$^{188}W/^{188}Re$ GENERATOR: FOR NUCLEAR PHARMACY OR FOR HOSPITAL USE?

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$^{188}W/^{188}Re$ generators are under development in many countries – USA (ORNL, Oak Ridge), Russia (IPPE, Obninsk; RIAR, Dimitrovgrad; Khlopin Radium Institute, Saint-Petersburg), Australia (ANSTO), China (CIAE, Beijing), Germany, etc. Generators produced by ORNL (USA), MAP (Finland), IPPE (Russia) are already available on a commercial base. A few years later a number of generator producers will make market proposals, that would ensure continuous supply of generators to hospitals. Competition of producers and suppliers will "work" for generator price drop-down, thus increasing rhenium-188 availability for patients. Nevertheless, it should be noted that nearly all generator producers are oriented at high specific activity ^{188}W, that can be produced in two high-flux reactors only – HFIR and SM (F_{th} = (1-2)$\cdot 10^{15}$ $cm^{-2}s^{-1}$). This factor decreases reliability of generators supply and their availability for final users. The situation can be improved by correction of approaches used at generator development (currently they are oriented at "standard de facto" – alumina type generator) and by "softening" requirements to the parent isotope specific activity. Thus, medium-flux reactors (F_{th} = (1-5)$\cdot 10^{14}$ $cm^{-2}s^{-1}$) can be used for tungsten-188 production, providing its specific activity at the 1-2 Ci/g level. The number of these reactors can be easily increased to 4-5, it will ensure reliable and continuous supply of tungsten-188 to the market.

In addition to the increased reliability of supply, increased number of producers of tungsten-188 will help to maintain relatively low price of generators that depends significantly on the price of parent isotope. In its turn, the latter is high due to the high price of high-flux reactor irradiation. The current price of 0,5-1 Ci generator is 6.000-8.000 USD. It can be considered as a convenient one for developed countries, but it will constrain wide clinical application of rhenium-188 in developing countries.

The most prospective way of rhenium-188 generator technology development is development of centralized generators, operated in centralized nuclear pharmacies. There are a number of arguments for:

- Rhenium-188 is relatively "long-lived" isotope ($T_{1/2}$ = 17 h), so its supply to relatively large distance is possible. Let us note, that despite more short half-life of technetium-99m and availability of not expensive and easily operated adsorption type generators, technetium-99m eluate is frequently produced and radiopharmaceuticals are synthesized in centralized nuclear pharmacies, if several hospitals using nuclear diagnostics are located in the same area.

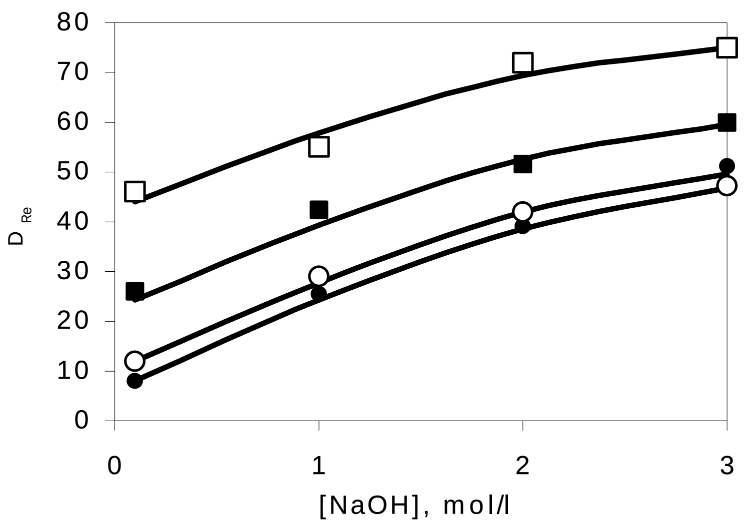
- Rhenium-188 is used for therapeutic procedures that are more easy to plan (as compared to diagnostics), so radiapharmaceuticals can be ordered in a centralized pharmacy “in advance”
- Rhenium-188, emitting high-energy beta-particles, requires more effective shielding devices, that more easy to realize in centralized nuclear pharmacy
- Operating rhenium-188 generator in a centralized nuclear pharmacy requires less number of highly skilled and highly paid personnel (as compared to operation in a number of clinical laboratories); it can effect (decrease) the price of final radiopharmaceuticals increasing their availability for patients, even in developed countries
- High level of skills of personnel working at centralized nuclear pharmacy will allow using more complex (in design) generators, providing, in its turn, using of low specific activity parent radionuclide; that will also increase availability of rhenium-188 for clinical use.

A number of other factors can be listed to prove advantages of centralized generators, but we think that factors already mentioned are essential to demonstrate expediency of that direction of generator development. This will provide wide clinical application of rhenium-188 in the nearest future.

What type of generator is most convenient for centralized use? The most common approach of generator development is based on reproduction of the most common $^{99}Mo/^{99m}Tc$ alumina type generator, that is widely used in clinical practice. The principal limitation is the specific activity of the parent radionuclide, tungsten-188, that can not be produced in a carrier-free state with the specific activity, typical for fission molybdenum-99m. That causes large weight of the parent radionuclide loaded into the generator column (that should be large too); large volume of eluting solution should be passed through the column to wash-out the daughter radionuclide producing low bulk activity of the eluate. At the same time, using of modern vehicles for rhenium-188 targeted delivery to organs and tissues, like monoclonal antibodies, required high bulk activity of eluate. That stimulated development of alternative technologies for generator production, like using concentrating systems, gel-type generators, etc. Unfortunately, no data can be found in literature dealing with development of extraction type ^{188}Re generators, despite their successful application for ^{99m}Tc separation from low-specific activity molybdenum-99m. Mostly, extraction with methylethylketone (MEK) from alkali solutions is used in these generators. After separation of aqueous phase, MEK can be easily evaporated by air-flow. The dry residue can be dissolved in a small portion of saline providing high bulk activity of ^{188}Re concentrate.

Experiments carried out in our laboratory have shown that extraction with MEK can be effectively used for rhenium-188 isolation from tungsten-188 solutions (Figure). Rhenium distribution ratio depends both on alkali concentration and that of tungsten; it grows up at concentration increase of these two components. Tungsten distribution ratio is not higher than $(2\text{-}4).10^{-2}$, that provides separation factor of rhenium and tungsten not less than 10^3, and rhenium yield not less than 95-98% (at equal volumes of organic and aqua phases). Solubility of sodium tungstate in sodium hydroxide solution is limited, nevertheless it is not less than 120-130 mg/l. At this concentration and at ^{188}W specific activity 1 Ci/g activity of 10 ml of aqua phase will be 1,2-1,3 Ci, i.e. the generator itself can be of compact size.

At the development of rhenium-188 extraction generator an attention should be focused on radiolysis and polymerization effects at high concentration of tungsten in an aqua phase and at long-term storage. If these effects exist, they can change parameters of rhenium and tungsten extraction. Effect of high activity on extracting agent properties should be also carefully studied, as its radiolysis products can have pyrogenic properties. We plan to carry out this study at nearest future.



Re-188 extraction with MEK from NaOH solutions in the presence of sodium tungstate.
$[Na_2WO_4]$ = 0,1 (●), 0,2 (❍), 0,5 (■) and 0,7 (□) mol/l.