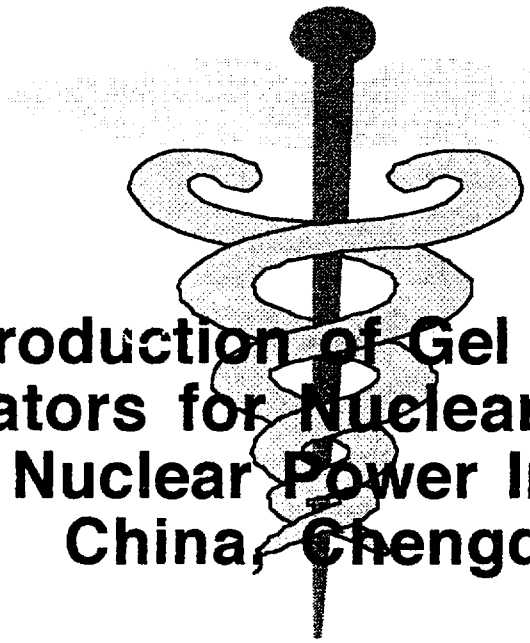
IAEA Technical Co-Operation Mission to China



Production of Gel ^{99m}Tc Generators for Nuclear Medicine at the Nuclear Power Institute of China, Chengdu

Model Project CPR/2/006

Task

Background Information:- The development and testing of the gel-type ^{99m}Tc generator technology has been going on for several years at the Nuclear Power Institute of China. This generator type has already been licensed by the Ministry of Health. With the co-operation of the IAEA, under **Model Project CPR/2/006,** it is intended to upgrade and optimise the existing facility for large scale production and continue to improve the generator performance in terms of quality and reliability of its use in nuclear medicine.

Duties of the Expert:- To carry out final laboratory tests to assess the performance of the gel-type ^{99m}Tc, locally produced, as well as to assess the suitability of the corresponding ^{99m}Tc eluate for nuclear medicine studies. In particular, the expert should test the suitability of the ^{99m}Tc for the labelling of sensitive biomolecules and its general performance in a nuclear medicine service.

IAEA Expert R.E.Boyd

^{99}Mo:^{99m}Tc Gel Generators Produced by the Nuclear Power Institute, China.

Preamble

From 15 to 30 June 1996 I visited the Nuclear Power Institute of China, Chengdu, on behalf of the IAEA, to assess the methods being used for the 'large scale' manufacture of gel generators and to make an in-depth study of the quality of these products.

Although it had been my intention to determine both inter- and intra-batch variation in quality, as it turned out I was unable to examine samples from more than one batch (*because the reactor had tripped out on my second day there, due to a violent rain-storm, and was not scheduled for a restart before my departure*). However I was able to examine three generators across a range of activities, according to a fairly comprehensive schedule of tests.

I witnessed the full manufacturing process and was able to make a cursory assessment of the Institute's degree of compliance to the principles of the Code of Good Manufacturing Practice.

At the end of my assignment I visited the nuclear medicine department of a major teaching hospital in Chengdu to obtain medical comments on the clinical utility of the generator, particularly in respect to its application to the labelling of sensitive biomolecules.

The results of the investigations are summarised below.

1. Objective Test Results

(i) Elution Efficiency

Elution efficiency is the quotient of the measured yield of ^{99m}Tc and the theoretically available amount.

Generator No.	Activity mCi ^{99}Mo	Results of Daily Elution Efficiencies (%)
16	**176**	**75.7, 82.6, 76.6 , 76.9 , 60.3 , 76.1**
25	**593**	**80.2, 86.2, 79.1, 79.4, 63.8, 88.8**
33	**902**	**81.1, 87.7, 80.5, 80.3, 66.12, 82.2**

To be successfully compared against the standard commercial generator (*based o n fission ^{99}Mo*), the elution efficiency of an alternative generator type should

consistently exceed 75%. With the exception of Eluate #5 which was obtained under non-standard conditions, all generator performances, as can be deduced from the table, were acceptable.

