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RESEARCH ESTABLISHMENT

LUCAS HEIGHTS RESEARCH LABORATORIES

VALIDATION OF THE STERILE MANUFACTURE OF THE AAEC MARK III MOLYBDENUM-99/TECHNETIUM-99m GENERATOR

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ABSTRACT

The Mark II molybdenum-99/technetium-99m generator now supplied to hospitals by the Australian Atomic Energy Commission is a non-sterile elution system. The Mark III version will be supplied as a sterile elution system.

A validation study has been undertaken to assess the capability of the new production facility, to evaluate up-to-date procedures for manufacturing sterile generators and to demonstrate that a sterile radionuclide generator can be made.

(Continued)

Generator manufacturing procedures and a time study of the validation are described. Microbiological methods for monitoring in-process aspects of manufacture, disinfectant efficacy and generator sterility are defined.

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RADIOISOTOPE GENERATORS; FABRICATION; MOLYBDENUM 99; TECHNETIUM 99; STERILIZATION; AAEC

CONTENTS

1. INTRODUCTION

The AAEC Mark II molybdenum-99/technetium-99m generator is now supplied to hospitals by the Australian Atomic Energy Commission [AAEC 1972]. The generator is loaded by remote handling and then assembled in a normal laboratory environment. Manufacturing procedures have been designed to minimise microbiological contamination to each unit, and routine laboratory tests have shown that untreated eluates are often sterile. However, the Mark II design generator is supplied to the customer as a non-sterile elution system.

The AAEC Mark III generator has been designed and will be supplied as a sterile elution system comparable with other systems on the market.

A validation study of the in-cell manufacture and the aseptic assembly of the Mark III generator was undertaken to assess the capability of the new production facility and to evaluate the up-to-date procedures required to produce sterile generators. The validation study involved the assembly of fifty non-radioactive generator units by each of four selected operators. After assembly and test elution, the units were incubated and the contents tested for sterility.

2. GENERATOR IN-CELL MANUFACTURE AND ASEPTIC ASSEMBLY

2.1 Generator Components

For the validation study, Mark III generators were manufactured from the following components. These components were assembled in stages to complete a generator unit (Figure 1).

Generator vial

This component consists of a double ended glass vial containing a sintered glass frit base. A 1.5 g alumina column was placed on the frit and secured by quartz wool. Vials were subsequently packed in units of ten in a stainless steel container, covered with a loose fitting lid, and sterilised in an oven at 160°C for a minimum of 4 hours.

Elution pipework

Sterile and pyrogen-free elution pipework was purchased. During in-cell manufacture, a unit was secured by remote handling to each vial opening (stage 1). To facilitate the in-cell operation, the units were aseptically removed from their sterile sachets and packed in groups of twenty in stainless steel containers which had been pre-sterilised at 160°C for a minimum of 4 hours.

Dispenser unit

The dispenser unit consists of a section of silicone rubber tubing connected to a piece of dispenser tubing. Covers were secured at each end and the entire assembly was sterilised by irradiation at an integrated gamma dose of 25 kGy. During aseptic assembly, the end of the attached silicone rubber tubing was connected to the downstream elution pipework unit (stage 2).

Charcoal filter unit

A 16 gauge by 1 in. stainless steel needle was connected to a charcoal filter unit. A cover was secured to the remaining end and the entire assembly sterilised at 25 kGy (stage 3). During aseptic assembly, the unattached end was connected to the upstream elution pipework unit.

0.9 per cent saline bag

Sterile and pyrogen-free isotonic (0.9 per cent) sodium chloride solution was purchased in 250 mL vinyl bags. A 1 mL aliquot of sterile distilled water was used to simulate the aseptic addition of chemicals needed to increase the elution efficiency of the generators.

2.2 Conditions of Validation

Staff performing the in-cell manufacture and aseptic assembly were trained in accordance with the procedures outlined by Saunders [1981] and prescribed by the Australian Department of Health [DOH 1976].

On commissioning, the manufacturing facility was cleaned and sanitised, a task subsequently performed once per week in accordance with procedures outlined by Davis and Saunders [1980].

New equipment was used throughout the trial, with the exception of twenty generator cases and twenty lead pots that had been commissioned at the beginning and re-used throughout the validation. The equipment was disinfected with sterile sponge wipers saturated in either a solution of 0.5 per cent chlorhexidine gluconate (Hibitane:ICI Aust. Ltd) and 70 per cent isopropyl alcohol, or a mixture of 2.0 per cent quarternary ammonium (Award: Diversey (A/Asia) Pty Ltd) and 70 per cent isopropyl alcohol, and then stored in airtight containers.

