SET-UP, GENERAL USE AND QUALITY CONTROL OF THE *ORNL* TUNGSTEN-188/RHENIUM-188 GENERATOR SYSTEM AND METHODS FOR CONCENTRATION OF RHENIUM-188 TO HIGH SPECIFIC VOLUME SOLUTIONS

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Radioisotopes from ORNL are pharmaceutically unrefined – Disclaimer - "If intended for drug purposes, CAUTION: for manufacturing processing or repacking in the preparation of a new drug, limited by Federal law to investigational use, unless recipient holds an effective new drug application." (UCN 2629, 4-84).

Oak Ridge National Laboratory (ORNL), managed by UT-Battelle, LLC, for the U.S. Department of Energy, under contract DE-AC05-00OR22725.

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CONTENTS

Introduction

The alumina-based generator prototype was developed in the ORNL Nuclear Medicine Program in the 1980's and since that time over 500 generators have been provided as a radiochemical to institutions throughout the world for research use and for a variety of important clinical applications in nuclear medicine, oncology and interventional cardiology. Currently, a current Good Manufacturing Practice (cGMP) Quality Program is being implemented to provide the tungsten-188/rhenium-188 generators as a non-sterile Bulk Pharmaceutical Ingredient (BPI), since ORNL is not licensed to provide approved agents for clinical use. It is expected that the Drug master File will be filed with the FDA in mid-2007.

General Comments

These procedures describe the set-up, use, daily operation and QC of the *ORNL* alumina-based tungsten-188/rhenium-188 generator and rhenium-188 bolus concentrator components. The various generator components which are described in these procedures refer to the generator system (**Figure 1**) described earlier (Knapp, *et al., Anticancer Research*, 17, 1783-1796, 1997; Knapp, *Cancer Biotherapy and Radiopharmaceuticals*, 13, 337-349, 1998). The Lucite system which we have developed for shielding the tandem concentration system for our research purposes at *ORNL* (**Figure 2**) may not meet the radiation protection or space requirements, etc., of other institutions, and other shielding may thus have to be designed. Many of our various clinical collaborators have developed their own systems - one group has the generator and concentrator unit installed in a small hot cell, other groups install the concentrator within a lead shield as shown on the diagram, others have constructed rectangular Lucite shields, etc. Each institution has to determine their own needs. In terms of external radiation readings, for a typical 1 Curie tungsten-188/rhenium-188 generator at equilibrium, typical radiation readings at the outside surface of the lead shield are about 350-400 mR/hr, which may be locally higher at the holes drilled through the lead shield through which the extension tubes pass, although these holes are off-set as shown in the diagram (**Figure 1**). The generators are shipped as "Type A" shipments, which require < 200 mR radiation reading at the surface of the shipping container.

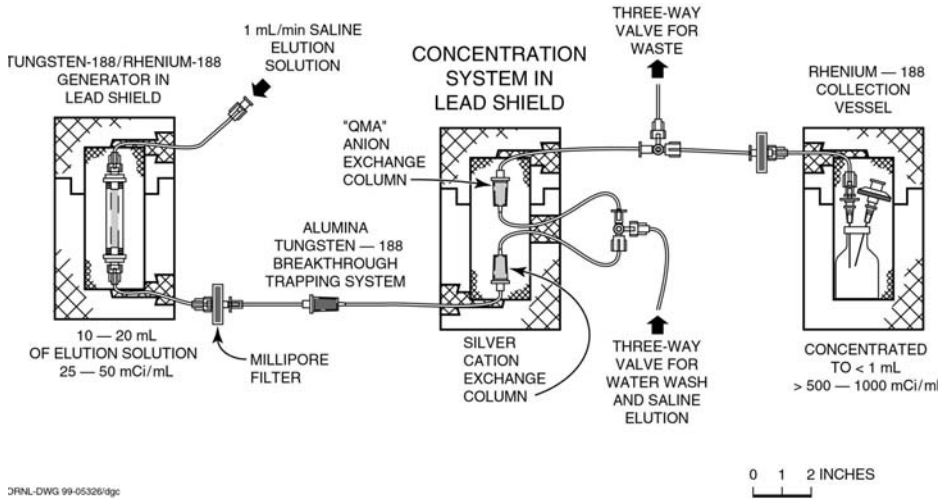
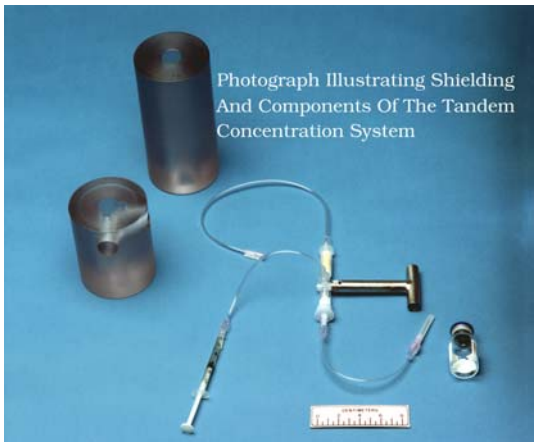


Figure 1. Schematic of tungsten-188/rhenium-188 generator set-up for elution

Although the yields of rhenium-188 at equilibrium are generally about 75-80 %, daily elution will provide about 45-50% yields of rhenium-188 (**Figure 3**) since about 62% in growth of rhenium-188 is available every 24 hours and the elution yields of available rhenium-188 are about 75-80%. The decay curve for tungsten-188 is illustrated in **Figure 4**.

PLEASE NOTE - The generator is provided as a radiochemical and is not approved by *ORNL* for human use since we are not licensed to distribute radiopharmaceuticals. For human use, it is thus the responsibility of the institution to evaluate the generator to insure that it is sterile and pyrogen-free and to obtain the required institutional and regulatory approval required for human use.

The commercially available alumina and anion ("QMA" Light) SepPak® cartridges (Waters) and silver-cation columns (Dionix and Alltech Associates) are only commercially available as non-sterile (**See Pages 20-22 for information on how to obtain these columns**).



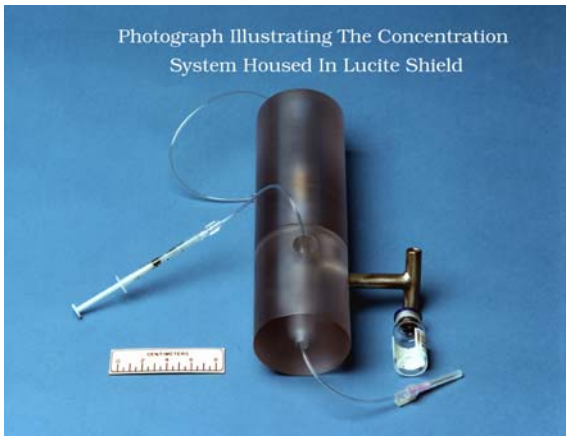


Figure 2. Photographs of components of the simple Lucite shielding unit housing the tandem silver-cation/anion system for concentration of the rhenium-188 saline bolus

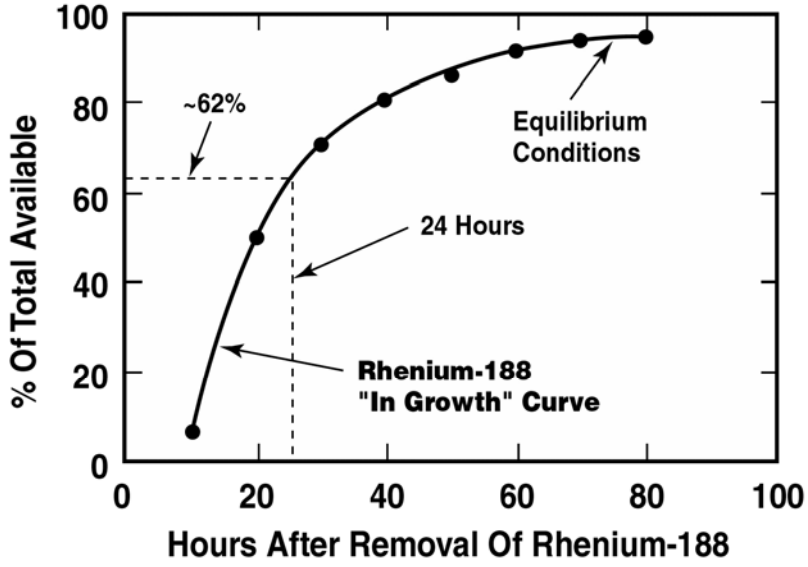


Figure 3. Illustration of in-growth and theoretical rhenium-188 yields following elution of the tungsten-188/rhenium-188 generator system