It is worth noting that it is common practice for commercial generator suppliers to understate the ^{99}Mo content in order to make the elution efficiencies appear higher. The results for the elution efficiency of the gel generators are based on actually measured ^{99}Mo contents and have been calculated according to a rigorous computer program which includes the ^{99m}Tc contribution residual from the previous elution.

One negative comment on generator performance is the lack of any performance enhancement component in the gel preparation. This means that, should a decision be taken to terminally sterilise the generator, there is a high probability that generator's performance would be adversely affected.

(ii) Elution Profile.

The elution profile of a generator is an indication of the volume of eluent necessary to separate the peak of ^{99m}Tc activity from the immobilised ^{99}Mo phase. Elution profiles vary with generator size and shape - *physically large generators require a greater volume of eluent to displace the peak activity; long columns cause a broadening and a retardation of the ^{99m}Tc peak due to the greater number of ion exchange events that are possible.*

Elution of the gel generators (*containing low specific activity 99Mo*)was performed by aspirating approx. 12.5 mL saline through the generator into an evacuated vial.

Measuring the partial elution, even for the largest of the generators, showed that the peak activity was eluted in 5-7 mL and that the separation process was essentially complete following the passage of 10 mL.

This is considered satisfactory for the majority of clinical applications.

(iii) Molybdenum-99 Breakthrough and Radionuclidic Purity

Molybdenum-99 is the most probable radiocontaminant in eluted ^{99m}Tc. The longer half-life and complex decay scheme involving beta-emissions have motivated pharmacopoeial specifications to stipulate that ^{99}Mo should not exceed 0.1% of the total activity injected.

For fission based generators more stringent specifications apply to other possible radiocontaminants (for example the BP 1993 states that ^{131}I and ^{103}Ru must be less than 5×10^{-3}%, ^{90}Sr less than 6×10^{-6}%, alpha emitters less than 10^{-7}%, other unspecified gamma-emitters less than 0.01%) . While ^{99m} Tc from the gel generator does not carry the risk of fission product contamination, it is important that it complies with the pharmacopoeial specifications for radionuclidic impurities. The table below shows the results of measurements performed:-

Generator Number	μCi ^{99}Mo per mCi ^{99m}Tc
16	0.025
25	0.026
33	0.031

Until my arrival it had been routine practice to estimate the radionuclidic purity of ^{99m}Tc solutions by means of a crude test utilising a dose-calibrator(Capintec), intended for use in hospitals as a guard against disruption of the generator's integrity. I stressed that such a test was not appropriate means of quality control for a generator manufacturer and ought to be routinely replaced by gamma-spectrometry.

Utilising equipment set up for low level environmental surveys, generator eluates (*contained within a thin-walled lead pot to attenuate the ^{99m}Tc radiation*) were subjected to analysis by gamma-spectrometry.

Samples from each of the three generators, fresh and then after 1, 3 and 5 days decay, were examined for the presence of radionuclidic impurities. The results not only confirmed the very low levels indicated in the table above, but also careful analysis of the photopeaks clearly demonstrated that ^{99}Mo was, in fact, the only radionuclidic impurity present in the eluates. A result which indicates that NPIC has access to a very pure grade of MoO_3 target.

(iv) Radiochemical Purity

An important aspect of quality is the degree to which the radionuclide exists in chemical forms other than the desired form.

Radiochemical impurities can arise from chemical reactions with the solvent, from changes in temperature, pH or light intensity and, most commonly, as a result of radiolysis producing highly reactive free radicals.

The presence of ^{99m}Tc in non-pertechnetate forms is undesirable and could cause complications in the secondary preparation of radiopharmaceuticals.

Using standard a paper chromatography/ acetone-HCl method, the radiochemical form of eluted ^{99m}Tc was repeatedly determined; the results are presented in the table below:-

Generator Number	Radiochemical Purity % as TcO_4
16	99.9, 99.6, 99.7
25	99.9, 99.9, 99.9, 99.9
33	99.9, 99.9, 99.5, 98.1

(v) Eluate pH

The gel generator is intended to produce an eluate which can be intravenously administered to humans with no further preparation. Accordingly it must satisfy all normal requirements of injections.