The disinfectants, which were alternated monthly, were prepared as a 70 per cent isopropyl alcohol:water base, dispensed in 500 mL aliquots, sterilised by irradiation (25 kGy), and then activated by passing the appropriate volume of Award or Hibitane through a 0.45 µm Millex (Millipore Pty Ltd) filtration unit.

2.3 Manufacturing Procedure

The non-radioactive Mark III generator was manufactured in two stages. The first stage comprised loading, saline washing, sealing and autoclaving the generator vials within lead cells flushed with filtered air under positive pressure.

The second stage involved the transfer of generator vials to lead shielding containers, insertion of these containers into generator carriers, connection of components, and test elution of the units; this stage was performed inside a room supplied and flushed with filtered air under positive pressure. Assembly and test elution of each unit was conducted inside a clean work station located within this environment. In stages 1 and 2, the air used to flush the lead cells and assembly room was passed initially through 0.2 µm filters.

Transfer of autoclaved generators from the cell area to the final assembly and elution area was effected by a mobile lead cell. Use of this cell enabled operators to place the vials inside lead containers by remote handling. An overhead crane was used to lower each lead container into a generator carrier, and a stainless steel trolley to transfer the generator carrier to the clean air unit.

2.3.1 In-cell manufacture

The first stage of manufacture, performed in Cell 1 (Figure 2), involved the removal of residual calcium hypochlorite solution from in-cell wash lines. This was effected by emptying and purging each line with 70 mL of sterile 0.9 per cent sodium chloride solution (saline). Peristaltic pumps housed in a clean air unit within the manufacturing facility extracted the saline from sterile containers and passed this solution via vinyl tubing to the Cell 1 wash lines. A 3 mL aliquot of saline was then sampled from each line into a sterile 30 mL Wheaton vial and monitored for the level and type of microorganisms present.

Sterile generator vials were transported to the first manufacturing cell and placed on a turntable, where they were loaded by pipette with 1 mL of sterile 1 M nitric acid. They were then transferred to wash stations, rinsed with 250 mL of sterile saline and passed to a second cell where each vial was secured at both ends with an elution pipework unit, placed in an autoclave and held at 115°C (-0°C, +4°C) for thirty-five minutes. Two biological monitors were included with each autoclave load (Figure 3).

2.3.2 Aseptic assembly

Two operators were required for the assembly operations. The first was responsible for the transfer of generator vials to lead containers, insertion of these containers into generator carriers, and transportation of the carriers to the second operator who performed the cleaner stages of component assembly and test elution. Because of the critical nature of these tasks, operators were assigned to and remained with specific operations for the duration of assembly.

After autoclaving, the generators were transferred by remote handling to lead containers, previously disinfected by procedures outlined in Section 2.2. Each container was transferred by overhead crane to a sanitised generator carrier secured on a stainless steel trolley and transported to the laminar flow cabinet for final assembly and test elution. During this time, the second operator placed inside the clean air unit the components required for aseptic assembly. On receipt of the generator carrier, this operator assembled the generator in the following manner.

Rubber septums as part of the saline bag and two test elution vials were swabbed with sterile 70 per cent isopropyl alcohol. The 16 gauge x 1 in. needle on the charcoal filter unit was inserted into a saline bag septum (stage 3), and the Luer connection at the opposite end of the filter connected to the upstream generator milking lead (stage 4).

The downstream generator milking lead was then connected to a metal needle on the dispenser unit. A sterile 19 gauge x 1.5 in. needle was attached to the dispenser unit outlet and the generator eluted into a sterile evacuated 10 mL Wheaton vial (stage 5). The generator was eluted a second time into a sterile evacuated 10 mL Wheaton vial containing a pellet of tryptone soya broth (Oxoid Aust. Pty Ltd).

Ten generators were manufactured in each batch. Of these, nine were eluted with normal saline and the tenth, prepared at random, was purged with either sterile fluid thioglycollate medium or sterile tryptone soya broth (both supplied by Oxoid Aust. Pty Ltd).

Where full test eluates of the assembled unit were unattainable, the units were tested as follows:

(i) For leakages due to faulty connections and parts, the generators were eluted to yield the maximum possible eluate.

(ii) If generator vials were broken through in-cell handling, crimping or autoclaving, or generator leads were broken due to mobile cell handling, an assembly was simulated and the generator by-passed.

The assembled generators were then removed from the lead containers and incubated at 37°C until the test was completed.

After completion of each daily operation, the facility and components were sanitised in preparation for the next batch. In addition, the wash lines were filled with calcium hypochlorite solution containing a minimum 1000 $\mu g\ mL^{-1}$ of chlorine contained in a saline solution at pH 6.0 - 6.5 [Farrington 1980].

