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RADIOISOTOPE HANDLING
FACILITIES AND AUTOMATION OF RADIOISOTOPE PRODUCTION

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FOREWORD

If a survey is made of the advances in radioisotope handling facilities, as well as the technical conditions and equipment used for radioisotope production, it can be observed that no fundamental changes in the design principles and technical conditions of conventional manufacture have happened over the last several years. Recent developments are mainly based on previous experience aimed at providing safer and more reliable operations, more sophisticated maintenance technology and radioactive waste disposal.

In addition to the above observation, significant improvements have been made in the production conditions of radioisotopes intended for medical use, by establishing aseptic conditions with clean areas and isolators, as well as by introducing quality assurance as governing principle in the production of pharmaceutical grade radioactive products. Requirements of the good manufacturing practice (GMP) are increasingly complied with by improving the technical and organizational conditions, as well as data registration and documentation.

Technical conditions required for the aseptic production of pharmaceuticals and those required for radioactive materials conflicting in some aspects are because of the contrasting contamination mechanisms and due consideration of the radiation safety. These can be resolved by combining protection methods developed for pharmaceuticals and radioactive materials, with the necessary compromise in some cases.

Automation serves to decrease the radiation dose to the operator and environment as well as to ensure more reliable and precise radiochemical processing. Automation has mainly been introduced in the production of sealed sources and PET radiopharmaceuticals. PC controlled technologies ensure high reliability for the production and product quality, whilst providing automatic data acquisition and registration required by quality assurance. PC control is also useful in the operation of measuring instruments and in devices used for packaging, identification and labeling.

This TECDOC summarizes major advances in the conditions of radioisotope handling facilities ensued with relation to the reliability, quality assurance, aseptic processing and automation. Examples of the major radioisotope production technologies are given together with several pictures of the devices discussed. Also included are a few papers submitted by the experts who attended the consultants meeting.

The IAEA wishes to thank the experts for valuable work and scientific contribution. Special thanks are due to L. Baranyai from the Institute of Isotopes, Hungary for the final compilation of the TECDOC. The IAEA officers responsible for this publication were D.V.S. Narasimhan and M.R.A. Pillai of the Division of Physical and Chemical Sciences.

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1. INTRODUCTION

In order to handle radioactivity, special facilities are required to shield the radiation emitted and to prevent contamination of the environment by the radioactive materials released during handling and processing. In production laboratories the processed activities are high and therefore the requirements for shielded facilities with well controlled ventilation and remote handling devices are greater. Several versions of shielded hot cells and remote handling devices have been developed and used over the years in major radioisotope production centres. The evolution of different designs has reflected the growing emphasis on optimization of protection and safety. As radioisotopes are increasingly being used in various fields, the demand for larger quantities has risen and more complex handling facilities are in need in the isotope production laboratories.

Some of the recent developments in the use of radioisotopes in medical field have also significantly impacted on the evolution of handling facilities. Application of pharmaceutical good manufacturing practice (GMP) requirements for air quality and processing conditions in the handling facilities of radioactive pharmaceuticals has led to significant improvements in the construction of isolator-like hot cells and clean rooms with HEPA filtered ventilation and air conditioning (HVAC) systems. Clean grade A (Class 100) air quality isolator-like hot cells compliant with GMP requirements for handling radiopharmaceuticals are now available commercially. Nevertheless, the application of clean room requirements in radioisotope laboratories in general and hot cells in particular is technically not an easy task. The technical problems have not been completely overcome and need on-going efforts.

Furthermore, GMP requirements exclusively designed to conditions for producing radioactive pharmaceuticals should be elaborated and distributed to facilitate the design, construction and operation of such facilities. GMP guidelines are guidelines for radioactive pharmaceuticals, by describing their specific character and refer to the production of sterile pharmaceutical products.

Due to the beneficial nuclear and chemical character of ^{99m}Tc radionuclide as well as its easy availability from the ^{99}Mo-^{99m}Tc generator, it is the 'workhorse' of the nuclear medicine and is widely used in nuclear medicine centres for diagnostic purposes. The manufacture of ^{99}Mo-^{99m}Tc generators ranges from small scale batch techniques through semi-automatic dispensing systems to fully automatic production lines. Their manufacture and quality control are also made under aseptic conditions to comply with GMP requirements.

The last decade has seen an increased use of positron emission tomography (PET) in regular diagnostic imaging and PET radiopharmaceuticals, (particularly ^{18}F-FDG in the hospitals). The 511 KeV, high-energy radiation needs thicker shielding and more sophisticated handling devices. In view of the short half-lives, the emphasis is also increasingly on the process and handling as per GMP than final QC. The clean area concept is more often applied to isolator-like hot cells for PET radiopharmaceuticals. The need for rapid, remote and reliable synthesis of PET radiopharmaceuticals has also been responsible for the introduction of microprocessor controlled synthesis modules. This experience has also led to the development of similar microprocessor controlled synthesis systems for other radioactive pharmaceuticals.

Miniature size radioactive sealed sources of ^{192}Ir, ^{125}I and ^{103}Pd have found widespread applications in brachytherapy of cancer. The production of such sealed sources together with that of the conventional sealed sources (^{192}Ir and ^{60}Co) also require remote precision welding using laser or arc and microprocessor controlled positioning devices.

Several radioisotope production centres have developed innovative devices and systems for remote handling of various important operations in hot cells such as target handling, capping and decapping, dispensing and autoclaving. Often these developments have resulted in significant reduction of radiation dose and increased the GMP compliance.

These developments in the radioisotope handling technology are of considerable practical value to radioisotope production laboratories in several Member States. Compiling the salient points of these developments in a technical report is expected to make the information readily available to them for reference. With this objective, a consultants meeting was held in Pretoria, South Africa from 17 to 20 February 2003 to review the recent developments in the automation and remote handling technologies as well in the aseptic production conditions of radioactive pharmaceuticals.

The topics for discussion in the above meeting included the description of radioisotope handling facilities, hot cell designs, devices specifically designed for hot cell operations, aseptic production conditions (clean rooms and isolators), PET synthesis modules, ^{99}Mo-$^{99}Tc^{m}$ generator production lines, technological equipment, microprocessor controlled technologies, automation in sealed source production, and batch processing in miniature sources.

This TECDOC gives the most recent information collected on the development of radioisotope handling facilities, process equipment and devices as well as automation of the production. The dissemination of these information may assist pharmaceutical grade radioisotope producers to design modern facilities complying not only with requirements relating to radioactive materials but also providing aseptic conditions for the production of radioactive pharmaceuticals. Automation in the radioisotope production enables producers to reduce radiation dose, to increase reliability of the systems and to improve quality of products.

This technical report consists of two sections. The first part summarizes the discussions of the above topics, ending with conclusions/recommendations by the participants. The second is a compilation of a few papers covering the experiences in the consultants' institutions.

This report is illustrated with several photos of the facilities and devices provided by the consultants.

2. FACILITIES FOR HANDLING RADIOISOTOPES

Due to the radiation emitted from radionuclides and the risk of radioactive contamination, the radioactive materials are potentially hazardous to their environment. Handling and processing facilities are therefore specially constructed to minimize radiation exposure.

Based on the risk of incorporation, radioisotope laboratories have been classified in some countries into C, B and A categories. As large quantity of activity is handled, radioisotope production facilities belong to the 'A' category. Such facilities must be designed for the safe handling of radioactivity with respect to personal safety and safety of the surroundings. This safety consideration should include the building's safety interlock system, surveillance equipment and radiation monitoring.

A radioisotope production facility is preferably constructed as a single storey building to remove any doubt whether the top floor can carry the weight of shielding. The general finish of the production laboratories need to be smooth; and corners between walls and floors are preferably rounded to ease decontamination. Doors and windows are designed to provide increased sealing.

A well planned ventilation system forms the basis of contamination control in a radioisotope laboratory. For this purpose filtered air has to be supplied to the laboratory and exhausted. Hot cells need to be provided with a separate exhaust system. *Direction of flow of air within the laboratory needs to be from the zones with the lowest levels of radioactivity towards the zones with the highest potential levels of radioactivity*. In practice, this is arranged by supplying fresh air to the corridors. This air is drawn through the production laboratories into the boxes and finally filtered before being exhausted to the atmosphere.

As radioisotope handling and processing centres are generally located not within or close to big cities or industrial areas, the air is usually clean enough to be fed into the laboratory through inexpensive, low grade filters. To cover the possibility of failure in the ventilation system, a warning system need to be fitted.

Change rooms are incorporated to divide the radioactive zone from the inactive area. A full-body radiation detector gate is placed between the two zones to check potential personal contamination before leaving the radioactive zone (Fig. 1). Consideration needs to be given to the provision of an emergency electric generator to be used, in the event of a main power failure.

FIG. 1. Radiation control gate for checking personal contamination (Source: IZOTOP, Hungary).

In order to prevent the uncontrolled spread of radioactive contamination, the processing of radioactive materials requires an exhausted and shielded special enclosure called hot cell. Hot cells are arranged in the production laboratory in series, in blocks or individually with provision accessibility to maintenance (Fig. 2).