The pH of the eluates was repeatedly measured and shown to be consistently in the range of 4 - 7.

(vi) Chemical Purity

The absence of potentially toxic trace chemical impurities has to be confirmed to decide the acceptability of the gel generator eluates. A comprehensive test schedule was not possible but in its place tests were performed to measure the concentration of the more likely chemical impurities.

The absence of molybdenum in the eluates was repeatedly implied in the results which indicated the very low levels of ^{99}Mo.

Zirconium contamination was measured routinely by colorimetric analysis and shown to be less than 3 ppm.

These results indicate that the most likely chemical impurities were well within acceptable levels. It is possibly necessary to use other techniques to validate the presumption that other undesirable chemical substances are not present in the eluates.

(vii) Sterility and Pyrogenicity

For the eluates from the gel generators to be administered directly to human patients, they must be shown to satisfy the general and special pharmacopoeia requirements for intravenous injections. That is in addition to being free from chemical toxins, the eluates must be shown to be compatible with human blood (isotonic) and free from viable micro-organisms (sterile) and endotoxins (pyrogens).

During the inspection of the quality control laboratories, a practical demonstration of freedom from pyrogens (LAL Test) was witnessed and documentary evidence that the eluates were sterile was also provided. However as referred to in later part of this report the conditions under which the generators are manufactured and assembled are not ideal and, as a result, only a limited confidence in the microbiological integrity of the product was obtained.

For a more appropriate determination of this aspect of quality, it is necessary for NPIC to provide more than satisfactory test results; evidence of levels of protection that would apply when a human or processing error occurs, is highly desirable. In the present production conditions, a guarantee of eluate sterility and apyrogenicity on the part of NPIC, is overly optimistic.

Summary of Test Results

The technetium-99m obtained from the gel generators was gauged by a battery of tests and compared against international acceptance standards. In most cases a sufficiently high quality was confirmed sufficient to indicate a probable and ready clinical acceptance.

This was subsequently confirmed at a meeting with nuclear medicine specialists when it was reported that, from a clinical perspective, ^{99m}Tc from a gel generator was indistinguishable from its fission-product counterpart.

Independent analysis of several more batches of generators is, however, a necessary requirement before a claim of product equivalence can be justified. The IAEA proposal to submit further sample generators to a group of radioisotope authorities is highly recommended.

At this juncture, however, it is not recommended that the gel generators be subjected to an international clinical trial because of doubts in respect to microbiological purity.
(See later comments in regard to compliance with Good Manufacturing Practice which endorses this caveat against clinical experiments.)

2. Inspection of the Generator Production Facilities at NPIC and an Assessment of GMP Compliance

The equipment, facilities and procedures used at NPIC for the production of gel-generators are sub-standard and would not satisfy an audit for GMP compliance. The major areas where improvements are necessary are in :-

Radiation Safety
Segregation of Work Areas
Cleanliness
Management Responsibility
Team Formation
Documentation and Procedures
Batch Traceability

In the absence of these GMP essentials, one is tempted to speculate on an explanation for such a superior product. Arguably, the answer ought to be resident in a firm technological foundation and a well conceived program of practical implementation.

The scientists and engineers at NPIC have benefited from the original work published by ANSTO (patent documents and IAEA Conference Vienna, Oct 1986), and, by not including the process of terminal autoclaving for the finished generators, have been able to avoid the need for a chemical enhancement of elution efficiency. However this may not be considered as a technological advance since the wider application of the technology may demand such a process step be included, in order to ensure a better guarantee of clinical acceptability.

Many of the anticipated practical problems associated with the manufacture of the gel have been successfully overcome. For example, the method of loading the generators is elegant in its simplicity and yet appears highly effective for mass production (it is claimed that 100 generators of different activities can be loaded in 15-20 minutes; I witnessed 10 being completed in 1 minute).

Assembly of the loaded generators is performed in a 'clean-room' environment which is not monitored for particles or pathogens. As a result the assembly process could not be realistically claimed as aseptic nor the resultant product as sterile. Furthermore significant opportunities exist for microbial growth and contamination of the generators. (*That no clinical problems have been reported is indeed surprising.*)

Too much work is performed on or near dust-laden floors and the flow of materials and personnel needs streamlining.