2.4 Time Study

The time taken to perform each stage of manufacture was assessed for the following conditions:

Stage 1 Preparation of ten inactive generators to the autoclave stage of manufacture.

Stage 2 Assembly and test elution of ten inactive generators.

Stage 3 Preparation of the manufacturing facility and component parts for an assembly of ten units.

Table 1 shows the time taken by four operators to complete each stage. These times represent composite work activity. Stage 1 would take longer if it were performed by one operator.

The following operations, normally followed during manufacture of radioactive generators, were excluded from the validation trial.

(i) Commissioning lead pots and generator cases from bulk storage facilities and their disinfection and storage in the generator manufacturing facility - approximately one hour for ten units.

(ii) Disinfection of molybdenum-99 stock solution in Cidex (Johnson and Johnson Pty Ltd) - approximately 30 minutes.

(iii) Loading and holding molybdenum-99 solution for thirty minutes on the alumina column - approximately forty minutes for ten units.

(iv) Calibration and measurement of generators - approximately thirty minutes for ten units.

3. MICROBIOLOGICAL MONITORING

3.1 Biological Indicators

Two biological indicators were included in each autoclave cycle. The monitors, prepared from paper strips impregnated with sufficient numbers of

Bacillus stearothermophilus spores to survive for five minutes at 121°C, were contained in a sterile Mark III generator vial, secured at each end with a sterile rubber closure and aluminium seal. Each monitor in a pair was prepared differently for autoclaving and testing, as is described below.

The twenty autoclave cycles monitored during validation successfully destroyed the Bacillus stearothermophilus spores contained in both types of biological indicator.

3.1.1 Type A monitor

For the type A monitor, spore strips were placed aseptically inside a sterile 1.5 g alumina column secured by sterile quartz wool (Figure 3). Twenty minutes before heat treatment, the column was purged with 10 mL sterile water for injection. Excess water was removed by passing air into the column via a 0.45 µm Millex filter unit.

After heat treatment, the monitor was filled with sterile tryptone soya broth and incubated at 56 ± 2°C for a minimum of 14 days. The eluate was then transferred to a sterile vial containing 10 mL tryptone soya broth, incubated for a further 4 days and examined for Bacillus stearothermophilus.

3.1.2 Type B monitor

For the type B monitor, spore strips were placed aseptically inside a sterile Mark III generator vial and within 20 minutes of heat treatment the vial was filled with tryptone soya broth (Figure 3). Following heat treatment, the vial was incubated at 56 ± 2°C for a minimum of four days and examined for Bacillus stearothermophilus.

3.1.3 Control monitor

An untreated type B monitor, filled with tryptone soya broth and incubated at 56 ± 2°C, was used to monitor the efficacy of the procedure.

3.2 Wash Lines

A 3 mL aliquot of saline was removed from each wash line into a sterile 30 mL Wheaton vial. This solution was passed through a 0.45 µm Swinnex filtration unit (Millipore Pty Ltd), the filter removed, placed in a Petri

dish containing tryptone soya agar incubated at 32 ± 2°C for a minimum of three days, and inspected for microbiological contamination. No microbiological contamination was detected in the 18 samples monitored during validation.

3.3 Air Monitoring

During validation, the environment was monitored daily by the exposure of agar plates. The plates were prepared in a clean air unit and stored in a sterile container until required; the gel surface was moistened with 1 mL tryptone soya broth before exposure. The procedure involved the exposure of Petri dishes, containing tryptone soya agar, for four hours between 1000 and 1400 hours, followed by incubation at 32 ± 2°C for a minimum of three days. The outer surfaces of plates used to monitor in-cell environments were protected from radioactive contamination by sterile plastic covers.

Exposure plates were sited at the following numbered locations (Figure 4):

(i) The Anteroom

1. Shelf above the conveyor outlet
2. Centre front top shelf
3. Centre front middle shelf
4. Centre front bottom shelf
5. Centre front underbench area

(ii) The Manufacturing Facility

1. Right front of bench
2. Centre front of bench
3. Left front of bench
4. Shelf adjacent to anteroom door
5. Centre front of Cells 3 and 4
6. Centre front of Cells 1 and 2
7. Centre of Cell 2
8. Centre of Cell 1
9. Centre of clean air unit housing wash lines
10. Centre of the clean air unit used to assemble generators
11. Right upper section of conveyor
12. Middle upper section of conveyor
13. Upper section of conveyor

Table 2 shows the mean and range values of the number of colonies detected at

the various locations.