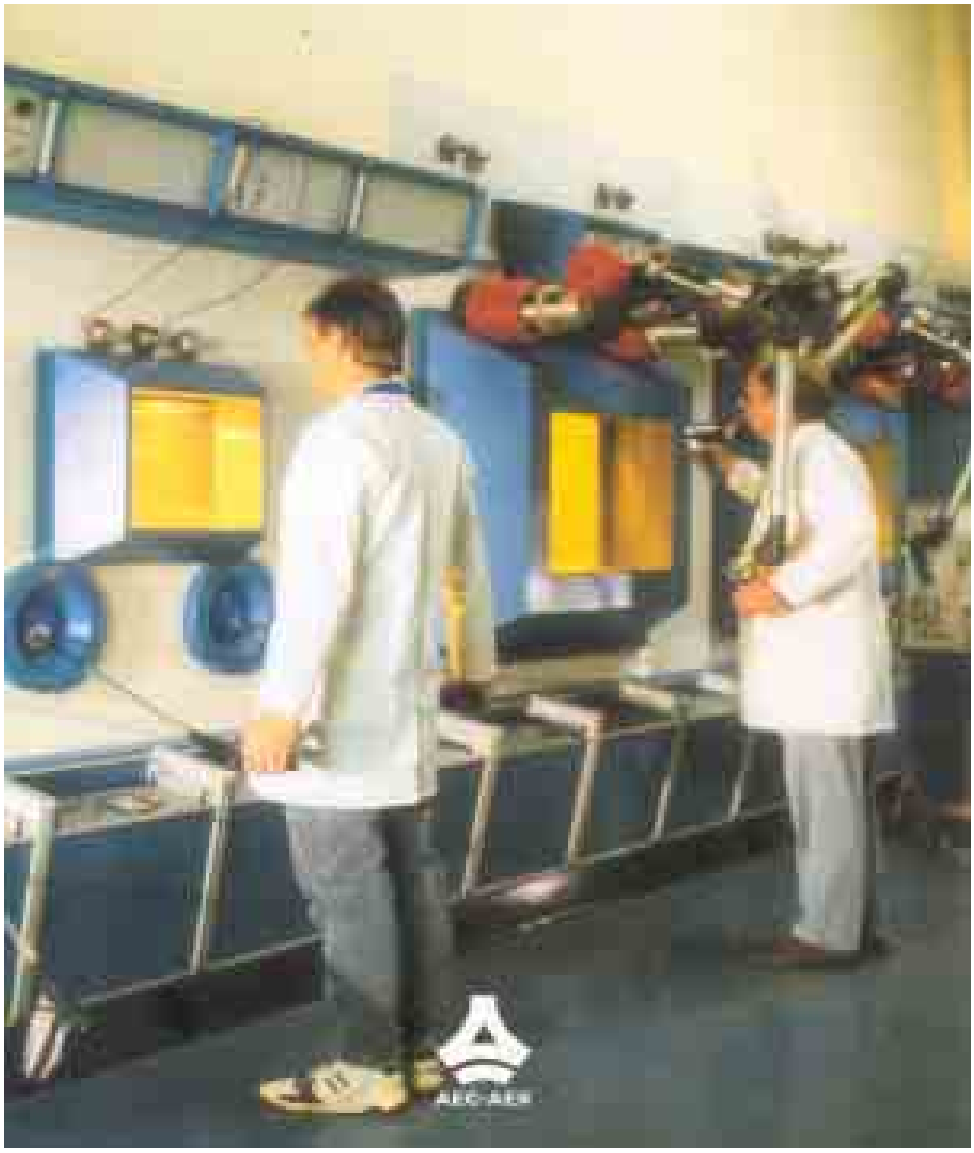

FIG. 2. Highly shielded hot cells for extremely high activities (Source: NTP, South Africa).

Radioactive materials are produced typically in small batch sizes using materials in small quantities. Heavy lead containers are used for protection from radiation and hence there is a need for a crane to move these containers within the area. Attention must be paid to radioactive waste disposal. Discharged liquid wastes are to be monitored and treated while solid wastes are disposed at authorized radioactive waste repositories.

Control devices placed in the front of hot cells serve for operating the technological equipment and measuring instruments (Figs 3–4).

FIG. 3. Hot cell series with remote handling tongs (Source: IZOTOP, Hungary).

FIG. 4. Front of a hot cell with remote handling tongs (Source: IPEN, Brazil).

The floor of the containment box is where most operations are performed and its use need be as effective as possible. Large items, such as autoclaves, ion-chambers storage containers and reaction vessels are sometimes better placed under the floor. Other than space saving, a further benefit could be the removal of services and their feed-through connectors from the box. Additionally these items can be shielded from the box or alternatively the box could be shielded from them. This may be done singularly, as in the case of the ion-chamber, or collectively where the whole floor of the box (and below box walls) is shielded. Storage of waste under a lead slab reduces the radiation damage to in-cell equipment and can reduce radiation to the operators (Fig. 5).

FIG. 5. Solid and liquid radioactive waste disposal equipment (Source: IPEN, Brazil).

In order to avoid cross-contamination individual hot cells or blocks of hot cells are preferred to whole series of hot cells used for different technologies. Separation of the front and rear of the hot cells from access and air supply point of view is is one of the options to provide better radiological protection.

The general facilities for radioactivity handling in conventional radiochemical laboratories including hot cells have not undergone dramatic changes. Major new developments are installation of aseptic production areas (clean rooms) within radioactive laboratory for the production and testing of pharmaceutical grade radioactive products.

HOT CELL DESIGNS

Hot cells are exhausted and shielded enclosures equipped with remote handling tongs or master-slave manipulators for processing radioactive materials. Application of hot cells is based on the principle that protection is the cheapest if containment is closest to the radiation source.

Conventional hot cells

Hot cells are generally made of ordinary mild steel covered by a good quality epoxy resin paint or made of stainless steel. Operations are carried out through one of the larger faces by using manipulators. Connections for services are welded into the bottom of the box or service lines may be brought in through a panel in the top face. An accessible door at the back provides access for maintenance and cleaning (Fig. 6).

Hot cells have to be shielded against radiation from gamma emitters for which a rigid support has to be provided. Various types of concrete, lead, lead glass, steel and depleted uranium can be used as shielding materials.

Thickness of the shielding must be calculated on the basis of the type, energy and activity of radiation to keep doses received by the operators within the internationally accepted limits.

FIG. 6. Rear side of a hot cell with maintenance door (Source: IPEN, Brazil).

The lead shield is equipped with viewing windows to overlook the area of operations in the cells. A 5 cm thick lead wall requires 10 cm thick windows of standard density of 5.2 g/cm^3. A lead shield is easily made of bricks with antimony content of 4-7% to increase the mechanical strength. The windows are mounted in frames fitting to the lead wall. To obtain the most economical result, shielding walls are to be placed as close to the source of radiation as is practically possible.

Remote-handling tongs and manipulators of various types may be obtained from commercial suppliers. Remote Handling Tongs with detachable heads allow change of the types of jaws without removing the tongs from the box. Sphere joints are used for tong handling through the lead walls. The whole joint is put together as a single removable unit.

Prior to putting a newly constructed hot cell into operation, a dose map indicating potential leakage of the radiation is to be drawn up using a sealed source containing similar isotopes as intended to be handled inside the hot cell and having known radioactivity.

As design considerations and dose calculations are well established principles applied for a long time, no dramatic changes in hot cell design from radioactivity and contamination point of view on conventional hot cells have been introduced. Some important considerations for the design and construction of the heavily shielded conventional hot cells to be used for extremely high activities are discussed below.

Adequate shielding

Optimization of radiation protection and safety principles need to be applied, with provision for accident conditions where the source moves to the minimum distance from the operator, while designing the shielding. Possible increase in future operations is to be considered at the time of

planning. Lead, and to a lesser extent steel, are the main shielding materials used for the smaller cells while concrete, both high and standard density, is popular for large cells. Although liquid filled windows are still in use, lead glass is preferred because of the perceived safety after an accident.

Access

The introduction of targets and reagents, and removal of product and waste require transfer systems that are reliable and safe. The safety encompasses that of radiation, contamination and conventional. There are a number of systems commercially available, such as the Padirac system from the CEA, which can be used for both input and output, but due consideration should be given to the exact requirements of the facility. An advantage of the Padirac and its inner container is the capability of introduction of sterilized items into the cell. The inner container can be coupled to a dedicated autoclave or similar equipment where the container and contents are sterilized and sealed. Liquid waste can be handled through shielded drains or absorbed on some suitable material and treated as solid. Although the latter appears to be inefficient, it may be advantageous when small volumes are produced. The drain method may require expensive maintenance.

Manipulation

There are two basic designs for handling equipment, the tong and master-slave manipulator. The tong, which could be seen as a fixed or manoeuvrable rod (with two degrees of freedom) is usually limited to shielding walls up to 150 mm thick as the lead ball, which gives it the swivel action, becomes too heavy in thicker walls.

The master slave manipulator provides far greater articulation but requires greater maintenance and is more costly (Fig. 7). Both tools require booting to effect air tightness to the box and the bootings should be easily replaceable.

FIG. 7. Highly shielded hot cells with master slave manipulators (Source: NECSA, South Africa).

Ventilation

The box needs to be held at a controlled negative pressure, the magnitude of which is dependant on the radio-toxicity and vapor pressure of the handled radioisotopes. Pressures of –200Pa to –500 Pa are normally chosen. Both inlet and outlet HEPA filters are required; the inlet determines the rate of air drawn into the box and the outlet filter must be able to handle the air flow when an opening occurs in the box. The rate of change of air through the box is determined by the minimum requirement of the air controller, the requirements for heat removal or the high flows that ensures aseptic clean operation environment. For exhausting, generally 0.5 m/s is adopted as the minimum linear inward air velocity through openings in a process enclosure used for treatment of radioactive materials.

Major changes in design will be needed to provide aseptic conditions for the production and testing of pharmaceutical grade radioactive products.

HOT CELLS USED UNDER ASEPTIC CONDITIONS

The hot cells constructed for the production of radioactive pharmaceuticals need to meet the requirements for a negative pressure isolator. The hot cells should be tight fitting according to the international technical standard. The walls of the hot cells should be smooth, impervious and unbroken and the corners are curved. Permanent installation of components, which cannot be sufficiently cleaned, should be avoided.

Stainless steel and organic glass are recommended as construction materials. The stainless steel surface inside the hot cell should be polished. The hot cells need to meet the general recommendations for rooms according to the GMP regulation.

During their operation, the hot cells are under negative pressure with a 20- fold air change per hour in case of handling radioactive pharmaceuticals. The in-air and exhausted air should pass through HEPA filters. Airflow should be controlled inside the hot cell. The sucked in air should be filtered.

The hot cell can be equipped with double door air locks. It is desirable to provide for a connection with a commercially available disinfector (e.g. hydrogen peroxide) and to have the front and/or back wall vertically movable in order to clean or change the devices inside the hot cell (Fig. 8).