The gel production equipment and hot-cells are new and capable of being isolated from the less than optimal surrounding environment; so far this isolation has only been partially achieved. These features are negated by insufficient attention paid to air-

conditioning, pressure differentials and flow-rates all of which imply that the condition of these new facilities will deteriorate. In the absence of a program of careful monitoring and maintenance, the degradation of the product seems inevitable.

These deficiencies in the facilities should be remedied as a matter of urgency.

On procedural issues, the documentation related to each batch is too fragmented and it is difficult to audit the manufacture of any particular batch. It is suggested that a more rigorous approach is required to bring gel-generator production into line with the discipline necessary for effective pharmaceutical manufacturing.

A comprehensive Batch Production Record was drafted for consideration (*See appendix*) which was meant to demonstrate the principles of pharmaceutical production through shared responsibilities. This document emphasises the need for a working team approach. It is recommended that NPIC engage help from the local College of Pharmacy for a more professional solution to these problems.

Summary of Investigation into Quality of the Manufacturing Facilities and Compliance to Good Manufacturing Practice.

The facilities at NPIC for the manufacture of gel generators, despite their newness and the satisfactory results currently exhibited by the product, are inadequate and would prevent the product being registered/licensed in any other country. (*It is common practice for national therapeutic goods authorities to conduct audits on a suppliers facilities before approving import.*)

Consequently these facilities must be upgraded.

In parallel to improving the facilities, NPIC must pay greater attention to manufacturing procedures, documentation and the organisation of responsibilities and duties.

R.E.Boyd
7 July '96

NUCLEAR POWER INSTITUTE OF CHINA, CHENDU

^{99}Mo:^{99m}Tc

GEL-TYPE GENERATOR

BATCH PRODUCTION RECORD

BATCH NO..... PRODUCTION DATE:.....

1. RAW MATERIALS

• Molybdenum trioxide	batch.....	quantity.....	reference.....
• Sodium hydroxide solution	batch.....	quantity.....	reference.....
• Zirconyl chloride solution	batch.....	quantity.....	reference.....
• Sulphuric acid solution	batch.....	quantity.....	reference.....
• Water for Injection	batch.....	quantity.....	reference.....
• Physiological Saline	batch.....	quantity.....	reference.....

Generator Components

Glass Columns-	Batch	.....	Tubing -	Batch	.....
	Inspected	..... Signature/Date		Prepared	..... Signature/Date
	Washed	..... Signature/Date		Inspected	..... Signature/Date
	Depyrogenated	..... Signature/Date		Sterilised	..... Microbiol/Date
	No. Used	..... Signature/Date			
Needles -	Inspected	..... Signature/Date	Connectors-	Inspected	..... Signature/Date
	Sterilised	..... Microbiol/Date		Sterilised	..... Microbiol/Date

2. PROCESS DETAILS

Operation	by	when
2.1 Radio-activation		
No. of Targets		
grams MoO_3 per target		
Irradiation period ..... to		
Flux ..... $n/cm^2/sec$		
2.2 Preparation of Facilities		
Pre-production cleaning		
Microbiological survey of hot cells, rear of cell areas, clean rooms		
2.3 Gel Preparation		
Dissolution of MoO_3	.....	.....
Adjust pH	.....	.....
Reaction with $ZrOCl_2$	.....	.....
Final pH	.....	.....
Gel drying start	.....	.....
Temperature	.....	.....
Gel drying finish	.....	.....
2.4 Loading of Generators		
Number of generators loaded ☐	.....	.....
Loading speed ..... ml/min	.....	.....
Washing commenced ..... hrs	.....	.....
Washing completed ..... hrs	.....	.....
Generators disconnected and transferred ..... hrs	.....	.....
Radioactive contamination survey	.....	.....
2.5 Aseptic generator assembly		
LIST THE CRITICAL STEPS	.....	.....
OF ASSEMBLY AND WHO	.....	.....
PERFORMED THEM AND WHEN	.....	.....
Microbiological supervision of clean room operations	.....	.....