3.4 Disinfectant Monitoring

3.4.1 In-use disinfectant solutions

During validation, in-use disinfectant solutions were monitored periodically for microbiological contamination. A 10 mL aliquot from each container was passed through a 0.45 µm Swinnex filtration unit, the filter washed twice with 10 mL sterile normal saline, removed and placed in a Petri dish containing tryptone soya agar, incubated at 32 ± 2°C for a minimum of three days, and inspected for microbiological contamination. No microbiological contamination was detected in the samples monitored during validation.

3.4.2 Efficacy of disinfectant solutions

During commissioning, the efficacy of mixtures of 0.5 per cent chlorhexidine gluconate or 2.0 per cent quarternary ammonium with 70 per cent ethyl alcohol, a mixture of 1:60 vol./vol. Formula 51 (Reckitt and Colman Aust. Ltd) with water, and 70 per cent isopropyl alcohol, was determined against microorganisms isolated from the manufacturing system.

Forty-eight isolates were purified, identified for genus [Bennett 1960; Cowan and Steel 1970; Buchanan and Gibbons 1974; Analytab 1977] and tested for resistance to the disinfectants.

Four Petri dishes, each containing tryptone soya agar, were prepared with a lawn of each type of organism. A filter disc containing 0.05 mL of the selected disinfectant was placed in the centre of each lawn, the plate refrigerated for 30 minutes to allow diffusion of the disinfectant, incubated at 32 ± 2°C for three days, then inspected for the presence of a zone of inhibition around each filter.

All isolates were sensitive to the 70 per cent ethyl alcohol and water based mixtures. Most isolates displayed reduced sensitivity, and many indicated resistance to 70 per cent isopropyl alcohol. Sixteen of the least sensitive organisms were tested against 70 per cent isopropyl alcohol containing either 0.5 per cent chlorhexidine gluconate or 2.0 per cent quarternary ammonium; they displayed a sensitivity similar to that of the

ethyl alcohol based disinfectants. Consequently, the disinfectants selected to sanitise the facility and components during validation were 0.5 per cent chlorhexidine gluconate in 70 per cent isopropyl alcohol and 2.0 per cent quarternary ammonium in 70 per cent isopropyl alcohol.

3.5 Sterility Testing

Media used to test the sterility of assembled generators were prepared in accordance with methods outlined in Appendix C of the Australian Code of Good Manufacturing Practice for Therapeutic Goods [DOH 1976]. Liquid media were used within eight weeks of manufacture.

They were tested for sterility by incubating all vessels at 20 to 25°C for a minimum of nine days, having first been tested for ability to support growth by reconstituting two vessels from each batch with the appropriate volume of sterile normal saline containing the respective microorganisms.

Vessels of fluid thioglycollate media were inoculated with either 100 viable spores of Clostridium sphenoides ATTC 19403, or 100 viable cells of Staphylococcus aureus ATTC 6538P, incubated at 32 ± 2°C, and inspected for growth after 24 hours.

Vessels of tryptone soya broth were inoculated with either 100 viable spores of Bacillus subtilus ATCC 11774 or 100 viable cells of Candida albicans ATCC 10231 incubated, respectively, at 36 ± 2°C and 23 ± 2°C and inspected for growth after 24 hours.

Evacuated vials, each containing a pellet of tryptone soya broth, were prepared and pretested by reconstituting, inoculating and incubating four vials in the above manner. The vials were stored at 20 to 25°C and used before the six month expiry date.

3.5.1 Sterility testing of eluates

During aseptic assembly, nine eluates from each run were prepared by priming the generator with normal saline and eluting into a sterile evacuated 10 mL Wheaton vial containing a pellet of tryptone soya broth. The tenth eluate was obtained by priming the generator with either fluid thioglycollate medium or tryptone soya broth and eluting into a sterile evacuated 10 mL Wheaton vial.

The fluid thioglycollate vial and alternative reconstituted tryptone soya broth vials were incubated at 32 ± 2°C, and the remaining reconstituted tryptone soya broth vials were incubated at 23 ± 2°C for a minimum of 14 days.

On completion of incubation, the vials were inspected for turbidity and a stasis test was performed on one vial from each group by inoculating 10 to 20 and no more than 110 organisms of the appropriate microbe, incubating the vial at the appropriate temperature for a further 24 to 48 hours, and inspecting the vessel for turbidity. A validated sterility test was obtained for all units tested in this manner.

All generators passed this sterility test; a total of 193 of the 200 units tested were fully assembled units. Of the remaining seven units, eluates were obtained from five generators which were incomplete because either the generator vial or the elution pipework unit was broken. The eluates obtained from these units passed the sterility test. The remaining two units could not be tested for sterility because of a mechanical defect in the generator assembly.