The so-called Mini-cells are commercially offered especially for the PET-technology (Fig. 9). The Mini-cells are used for the automatic synthesis of PET pharmaceuticals, the dispensing of pharmaceuticals in vials and syringes. The Mini-cell is a completely closed hot cell with controlled air flow (clean room class C and A are possible, refer Table 1). The Mini-cell is designed without manipulators.

FIG. 8. Hot cell with openable rear wall (Source: Wälischmiller GmbH, Germany).

FIG. 9. Mini cell for dispensing with controlled air flow (Source: Wälischmiller GmbH, Germany).

MANIPULATORS USED FOR HOT CELLS

Different manipulators are used for the handling of radioactive materials inside the hot cells (negative pressure isolator) for the production of radioactive pharmaceuticals. The manipulators have to be installed absolutely tightly. The use of ball tong manipulators and master slave manipulators depends on the necessary thickness of the shielding wall and the necessary manipulations inside the hot cell. Ball tong manipulators can be used up to a shielding thickness of 100 to 150 mm lead.

Master slave manipulators are to be used if the shielding thickness is greater than 100 to 150 mm lead. The master slave manipulators are recommended if complicated and sensitive operations inside the hot cell have to be carried out (Figs 10–11). The booting of the manipulators are to be resistant to agents, which is used for cleaning and disinfecting as well as the chemicals used in the production.

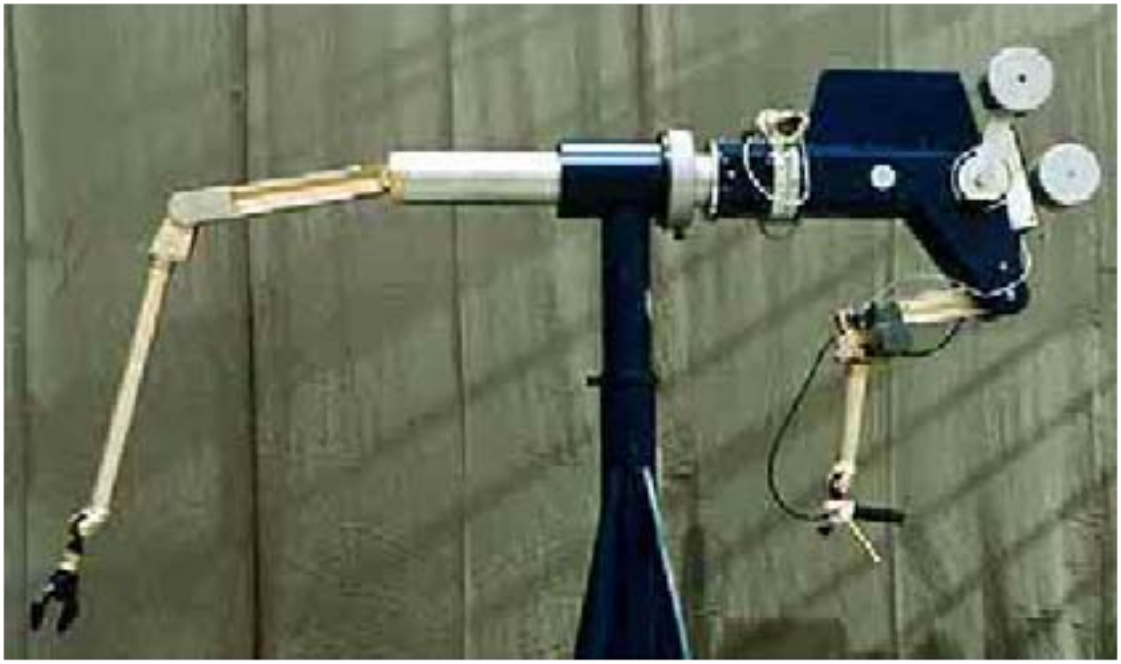

FIG. 10. Master slave manipulator for total remote handling (Source:Wälischmiller GmbH, Germany).

FIG. 11. *Hot cell with installed master slave manipulators (Source: Wälischmiller GmbH, Germany).*

The maintenance of the cell and in-cell equipment is technically demanding due to the high radiation and contamination levels experienced when the integrity of the facility is broken. This problem is to be addressed in the design stage and all routine maintenance operations are to be practiced in the commissioning stages. The routine service such as lubrication of joints and the adjustment of manipulator cables or tapes are examples of operations that do not pose undue radiological risk, whereas the replacement of booting does pose radiation hazard.

The standard manipulator access through the biological shield is located at the top of the cell allowing the safe removal of the manipulator. The replacement of its booting should be an easy operation subsequent to that. The removal of the tong and ball, required for its booting replacement, exposes the personnel to the cell's radiation. This implies that consideration be given to the development of procedures and designs to avoid this possibly irretrievable situation. Some of the useful devices are given in Figs 12–13.

Cell doors and port closures should be made to allow replacement, and cell lighting should be protected and placed outside the containment box if possible.

The outlet filters can become a radiation and contamination risk. It is recognized in the latest designs that these filters should be removed through the cell's waste system, as would booting and defective slave-hands.

In-cell equipment is usually produced or adapted in-house and therefore does not generally exhibit the same level of design refinement as commercially available cell equipment. Nevertheless, consideration should be given to factors such as little or no maintenance, the possibility of strategic component in-cell repair or replacement the necessity for cleaning and the avoidance of superfluous extras.

FIG. 12. Tong manipulator with accessories (Source: Wälischmiller GmbH, Germany).

FIG. 13. Ball brick for the installation of the tong manipulator (Source: Wälischmiller GmbH, Germany).

While conventional hot cells need only periodic decontamination, aseptic hot cells need sanitation too. Neither generally settled solution nor good applicator recommendable for this purpose are readily available. In most cases working surfaces are cleaned regularly by means of manipulators and full cleaning is possible only during maintenance periods. For sanitizing aseptic hot cells designed as isolator or operated in clean room, various spraying and evaporation methods are available.

Sanitation of aseptic hot cells can be carried out by any of the following methods:

— spray method with H_2O_2 solution
— evaporation of H_2O_2
— combination of saturated water steam/H_2O_2
— flowing saturated water steam
— different peracetic acid procedures
— formalin methods, etc.

To achieve clean grade, equipment and devices generating particles and/or vapours, aseptic hot cells (driving motors, vacuum pumps, cranes) - as far as possible - should be placed and operated outside the hot cell. Machinery of freeze-dryers should also be placed outside the clean room, only chamber should be opened to the clean area.

3. ASEPTIC CONDITIONS IN THE PRODUCTION OF RADIOPHARMACEUTICALS

Medicinal or medical products should be protected from microbiological contamination by their environment. As the direction of the potential microbiological contamination is from the environment and towards the material the ideal protection is to hinder movement of the surrounding air towards the product. This can be achieved by providing filtered airflow towards the product from the environment. Basically such a system creates overpressure in the production area so clean rooms operate with positive pressure relative to the environment.

According to the requirements of the GMP relating to medicinal products, sterile pharmaceuticals should be manufactured in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air, which has passed through filters of an appropriate efficiency. This protects the product from microbiological contamination by the environment.

Categories of clean areas according to the number of suspending particles and that of microorganisms in the air are given in Table I.

TABLE I. CATEGORIES OF CLEAN AREAS

CLEAN GRADE	Max. number of Particles equal or above 0.5 μm	Max. number of particles equal or above 5 μm	Maximum number of Microorganisms
A	(3 500 / m^3) (100 / ft^3)	0 / m^3 (0 / ft^3)	0 / m^3 (0 / ft^3)
B	3 500 / m^3 (100 / ft^3)	0 / m^3 (0 / ft^3)	5 / m^3 (<1 / ft^3)
C	350 000 / m^3 (10 000 / ft^3)	2 100 / m^3 (60 / ft^3)	100 / m^3 (3 / ft^3)
D	3 500 000 / m^3 (100 000 / ft^3)	21 000 / m^3 (600 / ft^3)	500 / m^3 (14 / ft^3)

Clean areas provide aseptic conditions for the manufacture of medicinal products for which basically the number of suspended particles (which carry bacteria) in the air should be reduced and at the same time working surfaces should be sanitized and microbiological contamination from other sources should be reduced (e.g. by protecting clothing).

For creating aseptic processing conditions two technical solutions have been developed which are discussed below:

CLEAN ROOMS

Clean rooms are laboratories or plant-sized clean areas in which HEPA filtered air is continuously introduced and recirculated. Positive air pressure relative to the surroundings is maintained with this air control. Personal and material flow is controlled through air locks to avoid the change of air between the zones.

In addition to the design and construction considerations assisting effective sanitation and limiting the spread of bacteria, measures and working rules are enforced to reduce the risk of microbiological contamination.

ISOLATORS

These are small-sized, local clean areas, which are hermetically sealed from the environment, excluding not only the surroundings but also the operator from the clean area. With their small sizes, isolators provide also economical result by isolating as close to the product as practically possible. Isolators can be supplied with doors or with air locks for supply of materials. Positive pressure isolators and negative pressure isolators are available according to the type of air flow control within the isolator.

For radioactive materials, the direction of potential contamination (and accordingly protection) is the opposite to that of microbiological contamination. Direction of contamination is from the material to the environment and for that reason the environment must be protected from vapours and/or particles of radioactive materials. From the ventilation point of view, the air needs to be exhausted from the shielded hot cells to maintain negative pressure within the hot cells.

As the direction of microbiological and radioactive contamination is opposite to each other, the protection methods should be combined for producing radioactive pharmaceuticals. In addition to the reduction of radioactive and microbiological contamination, radiation protection must also be taken into consideration. Harmonizing the three requirements is not easy and in some cases even conflicting. Where the conflict cannot be resolved radiation safety must have priority.

GMP guidelines are elaborated primarily for conventional pharmaceutical products and production conditions. They do not deal with radioactive materials in the required detail giving the basis for designing and operating radioactive facilities under aseptic conditions. The GMP describes only specific features of radioactive materials and refers to the production conditions of sterile pharmaceutical products. There is need to document harmonized design and operation principles relating to radioactive pharmaceuticals in every detail (not only referring to conventional sterile pharmaceuticals) because general solutions cannot be applied automatically for radioactive materials. Specifications for radioactive materials are specific in the following four aspects:

- To minimize the radiation dose to persons (radiation protection is necessary)
- Radioactive contamination caused by the material should be eliminated
- Mass of the active ingredient is extremely low so radioactive pharmaceuticals do not cause toxicity
- As administered volumes are low, dose of pyrogen materials injected is also low.