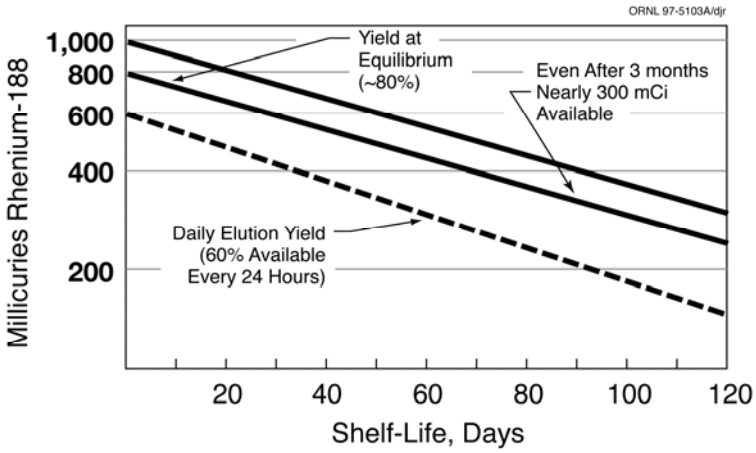


Figure 4. Decay curve for tungsten-188 and expected Re-188 yields over three months

Ordering the Generator from ORNL

The tungsten-188/rhenium-188 generators are available as a radiochemical on a routine basis from the *Isotopes Distribution Office (IDO)* at the *Oak Ridge National Laboratory (ORNL*). Although this generator system has not yet been approved by the *U.S. Food and Drug Administration (FDA)* as a commercial radiopharmaceutical for routine use, he *FDA* and regulatory agencies in various other countries have approved several specific clinical applications through physician-sponsored *Investigational New Drug (IND)* protocols. The generator is currently in clinical use, for example, in

Columbia, Greece, Germany, Great Britain, Hungary, Korea, People's Republic of China, Taiwan, Thailand, Uruguay, the U.S. and Vietnam, as described in the enclosed summary. Reprints and other information describing the use of rhenium-188 from the tungsten-188/rhenium-188 generator for radiopharmaceutical studies are available on request.

Generators up to 3 Ci are available from *ORNL*. For most clinical applications (Re-188-HEDP, Re-188-Lipiodol, etc.), generators one Curie or larger in size are required to provide the high activity solutions. An official summary of the prices which have been established by the U.S. Department of Energy *Isotopes for Medicine and Science Program* can be obtained from the ORNL *Isotopes Distribution Office* (IBO). Sufficient processed tungsten-188 is usually available for fabrication and shipment of the generators within 2-3 weeks after authorization/approved is received from the IBO.

The official "Isotope and Technical Service" Order Form can be downloaded from the Web at http://www.ornl.gov/isotopes/ca_10_90.pdf, and is also shown on Pages 7-10, and the sections indicated should be completed as shown. In addition to inclusion of the maximal license limit as indicated in Section # 7, both the name and signature of the responsible individual must be included in Section # 10, and Page 4 must also be signed. All four pages of the completed form, in addition to a copy of the Radiation License for domestic institutions and a Statement of Use form foreign institutions, should be returned to the *IBO,* who will also provide an official price Quotation upon request. It is important to insure that the appropriate license includes both tungsten-188 and rhenium-188.

Please Note - Because of shipping requirements, the shipping documents will indicate double the level of activity ordered, to account for both the tungsten-188 parent and rhenium-188 daughter present at equilibrium. Thus, for a 1 Ci generator, the shipping documents will indicate a total activity level of 2 Ci (i.e. 1 Ci tungsten-188 and 1 Ci rhenium-188).

To obtain an "official" price quotation and place an order, please contact: Ms. Betty Benton *ORNL Isotopes Business Office (IBO)*; Tel. (865) 574-6601; FAX (865) 574-6986; E-mail <bentonbal@ornl.gov>.

DOE Form
CA-10-90.COM Rev 3
(07/01)

U.S. DEPARTMENT OF ENERGY
ISOTOPE AND TECHNICAL SERVICE ORDER FORM

This form is to be used by all persons (except foreign persons requiring source or special nuclear material) ordering source, special nuclear or by-product material, technical services, stable isotopes, cyclotron produced radioisotopes, or other related services from the U.S. Department of Energy (DOE) or DOE facility contractor.

1. To: ☐ U.S. Department of Energy OR ☐ DOE Facility Contractor
Name and Address:

Oak Ridge National Laboratory
Managed by UT-Battelle for the Department of Energy
P. O. Box 2009
Oak Ridge, Tennessee 37831-8044

2. BUYER'S ORDER NO.:

3. DATE:

4. SHIP TO:

5. BILL TO:

6. VIA:

7. MATERIAL OR SERVICE

CATALOG ITEM NO. (if any)	SOURCE, SPECIAL NUCLEAR, BY-PRODUCT, OR CYCLOTRON PRODUCED RADIOISOTOPES: State isotope, chemical form, desired total activity, and desired specific activity. TECHNICAL SERVICE: State desired service and specification of final product. STABLE ISOTOPE: State isotope, chemical form, quantity, isotopic concentration, (specifying desired enrichments, minimum enrichments), and chemical purity (if applicable).	PURCHASE PRICE	RENTAL FEE
Shipping Schedule and Completion Date:	Technical Service Charge (if applicable)		
	Handling Charge (if applicable)		
	Total		

THIS ORDER CONSISTS OF FOUR PAGES AND IS SUBJECT TO THE TERMS AND CONDITIONS CONTAINED HEREIN. THE AUTHORIZED REPRESENTATIVE OF THE BUYER HAS READ, UNDERSTANDS AND AGREES TO SAID TERMS AND CONDITIONS.

8. The Buyer certifies that the Buyer or the Buyer's representative is authorized to receive the above described source, special nuclear, by-product, or cyclotron produced material by: *(Check block and give license number and expiration date if applicable.)*

(a) ☐ NRC or ☐ _____ (Name of State) License No. _____ which expires _____ (Month and Day), _____ (Year)

(b) ☐ Exemption or General License provided by U.S. Nuclear Regulatory Commission (NRC) regulations.

(c) ☐ Exemption or General License provided by _____ (Name of State) regulations.

9. **Accepted for and agreed to by:**

☐ U.S. Department of Energy OR

☐ DOE Facility Contractor _____

Printed Name _____

Signature _____

Title _____ Date _____

10. **Authorized and agreed to by the Buyer:**

Buyer _____

Signature _____

Printed Name _____

Title _____ Date _____

DOE Form CA-10-90.COM Rev 3 (07/01)

U.S. DEPARTMENT OF ENERGY

ISOTOPE AND TECHNICAL SERVICE ORDER FORM

Continuation Sheet

CATALOG ITEM NO. (if any)	SOURCE, SPECIAL NUCLEAR, BY-PRODUCT, OR CYCLOTRON PRODUCED RADIOISOTOPES: State isotope, chemical form, desired total activity, and desired specific activity. TECHNICAL SERVICE: State desired service and specification of final product. STABLE ISOTOPE: State isotope, chemical form, quantity, isotopic concentration, (specifying desired enrichments, minimum enrichments), and chemical purity (if applicable).	PURCHASE PRICE	RENTAL FEE
	DELIVERY: Delivery is FCA Department of Energy facility from which the order is filled. Legal and equitable title and risk of loss or damage pass to the buyer when the material is delivered to the common carrier. Transportation and insurance charges are the responsibility of the buyer. ☐ Please check this box if insurance against loss or damage is desired during transport. If the box is not checked no insurance will be requested.		

Shipping Schedule and Completion Date			
	Technical Service Charge (if applicable)		
	Handling Charge (if applicable)		
	Total		

ISOTOPE AND TECHNICAL SERVICES ORDER FORM
TERMS AND CONDITIONS

1. Definitions. "Buyer" means the person or entity placing this Order. "Government" means the United States of America. "Department" means the U.S. Department of Energy. "Contractors" means Department of Energy facilities' contractors and their employees who fill or participate in the filling of this Order, however, these Contractors are not agents of the Department. "DOE facility" means a laboratory, plant, or office operated by or on behalf of the Department.

2. Price of Material and Services. For material and services which are sold, the price or fee shall be fixed by the Department and in effect on the date of acceptance of this Order by the Department, said date shall be reflected in item 9 on page 1 of this Order.