3.5.2 Sterility testing of assembled generators

After assembly, generators primed with either fluid thioglycollate medium or tryptone soya broth were incubated, respectively, at 32 ± 2°C and 23 ± 2°C for a minimum of 14 days. At the end of the incubation period, each vessel was eluted into an evacuated 10 mL Wheaton vial and the generator system and eluate examined for turbidity. A stasis test was performed on each generator system in accordance with the methods described in Section 3.5.1. A validated sterility test was obtained for all units treated in this manner.

Generators primed with normal saline were held at 36 ± 2°C for a minimum of 24 hours. After incubation, a sterility test was performed by eluting duplicate 80 mL aliquots from each unit into two vessels each containing 10 per cent of 11 times concentrated tryptone soya broth and duplicate 45 mL aliquots were eluted into two vessels each containing 50 per cent of a twice concentrated fluid thioglycollate medium.

A saline bag incorporating an elution lead, sterilised by irradiation at 50 kGy, was included with each group of nine units to monitor the operators' technique, the reagents and the facility.

The two fluid thioglycollate vessels were incubated at 32 ± 2°C; one tryptone soya broth vial was incubated at 36 ± 2°C and the other at 23 ± 2°C for a minimum of 14 days. At the end of incubation, the vessels were inspected for turbidity and a stasis test performed on a minimum of one vial from each series of incubations in accordance with the methods outlined in Section 3.5.1. A total of 191 completely assembled generators passed this sterility test.

The remaining nine sterility tests were performed on incomplete generator systems. Six of the systems were incomplete and missing the generator vial/elution pipework unit which, in five cases, was damaged during manufacture and assembly and, in the sixth case, seized and would not allow liquid to pass. The remaining three systems contained filters which had seized during incubation and had to be removed for testing to proceed.

4. DISCUSSION AND CONCLUSIONS

This study was undertaken to assess the capability of the new production facility and up-to-date procedures for the manufacture of sterile radionuclide generators. Routine manufacture of such a system will enable the AAEC to supply a radionuclide elution system of a quality comparable to those produced by its competitors.

The generators were manufactured in two stages. The first stage, which comprised loading, washing, sealing and autoclaving of the generator vials, was performed inside lead cells flushed with air under positive pressure. The second stage, which involved transfer of generator vials to lead shielding containers, insertion of these containers into generator carriers, connection of components and test elution of the units, was performed inside a clean work station, situated within a room flushed with filtered air.

The validation study required training of four operators in aseptic procedures, assessment of the efficacy of the proposed disinfectants, a comprehensive environmental study on the facility, and sterility tests of the manufactured units.

Each operator prepared fifty non-radioactive generators in batches of ten per day. Of these, nine were flushed with sterile isotonic saline and the tenth with sterile microbiological media. A sterility test was performed on

the first eluate and the entire contents of each generator.

All units prepared during the validation study passed the prescribed criteria for sterility, thus substantiating the claim that the new production facility and procedures can routinely support the manufacture of a sterile radionuclide generator.

5. ACKNOWLEDGEMENTS

The authors are grateful to Messrs P. Brown, T. Gorman, K. Shephard and H. Smith who manufactured the units tested in the validation study and Mr P. Anderson whose work in solving facility malfunctions was greatly appreciated.

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TABLE 1
TIME STUDY OF ASSEMBLY OF MARK III GENERATORS

Operator*/Run	Time Taken by Each Operator		
	Stage 1	Stage 2	Stage 3
	h/min	h/min	h/min
Operator 1			
Run 1	1 30	2 15	1 00
2	1 30	1 45	1 00
3	1 30	1 25	45
4	1 15	1 20	45
5	1 10	1 25	35
Operator 2			
Run 1	1 45	2 00	1 00
2	1 30	1 45	1 00
3	2 15**	2 00	1 00
4	1 45	1 45	45
5	1 20	1 30	
Operator 3			
Run 1	1 30	2 00	
2	1 35	1 30	
3	1 30	1 30	
4	1 30	1 30	
5	1 15	1 30	
Operator 4			
Run 1	1 30	1 45	
2	1 30	1 25	
3	1 15	1 15	
4	1 30	1 25	
5	1 30	1 10	

* Each main operator was assisted by another operator
** Completed by one operator only