While the first two aspects are drawbacks causing significant difficulties in handling and in combining technical conditions with GMP requirements, the latter two features are advantageous from GMP point of view allowing reasonable compromises.

Harmonized solutions for the aseptic processing of radioactive pharmaceuticals are:

— Placing conventional hot cells (with –ΔP) in clean rooms (with +ΔP) where exhausted hot cells are supplied with filtered air from the surrounding clean room.
— Using hot cells with own air flow control (supplied with filtered in/air and exhaust air systems), designed and operated as negative pressure isolators (–ΔP). Such hot cells must be airtight to avoid air sucking from the surrounding (Fig. 14).

FIG. 14. *Hot cells (–ΔP) in clean room (+ΔP) (Source: IZOTOP, Hungary).*

Negative pressure isolators combine both types of protection (protection of the pharmaceutical product from the microbiological contamination of the surroundings and protection of the surroundings from the vapours and particles of the radioactive materials) within one space. If negative pressure isolators are supplied with appropriate shielding against radiation, radiation protection can also be provided. This solution is less expensive than placing conventional hot cells into high grade clean rooms, especially for small and medium scale production capacities.

Application of hot cells designed and operated as negative pressure isolator follow the same principle given for the hot cell design that protection is the cheapest if containment is closest to the contamination source.

Hot cells with controlled air flow operated as negative pressure isolator (supplied with filtered in/air and exhaust air systems) with grade A or C depending on the type of product are recommended for radioactive materials similar to cytotoxic products in the conventional pharmaceutical industry. The negative pressure isolator principle is well applicable also for radioactive preparation laboratories

in hospitals. Owing to the harmful character of radioactive materials air extracted from hot cells should not be recycled.

Based on the above considerations, when processing radioactive materials under aseptic conditions for use as pharmaceuticals, the following criteria can be adopted.

— For terminally not sterilized products (typically Tc-kits), 'A' class clean area with 'B' class background should be provided.
— For terminally sterilized products (e.g. autoclaved or filtered radioactive solutions) 'C' class clean area is recommended. Background class depends on the following considerations:
— If conventional hot cells are placed in clean room (air is sucked into the hot cell from the background) a clean room class dictated by the product treatment (selected according to the above principles) should be provided.
— If hot cells are self-supplied with controlled and filtered air (designed and operated on the negative pressure isolator principle) the inside clean class should be selected according to the product treatment (see above principles) and 'D' class clean room as background is recommended.

As design principles of 'D' class clean rooms are very close to those of radioisotope laboratories and as radioisotope laboratories are already equipped with ventilation, zoning system and changing rooms, a 'D' class clean room can be created and operated without serious additional investments, by replacing the existing low-grade filters to bacteria retardant HEPA filters; by supplementing cleaning agents with disinfection agents and by applying simple personal protection (changing aprons and covering hair).

As radioisotope handling facilities are generally big halls equipped with heavy machinery (e.g. cranes for lifting and transporting containers) which generate particles, and because the target treatment includes several dirty mechanical operations (e.g. target crushing, cutting) as well as several target processing technologies requiring operations with acid addition and evaporation, powder treatment, high temperatures, etc. these operations should be separated from further processing (e.g. bulk dilution, adjustment of radioactive concentration, dispensing, autoclaving, packaging) to allow aseptic conditions to prevail.

Because the final product (radioactive pharmaceutical) will be terminally sterilized (accordingly eliminating its bacteria and fungi contamination) and because the result of the target processing is a concentrated bulk solution which will be considerably diluted in the next phase of processing (accordingly ensuring that its pyrogen concentration is considerably lowered below the acceptable limit), acceptable microbiological purity can be expected from such separation of the technological operations (which must be validated).

However, filtering the bulk solution and using pyrogen-free distilled water throughout the whole technology, including dilution is recommended. In a typical dilution rate of 100x the majority of the product consists of sterile and pyrogen-free distilled water, which will determine its microbiological character.

With such a separation conventional hot cells can be used for target processing and hot cells operated under aseptic conditions should be used for pharmaceutical operations. The same separation can be applied to situations where radioactive bulk is imported and processed to pharmaceutical grade radioactive products. A drug master file characterizing the bulk and the radioactive pharmaceuticals and describing the procedure and conditions of the preparation is necessary in order to comply with GMP requirements.

Lead containers serving as shielding and providing secondary packaging material represent high mass and volume. To avoid introduction of lead containers into clean areas, it is recommended that well designed air locks be connected to the background or to the outside area. In this way, only

ampoules should be entered and treated in the inside clean area as is the case in conventional pharmaceutical plants. This is recommended because heavy lead containers are difficult to disinfect and can emit particles contaminating the clean area.

For disinfecting inside surfaces an H_2O_2 generator is the most sophisticated and most effective tool. Spraying disinfection agents and/or alcohol with a concentration of 70% is also applied. The evaporation and circulation method of H_2O_2- solution proves successful as a method with a good validation possibility. Suitable automatic devices on the basis of this H_2O_2- evaporation method are commercially available. Spraying bottles containing isopropyl-alcohol are commercially available and other known disinfectants can also be used by spraying. Whatever type of cleaning and sanitation method is selected, its efficiency and suitability must to be validated.

Cleaning and sanitation are important preparations to provide aseptic conditions for production. However, hot cells generally cannot be opened regularly for cleaning. Although, effective sanitation agents and decontamination agents are available, there is no easy-to-use applicator, unless hydrogen peroxide spraying head is installed. In the absence of hydrogen peroxide generator spraying for sanitizing agents, isopropyl or ethyl alcohol may be generally applied onto the surfaces. Efficiency of cleaning and sanitation methods needs to be validated.

Authorities in the Republic of Korea require adherence to GMP requirements for air quality in production of radioactive pharmaceuticals. In spite of significant improvements of hardware related to GMP, practically there are many conflicts in implementation of this regulation for production of radiopharmaceuticals due to the differences between radioisotopes and pharmaceuticals. In principle, it would be solved economically through the harmonisation of hardware and software related to GMP requirements within an achievable range. GMP requirements can be met by having good systems based on equipment and facilities as well as validation based on software. Conflicts occurring from the different properties between radioisotopes and pharmaceuticals need to be solved by a radioisotope producer by reflection of special circumstances due to radiation.

In the Republic of Korea, the committee of Korea GMP (KGMP) estimation recommended that the GMP guideline for production of radioactive pharmaceuticals be adopted. In principle, regulations for the general pharmaceuticals are correspondingly applied to radioactive pharmaceuticals, but the GMP regulations are not specific to radioactive pharmaceuticals. The production facilities for radioactive pharmaceuticals were completed in accordance with KGMP in 1998. As the regulation authority encourages adopting the regulation of KGMP certification, documents for the application of GMP certification are being prepared. In future all items such as medical radioisotopes, cold kit and radiation therapy sources need to be controlled by the code and standards of the Korean Drugs, Cosmetics and Medical Instruments under the KGMP regulation.

Recently the dose limit was drastically reduced from 50 to 20 mSv/man/y. In order to reduce the man/mSv exposition during the radiation work, it is essential to develop suitable accessories/ devices.

Despite all the above difficulties, radioisotope production must continue economically. It has been said that the first responsibility of a radioisotope producer is to define reality. The radiopharmaceutical production facilities are trying not only to survive these tough regulatory norms but also want to grow in these circumstances and leading the way by supporting health care programs in the world.

In order to solve these problems it is worthwhile to take into account the technological advances made in the past few decades especially in the field of remote handling and robotics. These measures will also reduce the human intervention during the production and quality control of radioisotopes. It is therefore essential to adopt automated operations for radioisotope production in future.

Parameters and methods applied for quality control of aseptic areas are as follows:

— Measuring the number of particles in the air with a particle counter e.g. Biotest APC Plus particle counter;
— Determining air microbiological contamination: e.g. Biotest RCS Plus air sampler with medium;
— Determining bacterial contamination of the product: e.g. culture on thyoglicolate-Bouillon medium;
— Determining fungal contamination of the product: e.g. culture on Caso/Bouillon medium;
— Determining pyrogen concentration in the product: e.g. LAL test.

Prior to operating aseptic areas (hot cells/isolators) they need to be qualified for the following parameters:

— Determining number of particles in air
— Determining microbiological contamination in air
— Measuring pressure, relative humidity and temperature
— Determining air flow rate
— Determining air exchange rate
— Determining air flow velocity
— Checking integrity of the HEPA filters
— Leak testing
— Determining cleaning rate of air.

In addition to equipment qualification, process validation is also required by quality assurance relating to pharmaceuticals (GMP). Critical parameters of the processes are to be incorporated into validation.

4. EQUIPMENT AND DEVICES FOR USE IN HOT CELLS

Design considerations for devices and equipment are as follows:

— Compact in size
— Operable with manipulator
— Drives and control devices to be placed outside the hot cell and
— Easy maintenance.

Devices presented by participants included dispenser, autoclave, peristaltic pumps, capping/decapping tools, target crusher, target cutter, container opening devices, can opener, activity transport lift system, pneumatic or electrical crane operation. A brief discussion on these is given below.

TARGET OPENER

Consists of two cylinders rotated by an electric motor and a cutting disc (Fig. 15). Aluminium capsule is laid on the cylinders and the cutting disc is pushed to the aluminium capsule while rotating.

FIG. 15. Target opener
(Source: IZOTOP, Hungary).

AMPOULE CAPPING DEVICE

It is a pneumatically operated crimper (Fig. 16). The ampoule with its cap is placed on its holder by manipulator and then the pneumatic sealing head is operated. While doing the operation in clean room, filtered air need to be introduced for pneumatic operations and the exhaust air has to be left outside the clean area.

FIG. 16. Ampoule capping device
(Source: IZOTOP, Hungary).