For material which is leased, the Buyer understands and agrees that he/she/it must pay all charges, costs, and value of material losses as provided in the Agreement for Lease of Stable Isotope Material.

In the event of unusual circumstances which would cause the costs of materials or services to significantly exceed the purchase price of this Order, the Department shall not be obligated to continue or complete the Order by incurring costs in excess of this Order, and shall have the right to cancel this Order as specified in paragraph 13, unless the purchase price has been increased by written amendment to this Order.

3. Payment Terms and Interest. Payment shall be made within 30 days for domestic or 45 days for foreign orders from the date of the Department's or the Contractor's invoice, unless advance payment and/or a shorter period is specified in this Order.

All amounts payable under this Order (net of any applicable tax credit under the Internal Revenue Code, 26 U.S. C. 1481), shall bear simple interest from the date of delinquency until paid, unless paid within 30 days of becoming due. The date of delinquency is the date the Department or the Contractor mailed or hand-delivered the billing notice or invoice. The interest rate will be set at the same rate as the Treasury's Current Value of Funds Rate (prescribed and published by the Secretary of the Treasury in the Treasury Financial Manual Bulletin) for the period in which the debt became delinquent.

An administrative charge shall be imposed per delinquent invoice per 30 day period from the date of delinquency to cover the costs associated with collecting the debt, unless paid within 30 days of becoming due.

A penalty charge, accruing from the date of delinquency, shall be assessed at 6% per year on any portion of a debt that is outstanding for more than 90 days, including any interest and administrative costs.

Payments shall be applied first to accrued penalty charges, then to accrued administrative charges, then to accrued interest, and finally to the principal, pursuant to 4 CFR 102.13(f).

Interest, administrative charges, and penalty charges do not apply to a) other Federal agencies, b) other management and operating contractors of the Department, and c) State and local governments.

4. Government-owned Containers. When shipment of material pursuant to this Order requires the use of returnable government-owned containers, title to such containers shall remain in the Government. The Buyer shall keep the containers in good condition, will not use them for any materials other than the materials shipped therein, and will deliver them to a carrier designated by the Department for return to the point of shipment, transportation prepaid, within 30 days from the date of receipt by the Buyer of the shipment. The Buyer agrees to pay to the Department a demurrage charge on each returnable Government-owned container for the period of retention which is in excess of the said 30-day period.

5. Delivery/Risk of Loss of Material Sold.

a) Delivery shall be FCA the Department facility from which the Order is filled. The Department shall arrange for transporting the material from the Department facility. The Buyer shall pay all costs related to transporting the material. The Department shall put the material in the possession of the Buyer's carrier at the Department facility from which the Order is filled;

b) Legal and equitable title and risk of loss or damage shall pass to the Buyer when the material is delivered to the Buyer's carrier.

6. Delivery/Risk of Loss of Material Leased.

a) Delivery shall be FCA the Department facility from which the Order is filled. The Department shall arrange for transporting the material from the Department facility. The Buyer shall pay all costs related to transporting the material. The Department shall put the material in the possession of the Buyer's carrier at the Department facility from which the Order is filled;

b) Legal and equitable title shall remain in the Department, except that in the event the material is determined to be unacceptable for return to Department's inventory under the provisions of the Agreement for Lease of Stable Isotope, title to such material shall pass to the Buyer as of the date the Buyer is billed for the material by the Department;

c) Risk of loss or damage shall pass to the Buyer when the material is delivered to the Buyer's carrier;

d) Buyer shall return such material to the designated Department facility when required in Agreement for Lease of Isotope Material. Delivery shall be CIP the Department facility with freight and insurance prepaid by the Buyer and not charged to the Department. The Buyer shall arrange for transporting the materials utilizing a carrier designated by the Department. Risk of loss or damage shall pass to the Department upon acceptance by the Department of the material.

7. Labeling, Shipping and Receiving. Package labeling, shipping and receiving activities shall be performed in accordance with applicable Department, Department of Transportation, Department of Commerce, and Nuclear Regulatory Commission regulations.

8. Specifications. The Buyer shall promptly notify the Department in writing if any of the material does not conform to the specifications set forth in item 7 on page 1 of this Order. The responsibility and liability of the Government, the Department, and the Contractors upon verification of such non-conformances, shall be limited solely to making reasonable efforts to a) correct such non-conformances, b) replace with material which conforms to said specifications or c) make appropriate adjustments to the purchase price. The Department will reimburse the Buyer for reasonable costs of packaging and transportation incurred by the Buyer in returning to the Department any material which does not conform to such specifications.

9. No Warranty. All implied warranties are hereby disclaimed. Neither the Government, the Department, nor the contractors make any warranty, express or implied a) that material will be delivered or services performed at a specified time, b) that material accepted for technical or analytical services will not be destroyed, damaged, lost, or otherwise altered in physical or chemical properties in the process of performing the requested technical or analytical service, c) with respect to the accuracy, completeness or usefulness of any information furnished hereunder, d) that the use of any such information may not infringe privately owned rights, e) that the services, material, or information furnished hereunder will not result in injury or damage when used for any purpose or are safe for any purpose including the intended purpose, and f) that the services, material or information furnished hereunder will accomplish the intended results.

10. Liability. Neither the Government, the Department, nor the Contractors will be responsible for any injury to or death of persons or other living things, or damage to or destruction or loss of property, specifically including material supplied by the Buyer, or for any other loss, damage or injury of any kind whatsoever resulting from the performance of services or furnishing of material or information hereunder, by the Government, the Department, or the Contractors, to the extent such injury, death, damage, destruction, or loss is not caused by the negligence or willful misconduct of the Government, the Department, or the Contractors.

11. Indemnification. To the extent permitted by state law, the Buyer agrees to indemnify and hold harmless the Government, the Department, and the Contractors from and against any and all liabilities, penalties, fines, forfeitures, claims, causes of action, and costs and expenses (including the costs of defense and/or settlement, including, but not limited to, attorney's fees), caused by, resulting from or arising out of, in whole or in part a) the breach of any term or provision of this Agreement, or negligent or willful act or omission, by Buyer, its employees, agents, officers, directors, or contractors, b) the failure of Buyer, its employees, agents, officers, directors, or contractors to fully comply with applicable statutory and regulatory requirements, c) performance by the Government, the Department, or the Contractors of acts, services, analyses, or tests, including furnishing material, required, specified, or directed by the Buyer to be performed or furnished under this Order to the extent the liability is not caused by the negligence or willful misconduct of the Government, the Department, or the Contractors.

12. Publication. The data produced under this Order will be provided to the Buyer who will be solely responsible for marking the data and removing the data from the facility by or before termination of this Order. The Department shall have the right to publish and use any data provided to or generated by the Department or the Contractors, and to permit others to do so unless such data is marked as "proprietary data" by the Buyer. The Department and the Government shall have unlimited rights in technical data (including proprietary data) which are not removed from the facility by or before termination of this Order. In addition, the Department and the Government shall have the unlimited right to perform similar or identical services for other buyers as long as the Buyer's proprietary data are not utilized. The Buyer agrees to deliver to the Department or the Contractors a non-proprietary description of the work to be performed under this Order.

13. Cancellation. The Department reserves the right to cancel this Order without further liability or cost a) in the event the license referenced to in item 8 on page 1 of this Order, which may be either the Buyer's or its authorized representative's license, is suspended, expired, canceled, or revoked, or does not authorize possession of the material, or b) when cancellation of this Order is determined to be necessary to the national defense, security, or environmental safety of the United States or due to lack of appropriated funds or facility capabilities or c) when the Buyer is delinquent on any payments due under this Order or any other Orders for isotopes or technical services related to isotopes from the Department.

The Buyer may cancel this order at any time by providing 180 day advance written notice to the Department. Buyer shall pay the Department, in addition to any costs owing under paragraph 3 above, any costs incurred by the Department in stopping the work and removing the Buyer's material as well as any other costs resulting from the cancellation.

14. Material Supplied by the Buyer. Material supplied by the Buyer may be held or stored by the Department in accordance with instructions of the Buyer, or in order to protect health, or to minimize other hazards to life or property. Buyer shall pay the Department all costs of such storage. Unless this Order specifies that the material is to be returned to the Buyer, the Department may dispose of material supplied by the Buyer for technical or analytical services and the Buyer shall have no claim for the value or replacement of material disposed by the Department. The Buyer shall arrange for and bear all costs of transportation of material to and from (if applicable) the designated Department facility.