3. MEASUREMENT OF GENERATOR ACTIVITIES

OPERATOR .....

Generator Number	Activity of Calibration Time	Generator Number	Activity of Calibration Time	

4. VERIFICATION OF MANUFACTURING PROCEDURES

I certify that the correct manufacturing procedures for this batch of generators has been rigorously followed, and that only approved/validated raw materials have been used and that the batch manufacturing record is complete and accurate in all details

..... Product Manager
(signature)

5. LABEL CONTROL

The label text is certified accurate		.....	Production Manager
Number of labels issued	a	.....	Label Officer
Number of labels used	b	.....	Production Manager
Number of labels returned	c	.....	Label Officer
Number of labels destroyed	d	.....	QC Manager

Note: a = b + c + d
b = no. of generators produced

Residual stock of labels is [ ] ..... Label Officer .../.../...

6. PACKAGING CONTROL

I certify that the generators are packaged according to the specification (refer SOP.....) and that the external surface of the lead pots and the plastic outer containers have been measured and found free from radioactive contamination.

..... Product Manager
(signature)

7. QUARANTINE OF FINISHED PRODUCT

The generators produced in this batch have been placed under quarantine, pending QC release.

..... Product Manager at .....hrs...../...../.....
(signature)

8. QUALITY CONTROL

8.1 Sampling

Generators [ ] , [ ] and [ ] , being representative of the batch have been selected for testing.

..... QC Manager

8.2 Pre-Release Testing

8.2.1. Molybdenum-99 breakthrough	Specification < 1μCi.mCi^{-1}
8.2.2 Eluate pH	Specification 4-7
8.2.3 Radiochemical purity	Specification > 99% TcO_4^-
8.2.4 Chemical purity	Specification < 5 ppm Zr

8.3 Pre-Release Test Results

Generator No.	Activity @ Calibration	^{99}Mo Breakthrough	pH	%TcO_4^-	Zr
Operator					

8.4 Release Authorisation

I certify that the Pre-Release Tests have been performed and that the results indicate that the release specification **are/are not** satisfied in every detail. Accordingly the batch of generators **is/is not** authorised for release pending **no further testing/further testing specified.**

..... Quality Control Manager at .....hrs...../...../.....

8.5 Retesting

The following retests are required [none/.....]

8.6 Final Release Authorisation

Batch ..... [is cleared for/is not approved for] release.

.....Quality Control Manager at .....hrs...../...../.....

8.7 Acknowledgement of Test Results

I acknowledge the results of the pre-release testing and have authorised the release of the batch.

..... Production Manager ..... hrs...../...../.....

or

I have impounded Batch ..... to prevent its release.

..... Quality Control Manager ..... hrs...../...../.....

8.8 Post-Release Testing

Generator No.	γ-Spec	Serial Elution Efficiency	Sterility Test	Pyrogen Test
	% ^{99}Mo % others	±	-ve/+ve	-ve/+ve
	% ^{99}Mo % others	±	-ve/+ve	-ve/+ve
	% ^{99}Mo % others	±	-ve/+ve	-ve/+ve
Specification	< 0.1% ^{99}Mo > 0.01% others	>60%	-ve	-ve
Operator	.....	.....	.....	.....

8.9 Final Assessment of Quality

An assessment of the overall quality of Batch ..... indicates that the full production specification is

satisfied/not satisfied

..... Quality Control Manager .....hrs...../...../.....

Final assessment is acknowledged

..... Production Manager.....hrs...../...../.....

8.10 Final Action

8.10.1 Records filed ..... QC Manager ...../...../.....

8.10.2 Product recalled ..... Production Manager ...../...../.....

8.10.3 Consult Senior Manager

(Delete those actions not considered appropriate)

9.	DOCUMENTS TO BE APPENDED
9.1	Results of microbiological surveys of production facilities
9.2	Results of disinfectant validation studies
9.3	Clean room particle count
9.4	Certified copy of labels
9.5	Gamma spectroscopy print-outs
9.6	Reports of adverse patient reactions or customer complaints and subsequent follow-up actions.