AUTOCLAVE

Small sized, manipulator-operated sterilization chamber with two trays for vials serves as autoclave (Fig. 17). Temperature and pressure controlled. Autoclaving is executed automatically by switching the control instrument on and is thereafter controlled for the main parameters (temperature, pressure, time). Measured parameters are displayed and recorded. Qualification of the equipment includes parameter verification, temperature distribution and sterilisation efficiency verified by test bacteria.

FIG. 17. Compact sized autoclave for ampoules (Source: IZOTOP, Hungary).

Pass-through autoclave

This is built into the hot cell or between two hot cells as an airlock providing transfer of the autoclaved product from the hot cell to the package area or from one hot cell to another (Fig. 18).

FIG. 18. *Autoclave built in the hot cell (Source: IPEN, Brazil).*

PERISTALTIC PUMP OPERATED WITH MANIPULATOR

Suitably modified peristaltic pump can be of great use in side the hot cell. A short arm serves to press the head of the pump down and to lift it up by means of manipulators (Fig. 19). Tubes can also be placed into the pump by means of manipulators. Such peristaltic pumps are commercially available.

FIG. 19. *Peristaltic pump operated with manipulator (Source: Commercially available).*

ACTIVITY TRANSPORT LIFT SYSTEM

The activity meter has to be tightly installed under the hot cell. The measuring chamber is a part of the hot cell and covered by a lid in the rest state (Fig. 20). It is recommended that a plastic insert be used inside the chamber, which can be easily removed and cleaned. The sample to be measured in the chamber is moved by an electrically controlled, vertical lifting device.

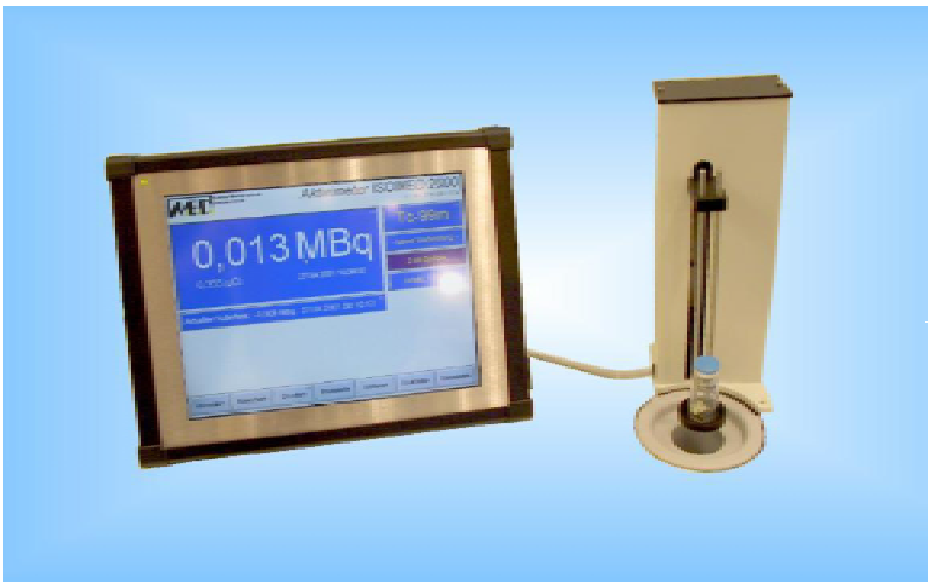

FIG. 20. Transport lift system for sample radioactivity measurement (Source: Wälischmiller GmbH, Germany).

DRY DISTILLATION EQUIPMENT FOR THE PRODUCTION OF ^{125}I

This consists of a compact electric oven for heating up the irradiated aluminium capsule to release the desorbed iodine, an acid scrubber and alkaline absorbers (Fig. 21). The oven is temperature controlled and values are displayed.

FIG. 21. Dry distillation equipment for ^{125}I production (Source: IZOTOP, Hungary).

DRY DISTILLATION EQUIPMENT FOR THE PRODUCTION OF ^{131}I

This consists of a compact electric oven for heating up the irradiated tellurium oxide granules contained in a silicium-carbide ceramic pot, followed by an acidic scrubber and alkaline absorbers (Fig. 22). Temperature controlled and supplied with a built-in activity meter.

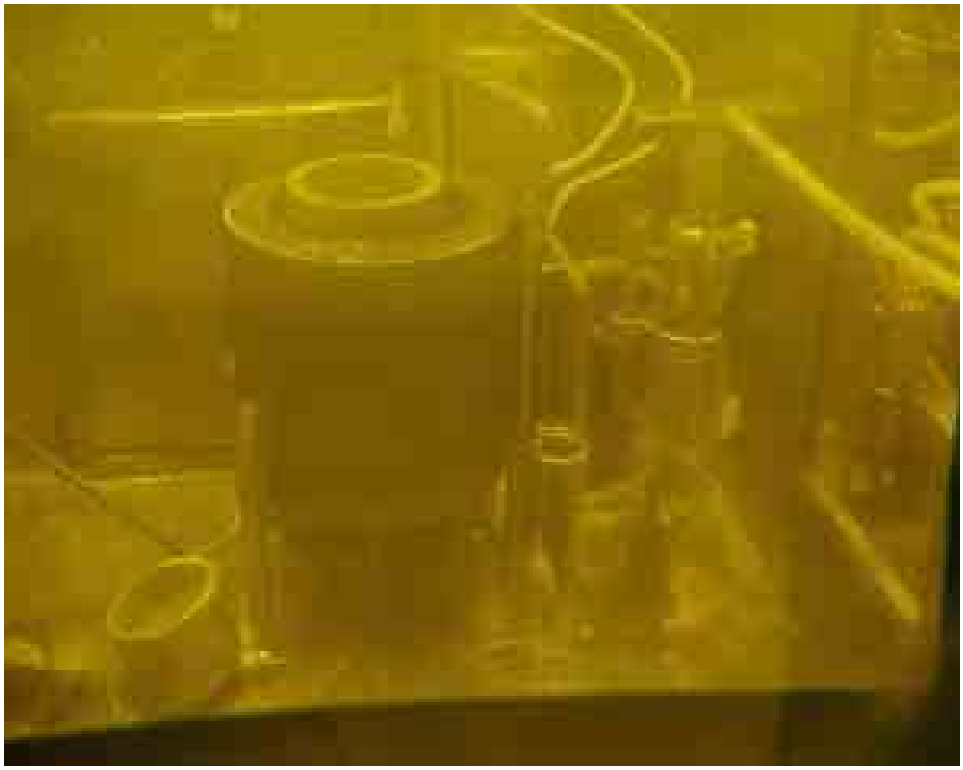

FIG. 22. Dry distillation equipment for ^{131}I production (Source: IZOTOP, Hungary).

PRODUCT SPECIFIC EQUIPMENT

These in cell equipment serve in the production of specific radioactive pharmaceuticals. The equipmnet for production of ^{131}I capsules is used for filling adsorbent in the first step followed by dispensing iodine solution and then capping the capsule (Fig. 23). Filled up capsules are dropped into lead container. Other examples are technological equipment for ^{67}Ga (Fig. 24) and ^{131}I-mIBG (Fig. 25) production.

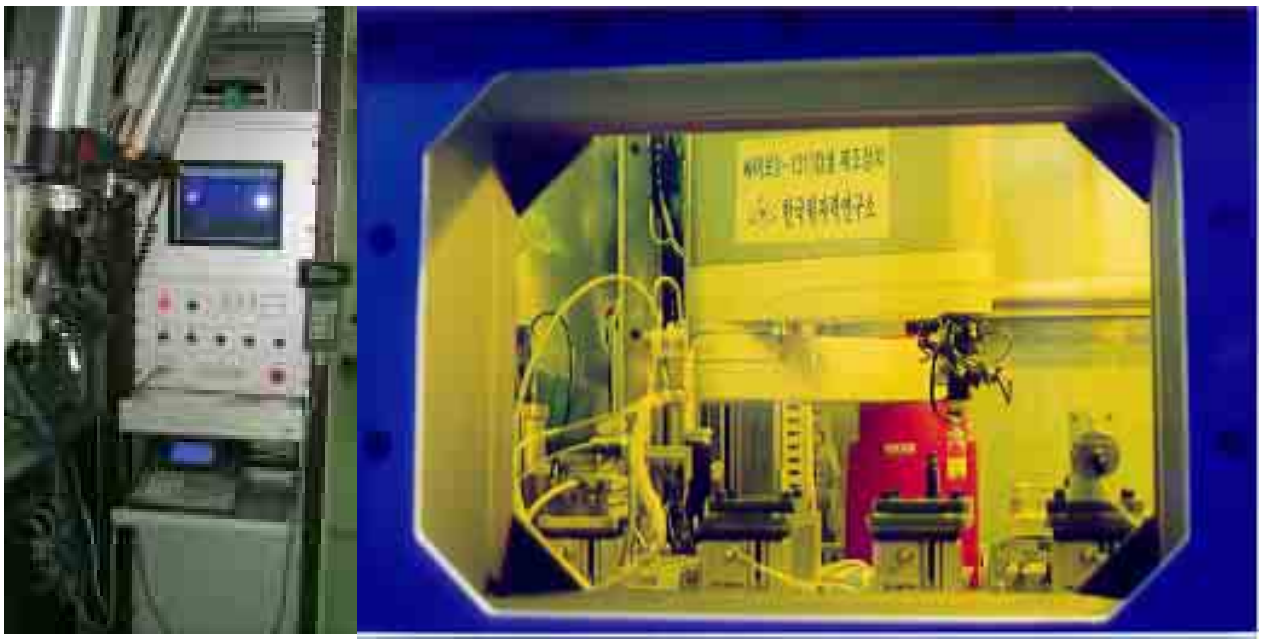

FIG. 23. ^{131}I capsule filling equipment (Source: KAERI, Republic of Korea).

FIG. 24. Technological equipment for ^{67}Ga production (Source: IPEN, Brazil).