15. Severability. Should any provision of this Order be unlawful, void, or for any reason unenforceable, that provision shall be severable and not affect the validity and enforceability of the remaining provisions of this Order.

16. Export Law Assurances. The Buyer agrees that it is responsible for and will comply with the United States export laws and the regulations thereunder relative to any export or re-export of material and/or information procured/obtained by the Buyer under this Order and any direct product thereof. The Buyer further agrees that neither such material and/or information nor any direct product thereof will be shipped, transferred or re-exported into any country prohibited by the United States export laws and the regulations thereunder or will be used for any purpose prohibited by such laws.

17. Facility Utilized. The Department, at its discretion, may fulfill its obligations under this Order through any of the DOE facilities.

18. Dispute Resolution. The parties agree to make good faith efforts to resolve any disputes using alternative means of dispute resolution. Substantive issues shall be determined in accordance with federal law. In the absence of federal law, substantive issues shall be determined in accordance with laws of the state of residence of the buyer at the time of the purchase. Should litigation be necessary, all actions shall be brought in Federal District Court.

Signature

Date

Receipt and Opening of the Generator "Type A" Package -

The generator is provided in a Department of Transportation (*DOT*)-approved shipping container ("cardboard box") containing a liner into which is placed the sealed can containing the generator surrounded by packing material. When the box is opened, the sealed can is removed and then opened with a small can opener which is provided. Although decontamination of the lead shield is always attempted, we cannot guarantee that the surface of the lead shield will not be contaminated, since it was removed from the hot cell before packaging and shipment. In general, we do not observe any contamination on the shield prior to packaging, but we recommend, however, that gloves always be worn when handling as part of good laboratory practice.

As shown in Figure 5, the top and lower sections of the lead shield are sealed with a length of plastic tape, which should never be removed. As illustrated in the generator photograph and illustration (**Figures 1 and 5**), the upper and lower access holes of the lead shield housing the generator are covered with short pieces of tape which are removed to expose the short sections of capped arterial extension tubing which are coiled within the recessed holes. The generator is eluted from top to bottom. ***It is important not to twist the extension tubing in a counter clock-wise fashion, since this may loosen the Luer tubing connector on the column connections.***

To insure reproducibly of the high rhenium-188 yields, we have found that elution should be performed with either a peristaltic pump or a syringe pump at a flow-rate of < 1 mL/minute. Although we have not quantified this effect, if the flow-rate is too high, the yields will decrease.

Figure 5. Photographs of lead shielding housing the tungsten-188/rhenium-188 illustrating the extension tubing used for generator elution

Set-up of the Generator and Rhenium-188 Concentrator System -

Good laboratory practices using sterile components must be followed to insure sterility of the rhenium-188 eluant. It is strongly advised that the generator, concentrator unit and collection vials, etc., all be placed in trays and housed in a hood or at least contained in a glove box or some other self-contained unit to eliminate the possibility of contamination of personnel and facilities in the unlikely event of a liquid spill.

Placement of a dedicated dose calibrator chamber in the hood or laminar flow area may also be a good practice to minimize exposure or possible contamination during transfer of the final dose vial of rhenium-188 into the calibrator for measurement. We enclose a small (< 10 MicroCi) calibrated equilibrium tungsten-188/rhenium-188 standard with the initial generator shipment to each institution, which is prepared using a *NIST*-calibrated germanium crystal detector system (HpGe).

The generator, concentrator, collection vessel, etc. should all be housed behind a lead shield, preferably with a leaded-glass viewing window. In this manner the external radiation exposure to personnel can be minimized. Because of the high energy beta irradiation from the rhenium-188 (**Figure 6**), great care should be taken in designing the use of this system and using sound *ALARA* (*"As Low As Reasonable Achievable")* principles of distance, shielding and exposure time to minimize radiation exposure.

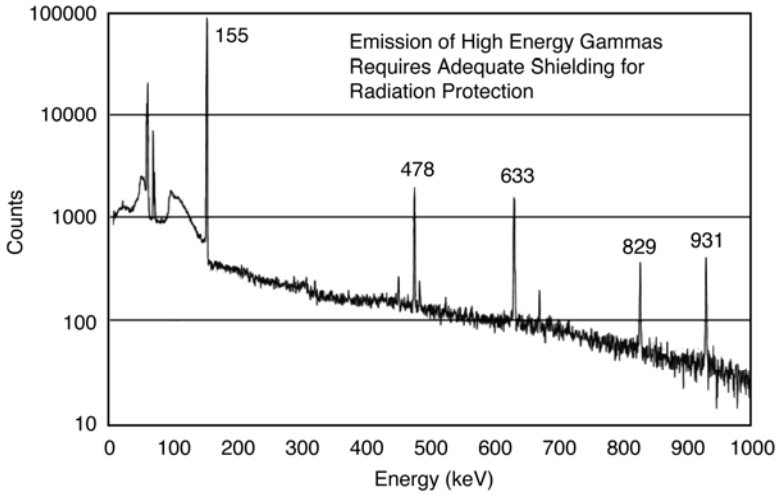


Figure 6. Gamma spectrum of rhenium-188.

It is also strongly recommended that one individual be trained and be responsible for the daily operation, quality control and documentation which is required for operation of the generator system. It is recommended that a Log Book be maintained and data for each elution, including sterility and pyrogen testing, be entered into this permanent log.

Referring to Figures 1, 7-9:

General Comments:

1. The generators are loaded with aluminum oxide, equilibrated with DI water and then tested with an Endoflator device at a pressure of about 50 lbs/in ^{2} (i.e. about three times the approximate 1 atm. pressure observed when eluted through the alumina SepPak® (Alumina A) and concentration system at a flow-rate of less than 1 mL/min). The generators thus must pass this pressure test at a pressure which is about three times the expected operating pressure before the tungsten-188 is loaded. ***The volume required to elute the generator is determined by the specific activity of the tungsten-188. The lower the specific activity, the greater the volume required for elution*** **(Please See Note 1, Page 17).**

2. The generators are eluted from top to bottom using a syringe pump or peristaltic pump at a recommended flow-rate of < 1 mL/min. After receipt, the generator should be slowly washed with 100-200 mL of saline, to re-equilibrate the generator system. The generator should not be attached to any of the cartridges for this elution. Based on the time period of in-growth of rhenium-188 after its removal during this washing (**Figure 3**), the yields of rhenium-188 for subsequent elutions can then be calculated.

Although evacuated vials can be used in a similar fashion to elution of the molybdenum-99/technetium-99*m* generator system from the bottom, the increased resistance from the larger generator bed, alumina SepPak® and tandem column concentration system (*vide infra*) can result in prolonged elution periods at indeterminate and probably non-reproducible elution rates. For human use, a sterile Millipore filter should be used for final filter sterilization of the rhenium-188 solution for filtration of the final rhenium-188-labeled radiopharmaceutical.

3. The alumina SepPak®, cation and anion columns should first be washed (wetted) simply by attachment to and elution with a syringe filled with sterile distilled water. ***If the filters are not pre-wetted, a high pressure can develop when elution is attempted.***

4. The Alltech and Dionix silver (Ag)-cation columns (**Figures 7 and 8**; ***See pages 20-22 for information for ordering***) have a maximum chloride binding capacity of about 2 milliequivalents (meq) per cartridge, which may even vary from batch to batch (available from Alltech Associates and Dionix Corp. – See ordering information Page 20). Dionix also provides a column with a maximum capacity of about 5 meq. Since the 0.9 % saline has a concentration of 0.15 M, the concentration of chloride ion is 0.15 mmoles per mL, and 10 mL of the 0.9% saline eluate thus represents 1.5 mequiv._ The minimum volume required to elute a 1 Ci generator is about 10-12 mL, which represents 1.5-1.8 mequiv., which is very close to the maximum binding capacity of a single 2 meq. Ag-cation cartridge. For this reason, it is a good idea to mount two of the 2 meq. Ag-cation cartridges in tandem if the larger cartridges are not available, to insure that sufficient chloride binding capacity is available. The number of cartridges will depend upon their capacity and the total bolus volume, since generators fabricated with low specific activity tungsten-188 will have larger bolus volumes. If sufficient silver ion is not available to trap the chloride anion available, then the Re-188 will not be trapped on the anion column.