TABLE 2
RESULTS FOR AGAR PLATES EXPOSED IN MARK III GENERATOR ANTEROOM AND MANUFACTURING FACILITY

Position	Number of Exposures	Colonies Per Four Hour Exposure	
		Mean	Range
Anteroom			
Conveyor Shelf	37	16	0-47
Top Shelf	37	1	0-18
Middle Shelf	37	1	0-6
Bottom Shelf	37	2	0-14
Underbench	37	3	0-46
Manufacturing Facility			
Right Side Bench	37	1	0-14
Centre Bench	37	2	0-16
Left Side Bench	37	1	0-4
Anteroom Doors	37	2	0-10
Cells 3 and 4	37	2	0-7
Cells 1 and 2	37	5	0-25
Centre Cell 2	37	0	0-1
Centre Cell 1	37	0	0-2
Clean Air Unit - Wash Lines	37	0	0-8
Clean Air Unit - Assembly	37	0	0-1
Right Side Conveyor	37	4	0-16
Middle Conveyor	37	1	0-5
Left Side Conveyor	37	2	0-12

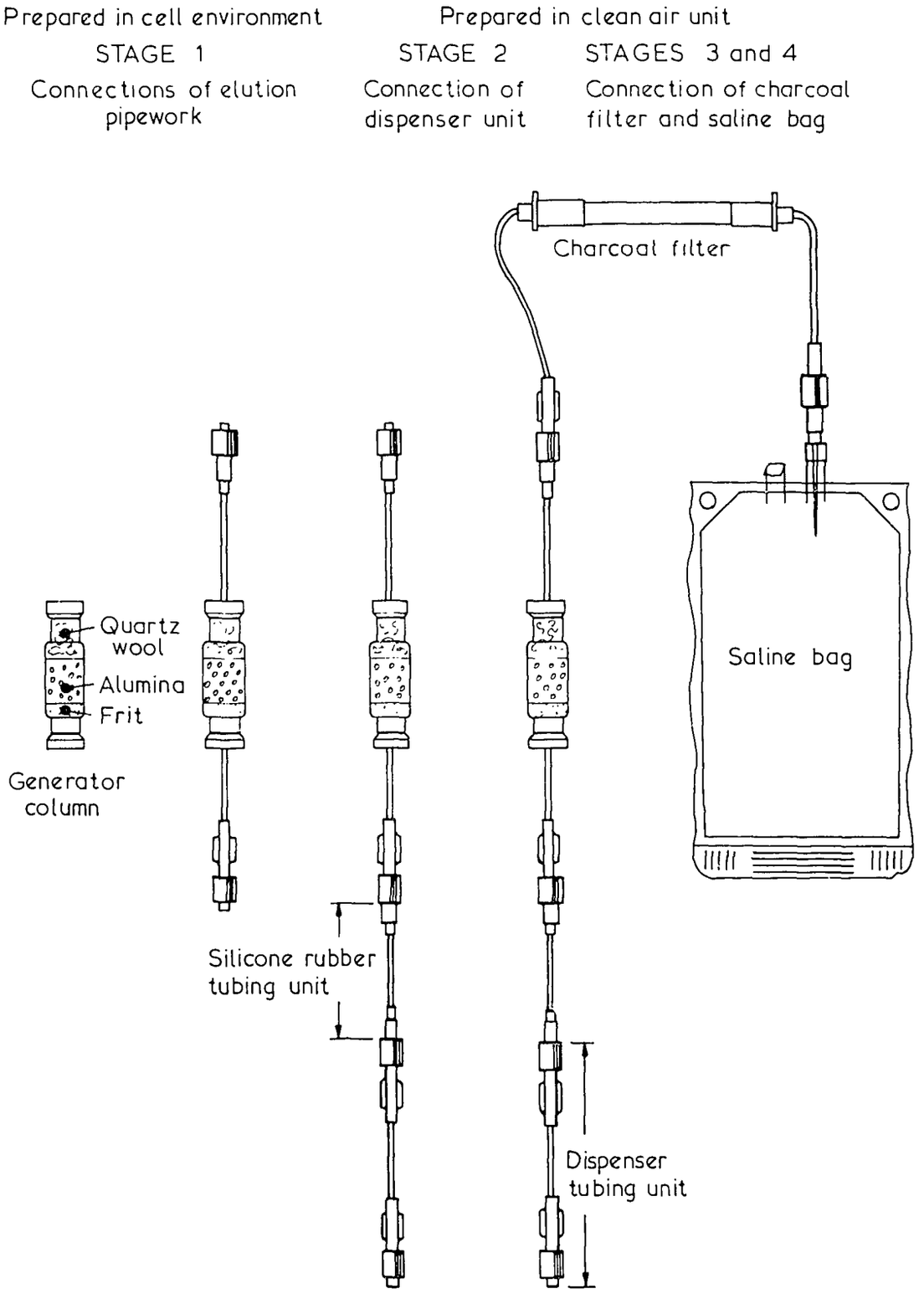


FIGURE 1. STAGES IN THE ASSEMBLY OF A MARK III GENERATOR

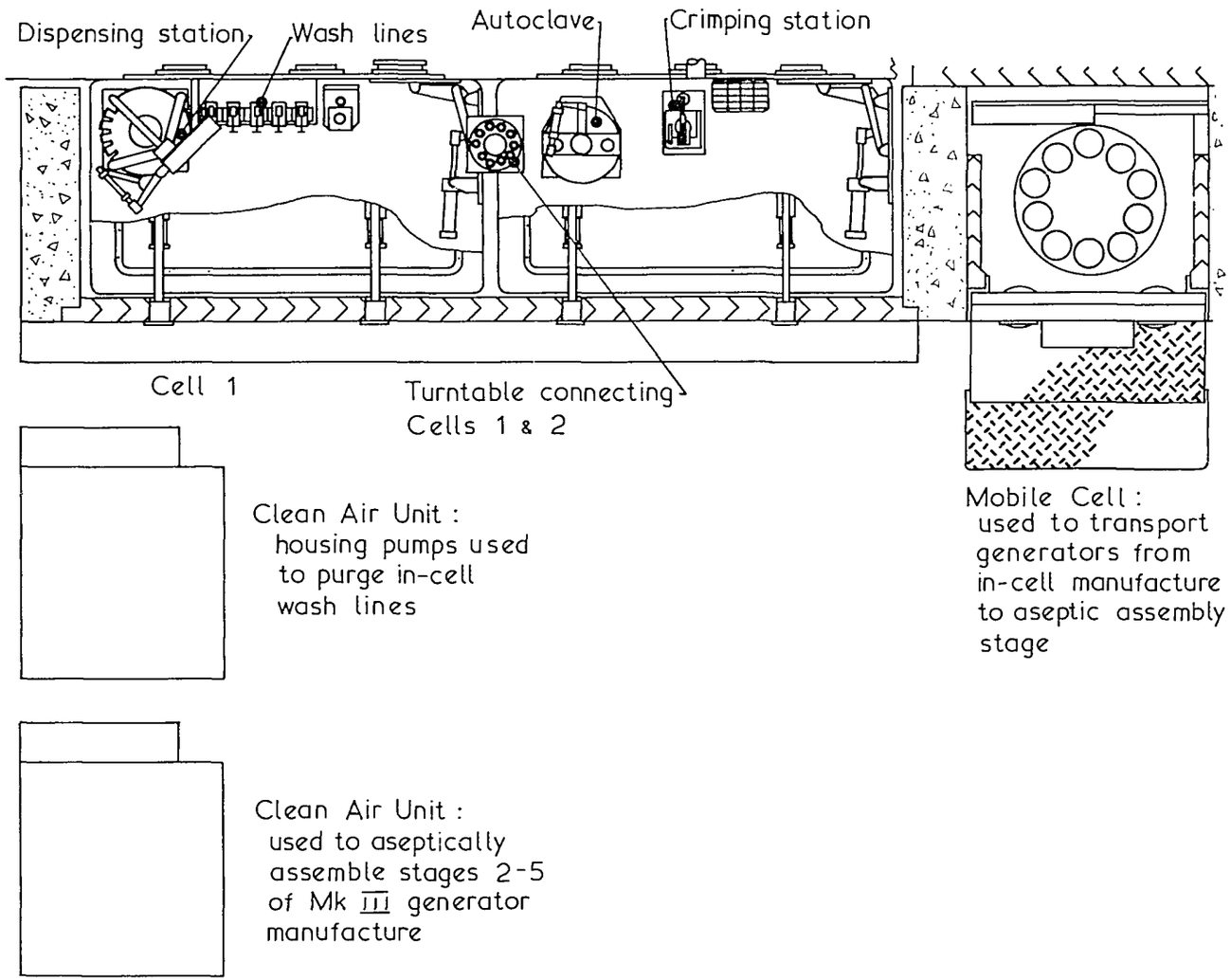
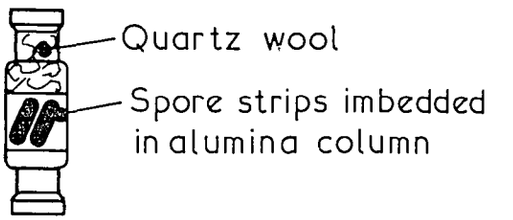
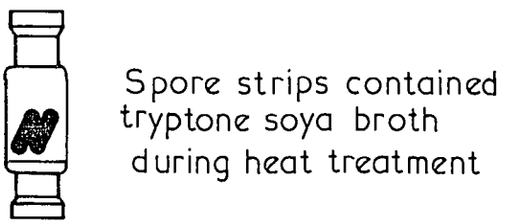