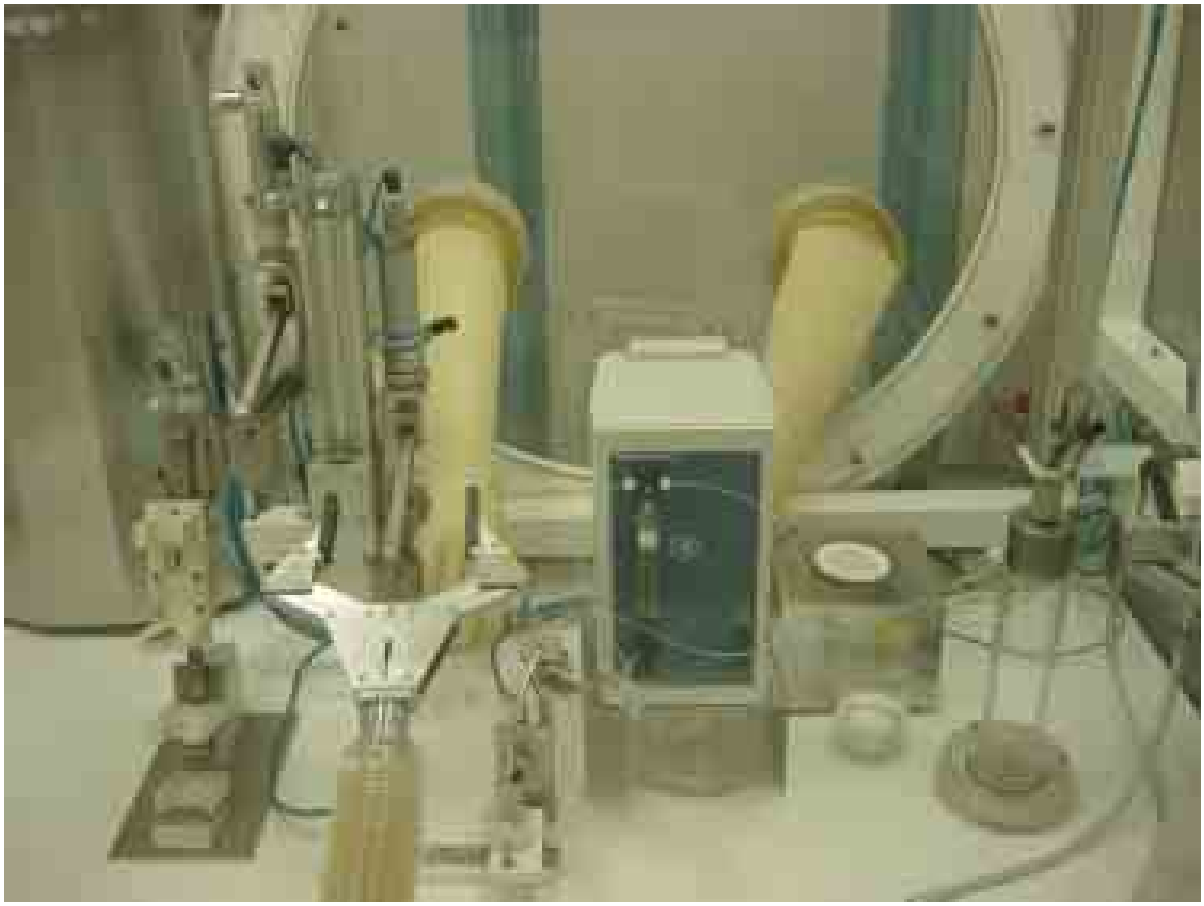

FIG. 25. Technological equipment for ^{131}I-mIBG production. (Source: IPEN, Brazil)

5. AUTOMATION, MECHANIZATION AND PC CONTROLLED PROCESSING

In the production of radioactive materials automation is important for the following reasons:

- Safety (reduces dose to personnel)
- Improved quality of product (e.g. welding seam)
- Speeds up production
- Ideal for large number of repetitive high dose and complex operations
- More GMP friendly – for automatic data records for GMP
- Fields which typically have been developed – PET isotopes, sealed sources, ^{201}Tl and ^{67}Ga, ^{131}I capsules, ^{99m}Tc solvent extraction
- Allows further automation /mechanisation where advised
- Cost/benefit combination.

There are many reasons for automation:

- To reduce personnel exposure to radiation
- To prevent human error for reliable quality control and precise work
- For mass production to improve the production rate
- To easily maintain the clean class without the human intervention
- To solve problems related to processing time, space and hazard.

Fig. 26 shows a typical automation system in sealed sources production in the Republic of Korea.

FIG. 26. Automation in sealed sources production (Source: KAERI, Republic of Korea).

During the planning stage of automation process, it is ideal to perform a feasibility analysis, proof-of-concept, benchmarking and prototyping for the process. In the development stage, concept design including software and detailed drawings are to be carried out. In the final stage, manufacture and installation of the mechanical parts and system operation and integration are done. The automatic processing system for ^{18}F-FDG synthesis modules was introduced in PET centers. At present synthesis module for production of SPECT radioactive pharmaceuticals such as m^{123}IBG synthesizer are available.

In case of m^{123}IBG module, the installation of a manual apparatus for the chemical process will need bigger space for installation and hence it is difficult to maintain clean class due to human intervention. In the field of PET radioactive pharmaceuticals, synthesis modules are very useful for saving the space and time as well as assuring the reliability in quality and routine supply. At present, the process automation in production of radioisotopes is expected to show many advantages but the introduction of full automation system for commercial supply will be considered on the basis of the investment for system development, maintenance, radiation effects of electric sensors, reliability of system operation, etc. In future it is hoped to have commercial standard component supplied as a package for automation of each process.

There are two kinds of machine in ^{131}I capsule manufacture used in Republic of Korea (Fig. 27). One is for therapeutic and the other is for diagnostic capsules. The main problems are solution dispensing and assembling the upper and lower capsules. The use of disposable syringe can be considered for economical and convenient preparation of diagnostic capsules. Dispensing precision is very important because small amounts of highly concentrated ^{131}I solution are used for production of therapeutic capsules. It is recommended that automatic systems be partially introduced for solution dispensing in order to improve reliability of dispensing precision and productivity.

FIG. 27. Automated ^{131}I therapeutic capsule filling system (Source: KAERI, Republic of Korea).

Further examples for automation in radioisotope production are found throughout this document under specific devices and/or products.

PC controlled processing not only provides high-level automation and reliability for the operations but also GMP conforming data registration and automatic document printouts.

6. EXAMPLES OF MAJOR RADIOISOTOPE PRODUCTION SYSTEMS

^{99}Mo-^{99m}Tc GENERATOR PRODUCTION LINES

Due to its favourable nuclear and chemical properties ^{99m}Tc is the most frequently used radionuclide worldwide in nuclear medicine for making millions of diagnostic images. It is obtained from three basically different sources:

— Eluted from fission ^{99}Mo based chromatographic column generator
— Eluted from irradiated ^{99}Mo based gel-generator
— Separated from irradiated ^{99}Mo compound by solvent-extraction.

Fission ^{99}Mo based chromatographic ^{99}Mo-^{99m}Tc generators became generally used in practice due to the simple processing and handling, reliability of product quality and high radioactive concentration. At the same time considerable efforts have been made to develop ^{99}Mo neutron irradiation based on so called ‘alternative generators’ with acceptable radioactive concentration.

Production centers developed different technical solutions for different scales of manufacture that are described below:

Ampoule filling batch method based on fission ^{99}Mo

This is used to produce small number of fission ^{99}Mo based generators. The procedure for the production of the generators is divided into three phases: the inactive preparation and assembling, the loading process and the final packaging. The aseptic assembling of the generators can be carried out completely as an inactive procedure. In this case an inactive test of the complete assembled generator system is possible.

The loading procedure of the generators, (handling the radioactive material), need to be as simple as possible. The loading steps are:

— dispensing the necessary portion of loading solution in vials
— steam-sterilisation of vials
— loading procedure according to the elution procedure.

The realization of the loading process according to the GMP-requirements can be carried out remotely controlled under a laminar flow module into a negative pressure isolator (shielded hot cell). The loading procedure can be carried out with an automatic system including sterile filtration. The packaging procedure need be automated as much as possible in order to reduce radiation exposure to staff.

Automated or semi-automated ^{99}Mo dispensing system and Tc-generator production line

Most production methods for ^{99m}Tc generators follow the steps of stock solution preparation, the loading of the Al_20_3 column with measured aliquot of the solution, the possible sterilization of the column, the assembly of the column in a lead pot with its elution needles and finally the complete assembly of the box or container. A degree of quality control testing usually precedes the packaging for transport.

Large scale generator production has necessitated the automation of some or all of the above steps. This is mainly due to reasons of quality in the first half and radiation safety in the second half of the process. A modern innovation is the loading of the generator column already placed in the lead pot and assembly. This implies a facility constructed from a standard cell coupled to an aseptic shielded assembly line. The active liquid is accurately measured and pumped through the wall of the cell directly into the pre-assembled generator in the aseptic area. Removable shields protect the operator while loading is taking place. A conveyor system takes the generator assembly to the packaging and dispatch areas.

The above system serve for producing large numbers of generators. Automatic dispensing techniques have also been developed, whereby dispensing takes place by vacuum suction of the dispensed ^{99}Mo solution through the chromatographic column. Column sterilisation is made before or after dispensing.

Dry ^{99}Mo bulk intended for supply in the near future by NECSA will provide low rate radiolysis with no liquid. If sterile solvent is used for dissolving the dry ^{99}Mo, extremely low pyrogenity of the product will be achieved by diluting the bulk with sterile, pyrogen-free distilled water or saline.

As Tc-generators produced from fission ^{99}Mo contain a built-in bacteria filter for the eluate, such generators are considered as terminally sterilized products needing ‘C’ class clean room for processing. However, in places where injection needles are connected to the column, microbiological

contamination should be considered as critical and hence local A - grade air flow or such grade hot cell is recommended for the critical operations.

GEL GENERATORS

In the production of ^{99m}Tc generators the gel generator option based on reactor irradiated molybdenum (i.e. low specific activity) provides an alternative to the fission generators. The irradiated molybdenum is incorporated into a zirconium molybdate gel, which is eluted with saline in the same way as fission generators representing identical qualities.