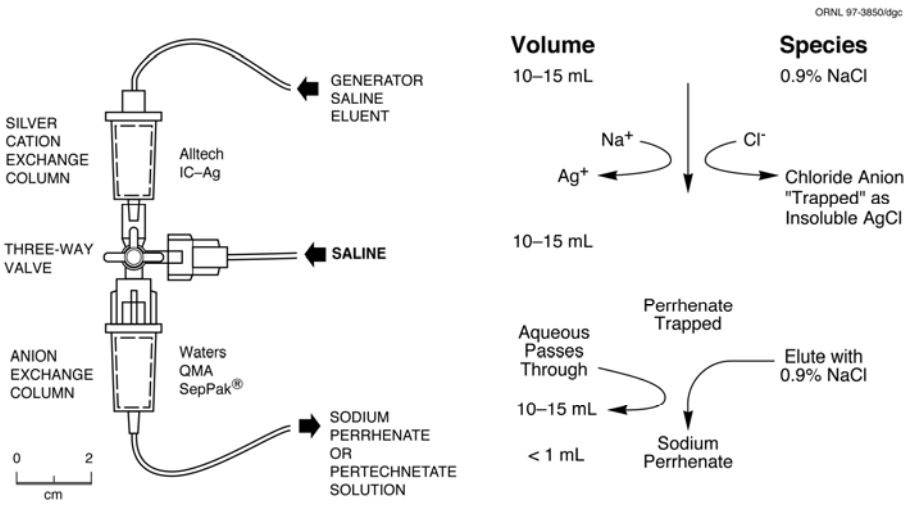


Figure 7. Illustration of the components and use of the post--elution silver-cation/anion tandem column system for concentration of the rhenium-188 saline bolus

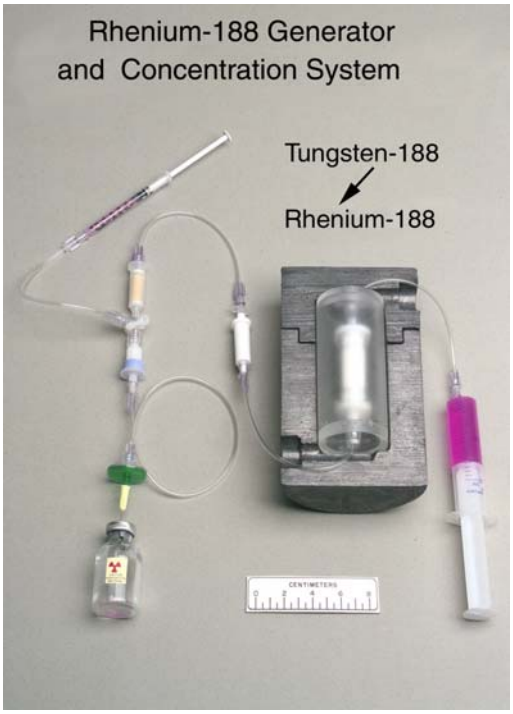


Figure 8. Photograph of a typical set-up of the post--elution silver-cation/anion tandem column system for concentration of the rhenium-188 saline bolus (colored solution used to illustrate fluid volumes)

5. Since each generator is custom fabricated and the specific activity of the tungsten-188 will vary and different level generators will require different amounts of alumina adsorbant, we also recommend that each site perform an elution profile for each generator after receipt with saline elution at a flow-rate of < 1 mL/min. In this manner, the exact volume required to remove the bolus can be determined. Since the amount of alumina and thus the size and void volume of the column increases with the levels of tungsten-188, the bolus volume also depends on the size of the generator, i.e. a 500 mCi generator generally requires less elution volume than a 1-2 Ci generator **(See Note 1).**

6. If the binding capacity of the Ag-cation column(s) is exceeded, significant activity will be detected in the initial waste volume, since chloride will pass through the cation column and the binding capacity of the QMA anion "trapping" column will be exceeded **(See Note 1).**

7. Rhenium-188 elution yields are generally predictably high over several months **(Figure 9)**, however, because of the effects of radiolysis which decrease initial elution yields of rhenium-188 after storing the "wet" generators, it is recommended that the tungsten-188/rhenium-188 generators be stored dry overnight and for longer periods when not in use. Although this is often not a major problem for small generators (500 mCi or less), for larger generators (> 500 mCi), if stored dry, the initial elution yields can often be much lower than expected (10-40%) for the initial elution after "wet" storage, until the generator has been washed with saline and re-equilibrated. ***For this reason, we recommend that the generators be dried after daily use by simple using a 20 mL syringe filled with air.***

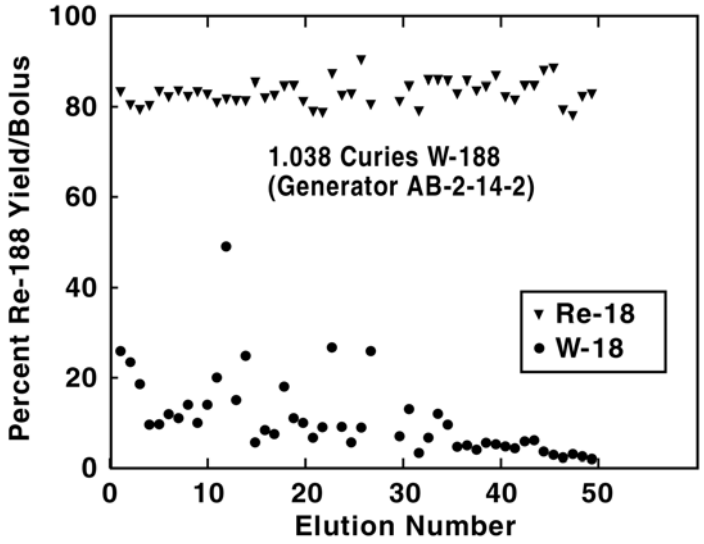


Figure 9. Typical tungsten-188/rhenium-188 generator elution data over a three-month period illustrating the consistently high rhenium-188 yields and low tungsten-188 breakthrough

8. Although the > 500 generators which we have provided to date have been found to be sterile and pyrogen free, it is important for institutional approval to be obtained for any human use of rhenium-188 from this system. The final eluant should be passed through a 0.22 micron Millipore filter to insure sterility and then checked by the Limulus test to insure the absence of pyrogens if the generator eluant is to be used in humans.

Quality Control Procedures

The following procedures are examples of the QC tests which can be obtained on the generator performance and the suitability of use of the rhenium-188 in humans.

1. Tungsten-188/rhenium-188 generators are provided from the *Oak Ridge National Laboratory (ORNL)* as a radiochemical and approval for human use is the responsibility of the clinical institution.

2. Generators should be evaluated for sterility and apyrogenecity (LAL) after receipt and on a recommended weekly basis.

3. ***Alumina Breakthrough*** - Although the in line alumina SepPak® should trap any small amounts of unexpected tungsten-188 parent breakthrough during generator elution, the alumina breakthrough should be checked with a commercial test kit, such as the *Biodex Alumina Breakthrough Kit*, which gives an intense red color with the indicator paper (*Product No. 151-780*). As an example, the *US Phamracopeia* allows a concentration of aluminum ion in an injection < 10 micrograms per milliliter (<10 μ/mL) in technetium-99*m* generators prepared from molybdenum-99 produced from fission of uranium.

4. ***Radiochemical Purity*** - The final rhenium-188 bolus after passage through the alumina SepPak® and the silver-cation tandem column concentration system is essentially radiochemically pure. If a multi-channel analyzer (MCA) system is available, the exact levels of any radiocontaminants in the rhenium-188 can be evaluated. The alumina SepPak® tungsten-188 trapping column can be quickly washed after generator elution, placed in a plastic bag and then counted on the MCA, and the low intensity photo peaks (227 keV, 0.22% and 290 keV, 0.39%) then used to directly quantitate the levels of any tungsten-188 which may be available. Alternatively, after a sufficient decay period to insure all of the rhenium-188 has decayed, the 155 keV photo peak for rhenium-188 can be used to indirectly determine the levels of tungsten-188 at equilibrium.

If the generator eluant is not concentrated, the presence of any low levels of tungsten-188 breakthrough can be determined as indicated above and the low levels of any osmium-191 and iridium-192 radiocontaminants which are formed in the reactor during the irradiation of enriched tungsten-186, and any other radiocontaminants which may be present, can also be determined with the MCA. Although the levels of these two radiocontaminants will vary for each irradiation dependent upon the irradiation conditions, period, etc., the following average levels have been detected in boluses from a 1 Curie tungsten-188 generator which have not been concentrated through the tandem system described below:

Tungsten-188	$< 5 \times 10^{-4}$ %/Bolus
Osmium-191	< 1 μCi/Bolus/Ci W-188 on generator
Iridium-192	< 10 μCi/Bolus/Ci W-188 on generator

NOTE - We have found that the low levels of osmium-191 and iridium-192 which may be present are removed by use of alumina SepPak™the tandem cation/anion trapping system.

