Color	Colorless	Colorless	Colorless
Mechanical inclusions	Not identified	Not identified	Not identified
Content of NaCl, mg/ml	8 - 10	8.8 - 9.2	8.9 - 9.3
Volume activity, MBq/ml	≥17	130-2200	170-2875
Nominal volume, ml	10	1 - 10	10
pH	4.0 – 7.0	6.0 - 7.0	6.0 - 7.0
Percentage:			
^{99}Mo, %	≤ 0.02	Not identified	Not identified

Other gamma-impurities, %	≤0.002	0.00002 – 0.00008	0.00003 – 0.00005
Radiochemistry purity, %	99.9	99.1-99.9	99.2-99.9
Sterility	Sterile	Sterile	Sterile

The level of chemical impurities was measured by atomic emission spectrometry with inductively coupled plasma and results are shown in Table 6.

TABLE 6. LEVEL OF CHEMICAL IMPURITIES OF «SODIUM PERTECHNETATE TC-99M, SOLUTION FOR INJECTIONS" FROM PORTABLE AND CENTRAL TYPE OF GEL GENERATORS

Micro impurities, ppm	Ph. Monograph (42- 930-2006)	Ph. Monograph (42- 930-2011)	Central type of ^{99m}Tc gel-generator (2001-2010)	Portable generator (9 batches, 2010-2011)
Al	2.0	2.0	0.001 - 0.1	0.001 - 0.05
As	1.0	1.0	<0.005	<0.005
Ba	0.1	0.5	0.026 - 0.085	0.052 - 0.167
Be	0.005	-	<0.00005	<0.00005
Bi	0.1	-	<0.0002	<0.0002
Cd	1.0	1.0	<0.0002	<0.0002
Cr	0.1	0.1	< 0.0005	< 0.0005
Cu	0.05	0.05	< 0.0005	< 0.0005
Fe	0.25	0.25	<0.005	<0.005
Hg	2.5	-	<0.0001	<0.0001
Mn	0.01	0.03	0.005 - 0.092	0.005 - 0.015
Mo	5.0	5.0	0.005 - 1.0	0.005 - 0.182
Ni	0.1	0.1	0.008 - 0.075	0.025 - 0.082
Pb	0.1	0.2	0.05 - 0.95	0.03 - 0.09
Sb	1.0	1.0	<0.0002	<0.0002
Sn	0.1	0.1	<0.0005	<0.0005
Zn	2. 5	2. 5	0.284 - 0.690	0.315 - 0.805
Zr	5.0	5.0	<0,0002	<0,0002

7. CONCLUSIONS

During 2007-2011, the technology for production of ^{99m}Tc portable gel generators using (n, γ) ^{99}Mo with low (0,8-1,5 mCi/g) specific activity was developed. High quality radiopharmaceutical “Sodium pertechnetate solution ^{99m}Tc for injection” from central and portable gel generators was registered certified and permitted for using in medical hospitals.

REFERENCES

1. BOYD R.E., “The gel generator option: available alternative source of technecium-99m for nuclear medicine, Appl.Radiat.Isot. Vol. 48(1997), 1027-1033.
2. “Production technologies for molybdenum-99 and technetium-99m”, IAEA-TECDOC-1065, 1999.
3. SARASWATHY P, SARKAR SK, PATEL RR, ARORA, SS, NARASIMHAN, DVS, RAMAMOORTHY N, “Evaluation of preparation and performance of gel column ^{99m}Tc generator based on zirconium molybdate-^{99}Mo”, IAEA-TECDOC-1029. 1999; 385-398.