The gel generator utilizes low specific activity (n,γ) produced ^{99}Mo which is processed post-irradiation into an insoluble zirconium molybdate hydrous gel structure. The dried gel contains about 25% by weight of molybdenum and has properties consistent with a cation exchanger.

The gel is insoluble and chemically stable within the pH range 2-9. It successfully withstands thermal (wet steam) autoclaving and consequently the gel generator may be presented as a terminally sterilized product

The passage of an aqueous eluant (typically either pure water or physiological saline) through the column of the gel releases the $^{99m}TcO_4^-$. The chromatographic separation of $^{99m}TcO_4^-$ from the gel column can be performed with the same degree of ease like the fission ^{99}Mo generator (Fig. 28).

FIG. 28. Internal view of ^{99}Mo-^{99m}Tc gel generator hot cell (Source: IPEN, Brazil).

The external view of a ^{99}Mo-^{99m}Tc column generator production facility is shown in Fig. 29.

FIG. 29. ^{99}Mo-^{99m}Tc generator production line (Source: IPEN, Brazil).

CYCLOTRON AND ^{18}F-FDG SYNTHESIS MODULES

Several radioisotopes for medical use can be produced in cyclotron by charged particle (protons, deuterons or alphas) irradiation. These include isotopes such as ^{201}Tl, ^{67}Ga, ^{111}In, ^{123}I, ^{81}Rb, ^{18}F, ^{13}N, ^{11}C and ^{15}O. The last four isotopes are used for positron emission tomography (PET) studies. Cyclotrons with energy in a range of 10–70 MeV for proton irradiation and of 5–20 MeV for deuteron irradiation are commercially available and the manufacturers offer cyclotron suitable for the planned application (Fig. 30).

MC-50 Cyclotron | Cyclone-30 | KIRAMS-13

FIG. 30. Cyclotrons with different proton energy (Source: KAERI, Republic of Korea).

Radioisotope production in Cyclotrons in Republic of Korea:

— MC-50 Cyclotron (50MeV proton, installed in 1986)
— KIRAMS-13 (13 MeV, installed in 2002)
— Cyclone 30 (30 MeV, under installation).

Among the cyclotron produced radioisotopes, ^{18}F is most widely used due to the general occurrence of glucose metabolism in biological systems. The ^{18}F-FDG synthesis can be run on commercially available automated synthesis modules. ^{18}F-FDG synthesis panels are the best automated systems among radioisotope technologies. Installation according to the instructions of the supplier is the only requirement in most cases.

^{18}F-FDG synthesis consists of the following steps:

— Separation of ^{18}F from target by ion-exchange
— Introduction of ^{18}F into organic phase with KF through phase transfer catalyst
— Fluorination of FDG precursor (mannose-triflate) by nucleophylic substitution
— Hydrolysis of the protecting groups by acid or alkali addition
— Separation of ^{18}F-FDG from reaction mixture through series of separation cartridges.

Typical synthesis time is less than 30 min providing a radiochemical yield around 70% and radiochemical purity of >99%. Residual activity on the panel is typically <1%.

For the routine production of ^{18}F-FDG a radiochemistry laboratory with a lead shielded hot cell for safe processing and easy, available maintenance should be provided. Both the hot cell and the laboratory must comply with requirements relating to aseptic production conditions and those of GMP.

Cyclotron irradiation does not need an aseptic environment. FDG panel need to be placed into class 'A' hot cell designed and operated isolator with D grade background (Fig. 31). In case of batch-type (openable) hot cell. A clean grade is reached within the validated time after closing the hot cell and switching the air flow on.

Before Installation **After Installation**

FIG. 31. FDG synthesis module
(Source: KAERI, Republic of Korea).

Dispenser

It is recommended that dispensers be used for the dispensing of radioactive pharmaceuticals where the manipulator can easily change the dispensing tube or syringe. The changeable tube or syringe should be available as sterilized components. The dispensing unit needs to have provision to guarantee the complete documentation of the dispensing procedure. A dispensing unit used in IPEN, Brazil is given, Fig. 32.

The module can be operated in class 'C' clean room if the filtration and dispensing is carried out in parts in another mini cell. Class A would be required only in cases where the complete process is carried out. For background at least class 'D' is recommended.

FIG. 32. FDG dispenser for use in isolator (Source: IPEN, Brazil).

The product solution is dispensed into open ampoules, which are closed with rubber closure and capped automatically. Air used by the built-in capping device for pneumatic operation need be bacteria filtered. If already closed and capped ampoules are used for dispensing, leak tightness of the ampoules need to be validated after several piercing.

Filled and closed ampoules are transferred to lead containers through an airlock operated by valves. Lead containers (as secondary packaging materials) are introduced only into the background clean room after spraying with 7`% alcohol.

It is very difficult to achieve effective cleaning of hot cells used for radionuclides with half life longer than 24 hours. The isolator is designed in such a way that the inner surfaces may be cleaned easily, have rounded corners; and doors or movable walls can be operated with ease. The necessary in-cell equipment need be as simple as possible, easy to clean and using sterilized one way components whereever possible. Installation of equipment generating particles and/or vapours needs to be avoided. If inner areas of the isolator are not accessible for cleaning because the isolator cannot be opened after each batch (for example the cleaning of a box by manipulator which is used for the handling of radionuclides with half life longer than 24 hours) then the frequency of dismantling the isolator and performing thorough cleaning needs justification.

A balance needs to be drawn between the frequency of complete cleaning and frequency of dismantling the isolator. The user of the isolator has to make and document a risk assessment justifying its practices.

Care has to be taken to see that the cleaning agents are compatible with the material used for the isolator construction (e.g. stainless steel, polymeric materials etc.) and the installed in-cell equipment (Fig. 33). Residue of cleaning agents is removed prior to sanitization in order to prevent the masking of micro-organisms by the sanitizing agent.

FIG. 33. Clean mini cell designed as isolator for PET-module operation (Source: Wälischmiller GmbH, Germany).

SEALED SOURCES PRODUCTION

Radioactive sealed sources are encapsulated in a suitable container or prepared in a form providing equivalent protection against mechanical disruption. In some cases protection against heat and corrosion effects also may be required. Production of radioactive sealed sources is carried out in shielded conventional hot cells supplied with master/slave manipulators or tongs.

Sealed radioactive sources are widely used for industrial (^{192}Ir for radiography, ^{60}Co for gamma irradiators, ^{60}Co and ^{137}Cs for process control measurements and gauging) and medical (^{192}Ir and ^{125}I for brachytherapy, ^{60}Co for teletherapy) applications.

Electric arc welding is generally used for capsule sealing and laser welding for miniature sources. Typical arc welding current is 10-20 Amp with welding speed of 4-5 mm/s at an electrode distance of <1 mm and rotation speed of 20 per min. Welding needs high precision to provide good quality welding seam and leak-tightness of the capsules. Leak test is generally made with nitric acid in an ultrasonic bath. To satisfy these technical needs automated welding machines with capsule rotating tools have been developed.

In addition to the conventional use of radioactive sealed sources, miniature size radioactive sealed sources of ^{192}Ir, ^{125}I and ^{103}Pd are being increasingly used for brachytherapy of cancer.

The production of such sealed sources together with that of the conventional sealed sources such as ^{192}Ir and ^{60}Co also require remote precision welding using laser or arc and microprocessor controlled positioning devices (Figs 34–36).

FIG. 34. Welding system for ^{60}Co sealed source production (Source: KAERI, Republic of Korea).

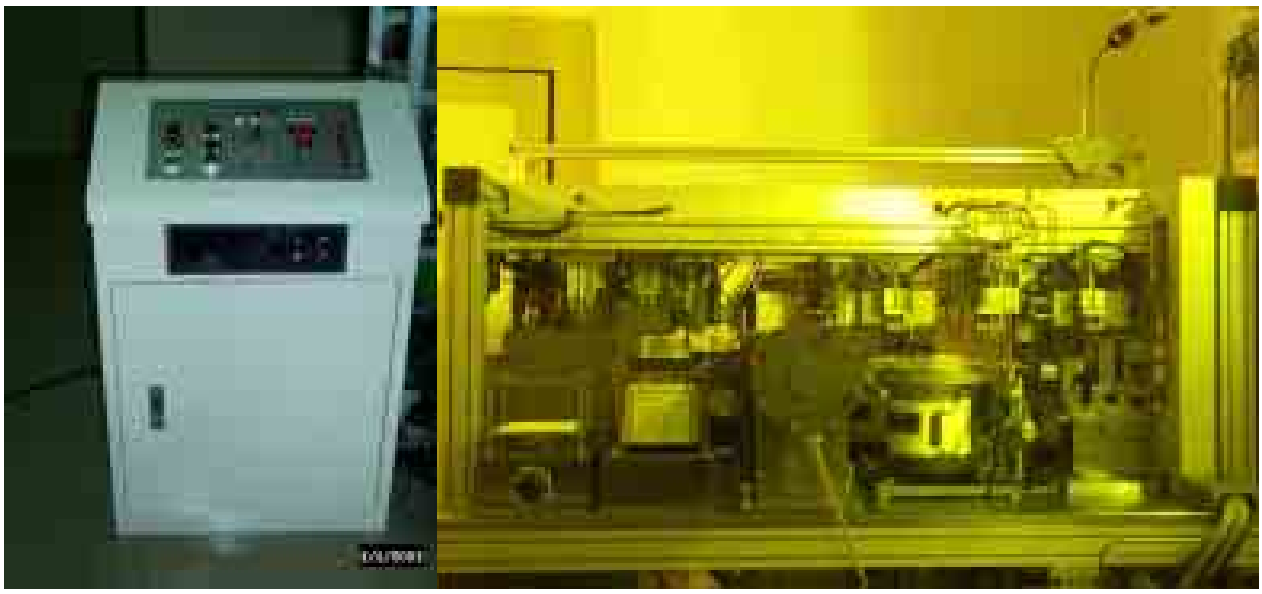

FIG. 35. Welding machine for ^{192}Ir sealed source production (Source:KAERI, Republic of Korea).