Using silica Gel G and the solvent system shown, the rhenium-188 perrhenate can be evaluated by TLC:

Solvent	Stationary Phase	Perrhenate R_f	Colloid R_f
Acetonitrile	Merck Si60	1	0
Saline	Gelman ITLC-SG	1	0

Note 1 - Generators which you will receive may be fabricated using larger amounts of the alumina absorbent than are normally used. We typically use tungsten-188 with a specific activity of 3-6 mCi/mg. The larger amounts of alumina necessary to bind lower specific activity tungsten-188 (> 25 gm *versus* 8-12 gm) will require larger volumes of saline for elution of the rhenium-188, accompanied by a concomitant decrease in the bolus specific volume (i.e. mCi/mL). Using the tandem silver cation/anion column system described earlier, the decrease in specific volume can be overcome by simply increasing the number of silver-cation cartridges in your concentration system (about 1 silver cation column per 10 mL saline eluant = 1.5 milliequivalents). Because the bolus profile and generator void volume will depend upon the tungsten-188 specific activity, it is not possible for us to estimate these values in advance, and we thus recommend that you determine the elution profile of the generators after receipt, which will also provide experience using this generator system. These eluitions will allow you to determine the exact volume required for elution of the complete bolus, which will also allow you to further increase the specific volume of the eluant by discarding the initial non-radioactive void volume prior to elution of the rhenium-188 bolus.

Use of the alumina SepPak® before use or concentration of the rhenium-188 bolus is also a good practice, which is probably a good QC procedure in general which we have recommended for use of our generators. The generators may be close to tungsten-188 binding capacity when low specific activity tungsten-188 (1 mCi/mg) is used, although the maximal loading capacity has not yet been determined.

For this reason, to insure that there is no increasing tungsten-188 breakthrough with repeated use, it is important that you please insure that your colleagues in the radiopharmacy who are eluting the generator, elute first through an alumina SepPak, since this will trap any tungsten-188 breakthrough.

If the alumina SepPak® contains significant activity, then this will be an indication that breakthrough has increased. The SepPak can be counted after the W-188 returns to equilibrium (i.e. 155 keV Re-188 photo peak) in a calibrated counter to determine the level of breakthrough.

Generator Elution and Bolus Concentration
(See Figures 1, 7-19)

See Pages 20-22 for information for ordering the alumina trapping column, and the silver-cation and QMA-anion cartridges for the tandem concentrator system.

1. For consistency and to minimize elution pressures, it is recommended that the generators always be eluted with either a syringe pump or a peristaltic pump at a flow-rate of < 1 mL/min. Under these conditions, the elution pressure should not exceed about one atm. (15 lbs/in ^{2}). The tubing used for the generator is standard medical extension tubing fitted with standard Luer lock connectors. The system which we use for the tungsten-188/rhenium-188 generators has a female Luer exposed at the top and a male Luer at the bottom tubing. The upper extension tube ("Top") is attached to the eluant tube from the pump which is attached to a reservoir (or syringe for the syringe pump) containing 15-20 mL of sterile saline. Please see note above to determine the minimum level of saline which will be required.

2. These generators have demonstrated consistently high rhenium-188 elution yields and low tungsten-188 parent breakthrough, as illustrated in **Figure 9**, for > 1 Ci generator eluted for over two months. The very low tungsten-188 breakthrough can essentially be decreased to undetectable levels by use of the tandem concentration system described below. Low levels of iridium-192 and osmium-191 radiocontaminants which are formed during reactor irradiation of the enriched tungsten-186 target, are also essentially completely removed by use of the tandem concentration system.

3. The lower extension tube from the generator housing is first attached (using an additional length of extension tubing if needed) to an alumina SepPak® which will "trap" any low levels of tungsten-188 parent breakthrough.

4. The exit end from the Alumina SepPak® (**See pages 20-22 for ordering information**) is attached with a length of tubing through the top of the Lucite shield of the concentrator system to the cation cartridge(s) (**Figure 7**), connected by way of a three-way valve with the anion tandem "trapping" column system. The whole "tandem" unit is assembled in advance and housed in the thick Lucite shield (**Figures 2, 7 and 8**), or similar device, to minimize radiation exposure to personnel.

5. For the ORNL tandem column shielding system (**See Figure 8**), the three-way valve is turned by inserting the stainless steel tool through the access hole in the Lucite shield. The free port of the three-way valve (**3**) is initially connected for washing the anion column with a 3-5 mL sterile syringe filled with sterile water.

7. The exit end of the QMA Anion column (**2**) is connected with a length of sterile extension tubing fitted at the end with a sterile 0.22 mm Millipore filter and sterile needle initially to a waste container with a volume of > 20 mL. If a sterile waste container fitted with a septum is used, a sterile venting filter is also required.

8. With the three-way valve in the position "A", the syringe or peristaltic pump is activated and the generator eluted with 15-20 mL of saline at a flow-rate of < 1 mL/min. The rhenium-188-perrhenate is trapped on the anion column housed in the Lucite shield, and the 15 mL volume of waste (essentially containing only traces of radioactivity) is collected in the waste container. As discussed above, detection of any significant levels of activity is in the waste container probably indicates that the binding capacity of the Ag-cation column has been exceeded.

9. The three way valve is then turned to the "B" position, and the anion column washed with 2-3 mL of sterile water which is also collected in the waste container and which should not contain any significant levels of radioactivity.

10. The waste container is then replaced with a vented (i.e. Millipore Filter) 5-10 mL sterile multidose vial housed in Lucite or lead shield container.

11. The 3 mL syringe attached through the Lucite shield to the three-way valve (**3**) is then replaced with a sterile 1 mL tubercilin syringe containing 1 mL of sterile saline and the rhenium-188-perrhenate eluted from the Anion column into the sterile collection vial. It is recommended that a 10 mL vial be used for collection of the rhenium-188 solution, since following calibration, a dilution may be required to obtain the desired specific volume of 100-150 mCi/mL, as described below. If required, dilution with the appropriate contrast agent may also be performed at this time, or the rhenium-188 and contrast solution can be mixed later prior to balloon inflation, since some protocols use contrast.

12. The level of activity in the sterile vial containing the rhenium-188 is then determined using a calibrated dose calibrator. The setting which has been established by the National Institute of Standards and Technology (*NIST)* for the dose calibrator is 631 x 10, for a Model CRC-12 Capintec dose calibrator, but this is dependent upon the total volume and type of vessel, etc. (Zimmerman, *et al.*, "A New Experimental Determination of the Dose Calibrator Setting for Rhenium-188," *J. Nucl. Med.*, 40, 1508-1516, 2000) The same type and size of vial should be used for the calibration and all measurements to minimize any errors resulting from geometry, attenuation, etc.

13. If the system is not regularly used, following an appropriate decay period for decay of the residual rhenium-188 or just before the next elution, the concentrator components can be disposed of before replacement. If a multichannel anlyzer (Ge) detector is available, a decayed aliquot of the concentrated rhenium-188 solution can be analyzed to determine if low levels of any long-lived radioisotopic impurities are present. In several detailed studies with clinical-scale generators (500-1500 mCi) over periods of > 8 weeks, we have not detected any significant levels of any radioisotope impurities in the final rhenium-188 solution.

14. Each institution will have to determine what schedule will be required to evaluate samples of the decayed eluant for sterility and pyrogenicity testing.

15. All information for each elution should be maintained in an appropriate Log Book.

Concentration of Rhenium-188 for Use in Liquid-Filled Balloons for Therapy

1. For vascular radiation therapy or for other applications which require a rhenium-188 liquid-filled balloons, the pooled experience obtained thus far from several collaborative clinical sites, a total volume of 1.5-2 mL of the rhenium-188 solution with a specific volume (up to 250 mCi/mL) which is required for use in the Catheterization Laboratory. Although the actual balloon volume will probably not be greater than 0.15 - 0.20 mL even for large coronary vessels, the extra volume is required for filling the lines, valves, etc., and to have sufficient back pressure in the inflation syringe.

2. For irradiation of the larger diameter peripheral vessels, the volumes and levels of activity have to be estimated, since the balloon volumes are much larger and the inflation times for irradiation can also be much longer. The protocols which will become available will advise on this aspect.