FIGURE 2. MARK III GENERATOR MANUFACTURING FACILITY



TYPE A MONITOR



TYPE B MONITOR

FIGURE 3. BIOLOGICAL INDICATORS USED TO MONITOR THE STERILISATION OF MARK III GENERATOR COLUMNS

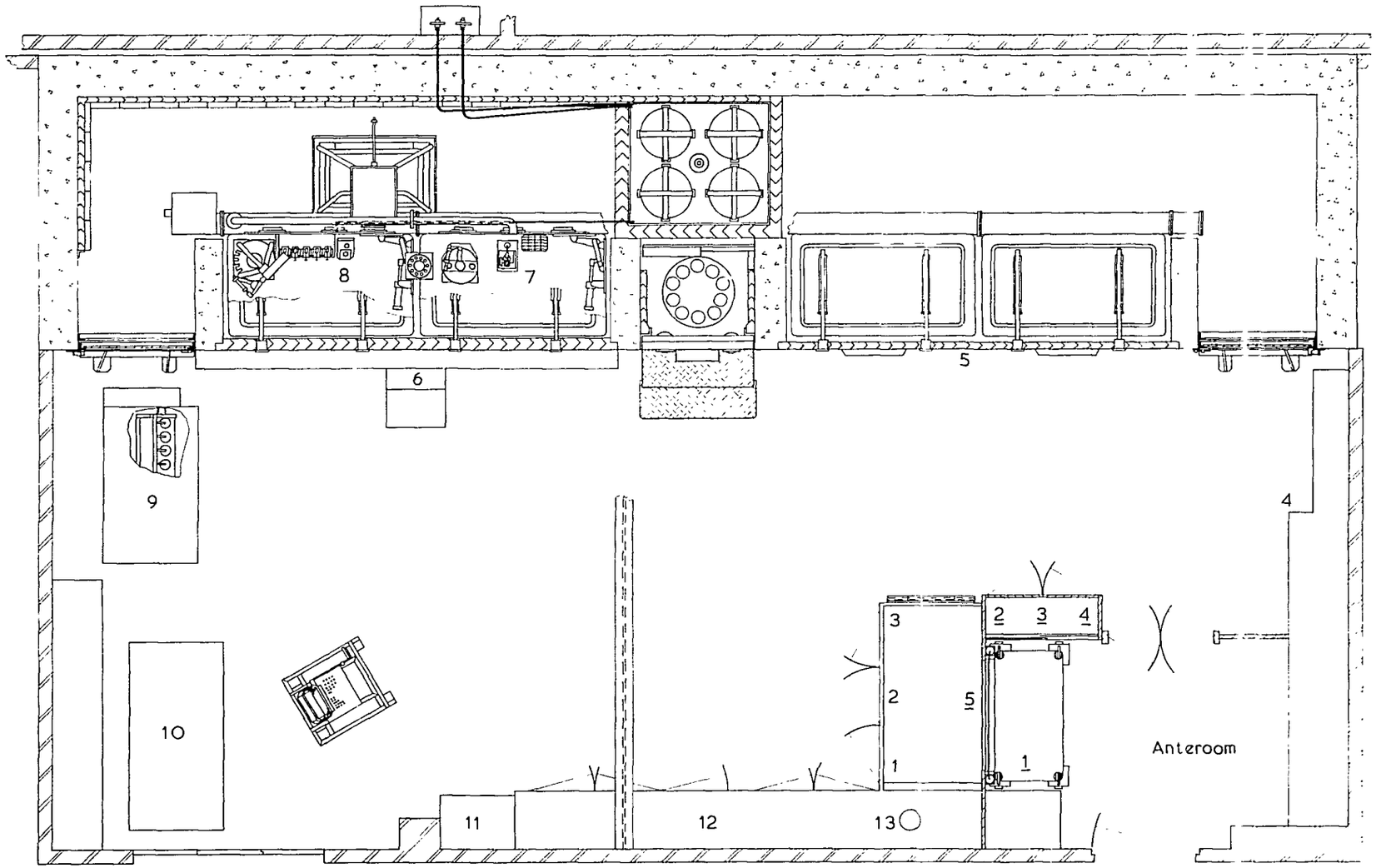


FIGURE 4. LOCATION OF AIR EXPOSURE PLATES IN MARK III GENERATOR ANTEROOM AND MANUFACTURING FACILITY
(exposure plate positions are identified in Section 3.3)