3. As described above, once the exact activity level of the calibrated rhenium-188 solution is known, the solution will have to be diluted to the required volume and specific volume and the required aliquot then transferred with a shielded syringe or some other device into a sterile delivery system or syringe which will then be transferred to the Catheterization Laboratory in an appropriately shielded device.

4. The size of the generator used for the coronary studies will also have to be determined. Most clinical sites have used 1 Ci generators for this application, but it is suggested that the license limit be at least 2 Ci, since an inventory of generators which cannot be used when they decay below some level, say 200 mCi, will be required at least for a limited time period prior to disposal and shipment back to *ORNL*. Although we suggest that they be returned to *ORNL*, you still need some leeway to insure that you can have a new generator and the used generators on the premises at the same time and not exceed your license maximum.

Silver Cation Cartridges -

The silver cation cartridges are used for trapping the chloride anion from the saline eluant using the tandem column trapping system are available commercially from two manufacturers (Alltech and Dionix), or can be prepared in-house at much less expense using a method similar to that described on the next page. We have found that either of the commercial columns perform in the same way and we have no preference, The advantage of the Dionix columns is that they have a Luer lock on one end, but the Alltech cartridges are slightly less expensive.. Often one manufacturer will have columns available when the other inventory is exhausted and must be back-ordered.

In-house silver cation columns can also be prepared similar to the process described on Page 21. Although we have not yet used these columns with tracer rhenium-188, silver nitrate titration studies of the eluants have shown that the silver binds to the resin as indicated.

Alltech, Inc. - Alltech has representatives in most countries as described on their Web Page at: <http://www.alltechweb.com/MainHome.asp>.

The “maxi-Clean IC-Ag Plus” cartridges are available:

1.5 mL bed volume, 1.5-2.0 meq/cartridge - # 30258, $ 189/50 cartridges

Dionix, Inc. - US Tel. (408) 737-0700; FAX (408) 730-9403;
<www1.dionix.com/en-US/index.html>
Dionix has offices in most countries. This information can be accessed on their Web Page at:
<http://www.dionex.com/app/tree.taf?asset_id=3950> or
<http://www.dionex.com/app/tree.taf?asset_id=68212>

Different size “On Guard-Ag” columns are available:

OnGuard-Ag Cartridge, 1 mL volume, 2.0-2.2 milliequivalents (meq)/cartridge:
039637 - $ 190/48 cartridges, **Or**
OnGuard II-Ag Cartridge, 1 mL volume, 2.0-2.2 meq/cartridge - # 057089, $ 190/48 cartridges
OnGuard II-Ag Cartridge, 2.5 mL volume, 5.0-5.5 meq/cartridge - # 057410, $ 425/48 cartridges

IN-HOUSE PREPARATION OF AG-CATION COLUMNS

1. Commercially available Bio-Rad # 737-15-12 Econo-Column (1.5 cm o.d. x 10 cm length) fitted with Luer Lock fittings was used - Larger columns can be used if increased chloride trapping capacity is required. The glass columns have a glass frit at the bottom and the top is a plastic pressure fit Luer assembly

2. Use AG 50-X4 sulfonic acid resin, 200-400 Mesh - this size column holds about 8 grams of the resin (dry weight) - Wet thoroughly with distilled water. Pack top of column with fine glass wool plug

3. Use 14-15 mL of 1 N silver nitrate solution to load column and then wash with water

4. If quantification required, a sample of the total eluant/wash can be titrated with chloride to determine how much silver ion was present and thus how much was bound to the resin

5. About 50-55 mL of saline can be passed through a column prepared in this manner, before the chloride anion is detected by elution into a silver nitrate solution

6. In this way a single silver/cation column can be prepared which can trap any volume of saline

7. Since the cation resin is not tightly packed as in the commercial columns, the generator/tandem-trapping system should be eluted at a low flow rate (0.25-0.30 mL per minute). Lower flow rates will also minimize back-pressure from the complete system

8. Would suggest adding a tracer level of rhenium-188 to the saline solution to do a few test elutions through the Ag-cation column until the conditions are optimized for use with the generator

9. Presumably, if the silver-cation columns are thoroughly washed after use, following decay of the residual rhenium-188, the packing can be carefully removed and discarded and the column packed again for re-use

Please let us know your experience/improvements using this system.

File-FFK-SILVER-COLUMN-PROCEDURE-2-17-03

Information on QMA-Anion and Alumina Columns

Anion Trapping Columns

Waters, Inc. - The anion trapping columns are used for trapping the rhenium-188 following passage of the bolus through the silver-cation trapping column.

US Tel. (508) 478-2000; FAX (508) 872-1990

The Waters Web page containing the country listings for contacts is found at:

< http://www.waters.com/WatersDivision/Contentd.asp?ref=KGLY-5JY48V&WT.svl=2 > -

Accell Plus QMA columns, either “Plus” #WATO20545, or “Light” # WATO23525

Alumina Guard Column

The alumina column is inserted in the elution line after the generator to trap any low levels of tungsten-188 breakthrough from the generator. These columns can also be obtained from Waters as follows:

Alumina A columns, either “Plus” #WATO20500, Classic #WATO51800 or
“Light” # WATO23549

Specifications for the Rhenium-188 Eluant Obtained from the Tungsten-188/Rhenium-188 Generator System Provided as a Non-Sterile Non-cGMP Bulk Pharmaceutical Ingredient (BPI) Available from the Oak Ridge National Laboratory (ORNL) – 12/11/08	
Parameter	**Specifications**
Generator Specifications and Information:	
Weight of non-returnable Type A generator package	Approx. 16 kilo
Generator Activity levels	Loaded with up to 3 Ci of W-188 – as requested by customer
Calibration	2 days after shipment (North America) 7 days after shipment (Foreign shipment)
Expiration	User defined - At least 6 months after production - Unlimited shelf-life performance expected
Rhenium-188 Eluant Specifications:	
Physical Appearance	Clear, colorless solution
Rhenium-188 Elution Yield	65-85 % (available Re-188)
Eluant pH (Saline elution)	pH 4.5-6.0
Radioisotope identity	Rhenium 155 keV peak predominant
Radionuclidic purity	Product > 99.9% rhenium-188 photon emission at 155 keV
Radionuclidic purity	Total contaminants <= 0.1% (osmium-191, iridium-192, cobalt-60)
Radiochemical purity	> 95% Perrhenate by thin layer chromatography (TLC)
Specific activity/volume	As Required by Customer if post elution concentration is required
Tungsten-188 breakthrough	$<=10^{-2}$ % (290 or 227 keV peak)
Alumina breakthrough	<= 10 µg/mL (Biodex)

FILE:FFK:SPEFICICATION-W-RE-GENERATOR-12-11-08

Example of Certificate of Analysis Form Provided with the Generator Shipment

Certificate of Analysis
Tungsten-188/Rhenium-188 Generator
Non-Sterile Non-cGMP Bulk Pharmaceutical Ingredient (BPI)
Nuclear Medicine Program
Oak Ridge National Laboratory (ORNL), Oak Ridge, TN

Generator Data: Designation _____

Customer/ORNL Authorization Number _____

Shipment Date _____

Activity/Calibration Date _____

Tungsten-188 Specific Activity _____

Grams Alumina _____

Rhenium-188 Bolus Data:

Appearance and pH _____

Rhenium-188 Yield (% W-188 at Eq.) _____

From Decayed Bolus (Data expressed as % of rhenium-188 bolus yield):

Tungsten-188 Breakthrough/Bolus _____

Other Radionuclide Impurities/Bolus _____

Rhenium-188 Perrhenate by TLC _____

Alumna Breakthrough – Biodex Kit _____

Approvals –

_____ _____
Signature Date

_____ _____
Manager, Nuclear Medicine Program or Designee Date

Summary of Clinical Trials in Progress and Research Studies as of November 2006 Which have used Rhenium-188 from the ORNL Tungsten-188/Rhenium-188 Generator System

The attached Tables summarize the available data as of November 2006 for clinical protocols involving use of rhenium-188 from the ORNL tungsten-188/rhenium-188 generator system.

Russ Knapp, Jr. *ORNL* - revised 2/11/07

Table 1. Oncology Applications - Examples of Clinical and Research Protocols Using Rhenium-188 From the Alumina-Based Tungsten-188/Rhenium-188 Generator Available from the Nuclear Medicine Program, Oak Ridge National Laboratory (*ORNL)* (November 1, 2006)

Application	Agent	Principal Investigators/Institution	Comments	Approx. #Patients Treated/Protocol
Palliation of Metastatic Bone Pain	***HEDP***	H.-J. Biersack, M.D., H. Palmedo, M.D., Bonn, Germany J. Gaudiano, M.D., *et al.*, Montevideo, Uruguay J. Kropp, M.D., *et al.*, Dresden, Germany L. Pavics, M.D., *et al.*, Szeged, Hungary A. Bockisch, M.D., Essen, Germany G. Limouris, M.D., Athens, Greece J.-K. Chung , M.D., *et al.*, Seoul, Korea J. Vandeviviere, M.D., *et al.*, Antwerpen, Belgium S.M. Lim, M.D., Ph.D., *et al*. Seoul, Korea F. Sundram, M.D., *et al.*, Singapore General Hospital	Studies in progress Studies in progress Studies in progress Studies in progress IND approved Studies in progress Studies in progress Expected to begin 2003 Studies in Progress Studies in Progress	>100/ 40/ 17/ 15/ 0/ 6/ 10/ 3/ 2/
	Re(V)-DMSA	M. J. O'Doherty, M.D., *et al.*, Canterbury, England J. Vandeviviere, M.D., *et al.*, Antwerpen, Belgium	Trials in progress - Prostatic/Breast Expected to begin in 2003	10/20
Tumor Therapy	***Re-188-Antibodies***	Nottingham, England - C595 MoAb for Bladder Cancer York Medical, Inc., Ontario, Canada Resolution Pharmaceuticals, Ontario, Canada	Pilot Clinical Study - 2000 Preclinical - Re-188-AntiEGF MoAbs Preclinical - RP527 Peptide	
Synovectomy	***Tin Colloid***	J.-K. Chung , M.D., *et al.*, Seoul, Korea J. Vandevivere, M.D., *et al.*, Antwerpen, Belgium	Studies in progress - Re-188/Sn Colloid Expected to begin 2003	17/?
Bone Marrow Ablation	***AntiNCA95 (Anti CD66)***	J. Kotzerke, M.D., *et al.*, Ulm, Germany W. Knapp, M.D., *et al.*, Hannover , Germany	Studies in Progress Studies in Progress	+51/
Liver Cancer	***Lipiodol Analogues/ Particles***	***IAEA*** "Thematic Program" organized by A. Padhy, M.D. - Health Care for the Asia and Pacific Region - Multi-Center Trial J. Harvey Turner, M.D., *et al.*, Fremantle, Australia	10 clinical sites participating. Trial in progress	Phase I study complete 10 pts. Treated
Lung Cancer	***P8045 Peptide***	Diatide, Inc., Londonderry, NH - Phase I studies in North America complete	Pashe II trial expected to begin at 4 sites - Spring 2003	
Therapy of Pleural Effusions-Breast CA	***RC-160***	H.-J. Biersack, M.D., H. Bender, M.D., Bonn, Germany	IND approved through German regulatory authorities - Patient studies in progress	2/

Table 2. Restenosis Therapy - Examples of Clinical and Research Protocols Using Rhenium-188 From the Alumina-Based Tungsten-188/Rhenium-188 Generator Available from the Nuclear Medicine Program, Oak Ridge National Laboratory (*ORNL*) (November 1, 2006)

Application	Agent	Principal Investigators/Institution	Comments	Approx.#Patients Treated/Protocol
Inhibition of Restenosis after *PTCA* - ***Liquid-filled Balloon Approach for Coronaries***	***Perrehnate***	N. Eigler, M.D., J. Whiting, Ph.D., *et al.*, Cedars Sinai Medical Center Los Angeles, CA - "RADIANT" System G. Mews, M.D., *et al.*, Perth, Australia J. Kotzerke, M.D., *et al.*, Ulm, Germany A. Shoemig, *et al.*/ U.S. Surgical, Munich, Germany "RADIANT" System J. Kropp, M.D., *et al.*, Dresden, Germany - "DIRRT" Trial "RADIANT" System Augsburg, Germany P. L. Kuan, M.D., *et al.*, Taipei,Taiwan S. W. Leung, M.D., *et al.*, Taichung, Taiwan Eastern Heart Clinic, Sydney, Australia M. Horrigan, M.S., Austin Repat. Med. Ctr., Melbourne. Australia ***IAEA*** "Thematic Program" organized by A. Padhy, M.D. - Asia /Pacific Region - Multi-Center Trial Breach Candy Hospital, Mumbai, india Prof. Moka, University of Cologne, Germany	Trial complete - Initiated - October 1998 Initiated - Nov. 1997 - "In Stent" Initiated - Dec. 1997 Initiated - March 1998 Initiated - August 1999 Expected to begin, Summer 2001 Initiated - Spring 2000 Studies in Progress Studies in Progress Expected to begin, summer 2000 13 clinical sites established - Will be initiated Nov. 2001 Initiated 1999 Initiated January 2001	13/500 25/25; New /100 40/200 12/500 42/600 Rand. Trial Begun ?/40 30/60 40/50 0/? 5/
		10 Center South Korean Multi-Center Trial, Initiated, January 2001 ***IAEA*** Multi-Center Trial organized by A. Padhy, M.D.	10 clinical participating sites. 13 clinical sites chosen	Trial began 2002
	MAG3	J. Weinberger, M.D., Ph.D., *et al.,* Columbia University, NY, NY D. Moon, M.D., *et al..*, Asan Medical Center, Seoul, Korea	Trial complete - Initiated Sept. 1997 Initiated 1999 Initiated 1999 "in Stent" - "R4" Trial	35/60 "CURE" Study 40/60
	DTPA	I. H. Chai, M.D., J.-K. Chung, M.D., M. C. Lee, M.D., *et al.*, Seoul National University Medical Center, Seoul, Korea 10 Center Korean Muli-Center trial - "5R Trial"	Initiated 1999 Initiated January 2001	136/
Restenosis Therapy - ***Liquid-filled Balloon - Peripheral Vessels***	***Perrehnate***	R. Spencer, M.D., S. Stevens, M.D., *et al.*, Univ. TN, Knoxville, TN	Using Swine Ileal Artery Stent Injury Model - "VOLS" study	
Re-188-Coronary Stents	***Activated Stents***	InnerDyne, Inc./BNL/Washington Hospital Schering AG, Germany University Hospital, Aachen, Germany	Effective in Swine Model Studies in Progress Studies in Progress	

Table 3. Examples of Rhenium-188-Labeled Therapeutic Agents Under Development using the Alumina-Based Tungsten-188/Rhenium-188 Generator Available from the Nuclear Medicine Program, Oak Ridge National Laboratory (*ORNL*) (November 1, 2006)

Application	Agent	Principal Investigators/Institution	Comment/Status
Peptides for Tumor Therapy	***Re-188-Peptides***	Diatide, Inc., Londonderry, New Hampshire York Medical, Inc., Ontario, Canada Resolution Pharmaceuticals, Ontario, Canada	Peptide for lung tumor therapy - Animal Data Promising - Initial Phase IClinical trials complete 2002 Peptides for tumor therapy - Being developed with MURR
Bispecific Antibodies for Tumor Therapy	*Antibodies*	Immunmoedics, Inc., Morris Plains, NY	With "Bifunctional" antibody - Animal Studies Promising
New rhenium-188 "Bifunctional" Radiolabeling Approaches	***Hynic Chelates***	J. Bartis, Ph.D., *et al.,* Dupont Pharm., Boston, MA S. Guhlke, Ph.D, *et al.*, Bonn, Germany	
	Re(V)-HEDP "Kits"	S. Guhlke, Ph.D, *et al.*, Bonn, Germany J. Smalljohan,Ph.D., *et al.*, Vienna, Austria	Paper submitted for Publication
Bone pain palliation and tumor therapy	***Re-188-Antibodies***	N. Izago-Escobar, *et al*., Havana, Cuba	"Direct" labeling methods
	Re-188-Antibodies, DMSA and new Phosphonates	Ferro-Flores, Ph.D., *et al.*, National Institute for Nuclear Research. Toluca, Mexico	
Coronary Restenosis Therapy After PTCA	***Coated Angioplasty Balloons***	J. A. Jeong, J.-K. Chung, *et al.*, Seoul National University Hospital	Technology established - animal studies in progress
Magnetic Targeted Carrier ("MTC")	***Activated Carbon Particles***	U. Hafeli, *et al.*, Cleveland Clinic Ferx, Inc., Arvada, Colorado	Rhenium-188-labeled particles are intra arterially injected and localized in target tissue with focusing magnet. Particles are extravasated and permanently trapped in target tisuues