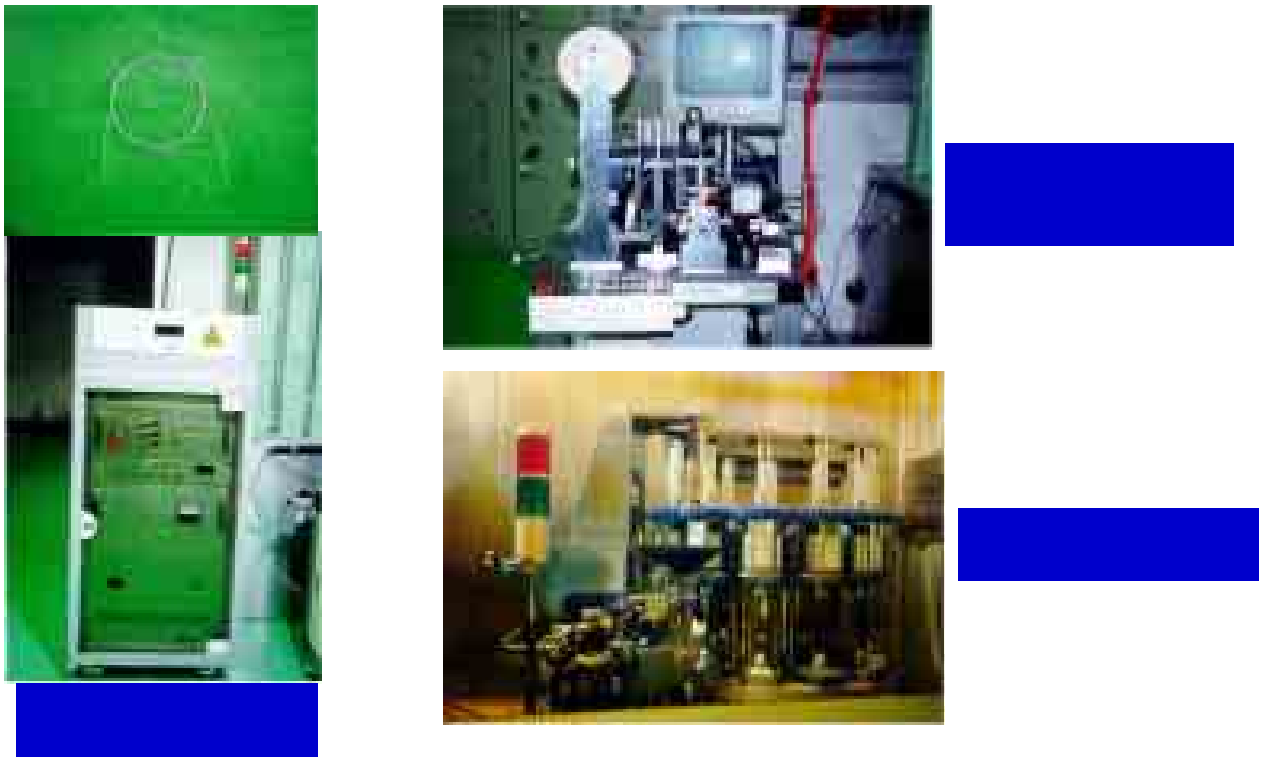

FIG. 36. ^{192}Ir sealed source for brachytherapy (Source: KAERI, Republic of Korea).

As production of radioactive sealed sources consists of mechanical processes, the rate of automation is the highest in this field. Procedures such as capsule loading, array, welding, welding seam control, marking, unloading, storage, inventory, etc. are generally fully automated processes contributing to the reliability, precision, decreased radiation dose and increased production capacity.

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PRESENTATIONS

AUTOMATION SYSTEMS FOR RADIOISOTOPE LABORATORIES

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Abstract

For more than 50 years the company Hans Waelischmiller GmbH (HWM) has worked in the field of nuclear technology worldwide and designed and manufactured equipment for nuclear installations as well as complete turnkey projects. This report deals with the activity of HWM in the field of production of radioisotopes and radiopharmaceuticals as well as in the handling of radioactive materials in nuclear medicine departments in hospitals.

Introduction

The company HWM is engaged in supplying complete turnkey production lines and equipment components for radionuclides and radioactive pharmaceuticals. Some of the product lines that are useful for radioisotope handling are given below.

- Complete turnkey production lines for different radionuclides, diverse radiopharmaceuticals, especially for ^{131}I labeled products as well as for the ^{99}Mo-^{99m}Tc sterile generators
- Complete turnkey PET-centers including radiopharmaceutical laboratories for preparation and quality control, PET-camera, high-performance computer and software for data processing and visualizing procedures as well as for other medical equipment such as radioactivity measurement instruments and dose rate meters
- Completely equipped nuclear medicine laboratories
- Separate PET- cells (hermetic cells welded of stainless steel sheets and adequately shielded by lead brick construction with liftable/lowerable shielding doors)
- Air conditioning and ventilation systems with highly efficient air filters to retain any airborne radioactive contamination (delay pipes, cooling trap or exhaust air filters).

HWM supplies hot cells for the production of radioisotopes and radiopharmaceuticals. The hot cells are equipped with the necessary in-air and exhaust air filter systems, lead brick shielding with steel frame including lead glass windows, locks and control panels. The hot cells are tight according to the international standards. The construction material is stainless steel and polymeric materials. The walls of the hot cells are smooth, impervious and unbroken. The corners are round. The hot cells constructed for the production of radiopharmaceuticals meet the requirements for a negative pressure isolator and GMP.

Various manipulators are used for the handling of the radioactive material inside the cell. In all cases the manipulators are installed absolutely tight. The ball tong manipulators can be used up to shielding thickness of 100 mm to 150 mm lead. Different master slave manipulators are available for the handling of the radioactive material inside the cell. The master slave manipulators are used if the shielding thickness is greater than 100 mm to 150 mm or very complicated and sensitive operations take place inside the cell. The booting material of the manipulators is resistant to the agents used in the cell.

HWM supplies complete in cell production equipment for various radionuclides and radioactive pharmaceuticals as well as for complete turnkey facilities.

FACILITY FOR PRODUCTION OF $Na^{131}I$ -SOLUTION

The production of $Na^{131}I$ by dry distillation and the dispensing of the $Na^{131}I$ solution are carried out in remote controlled conditions in two lead shielded hot cells. The irradiated TeO_2-powder is placed in a quartz furnace located in a closed furnace casing and heated up to approximately 700 °C. The volatilized ^{131}I as iodine is transported in an air stream over a separator for adsorption of dust to two so-called winding traps. The released iodine will be adsorbed in a weakly alkaline, aqueous buffer solution with high efficiency. The process takes about 1 hour per batch. $Na^{131}I$ solution is obtained with a very high radioactive concentration (50 to 500 GBq/ml are possible), which can be processed for producing other radiopharmaceuticals such as capsules for diagnostic or therapeutic application (Figs 1–2).

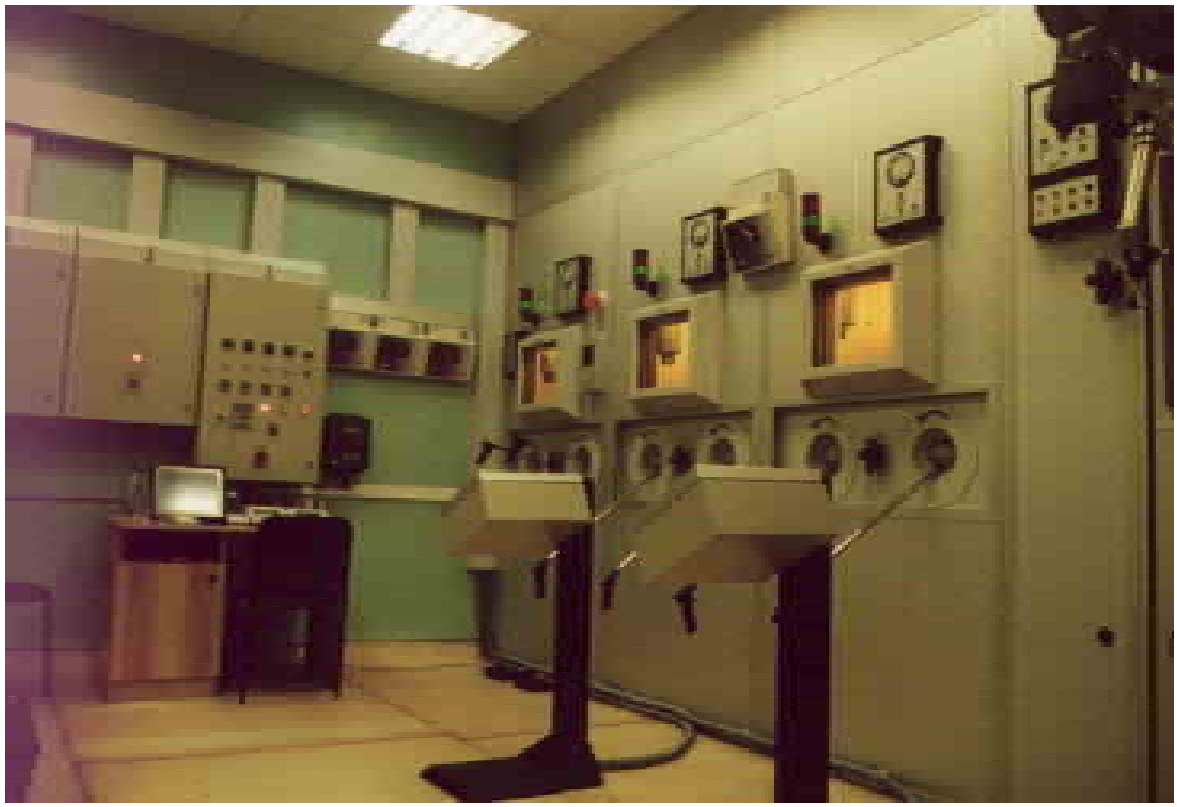

FIG. 1. Turnkey production facility for $Na^{131}I$ solution.

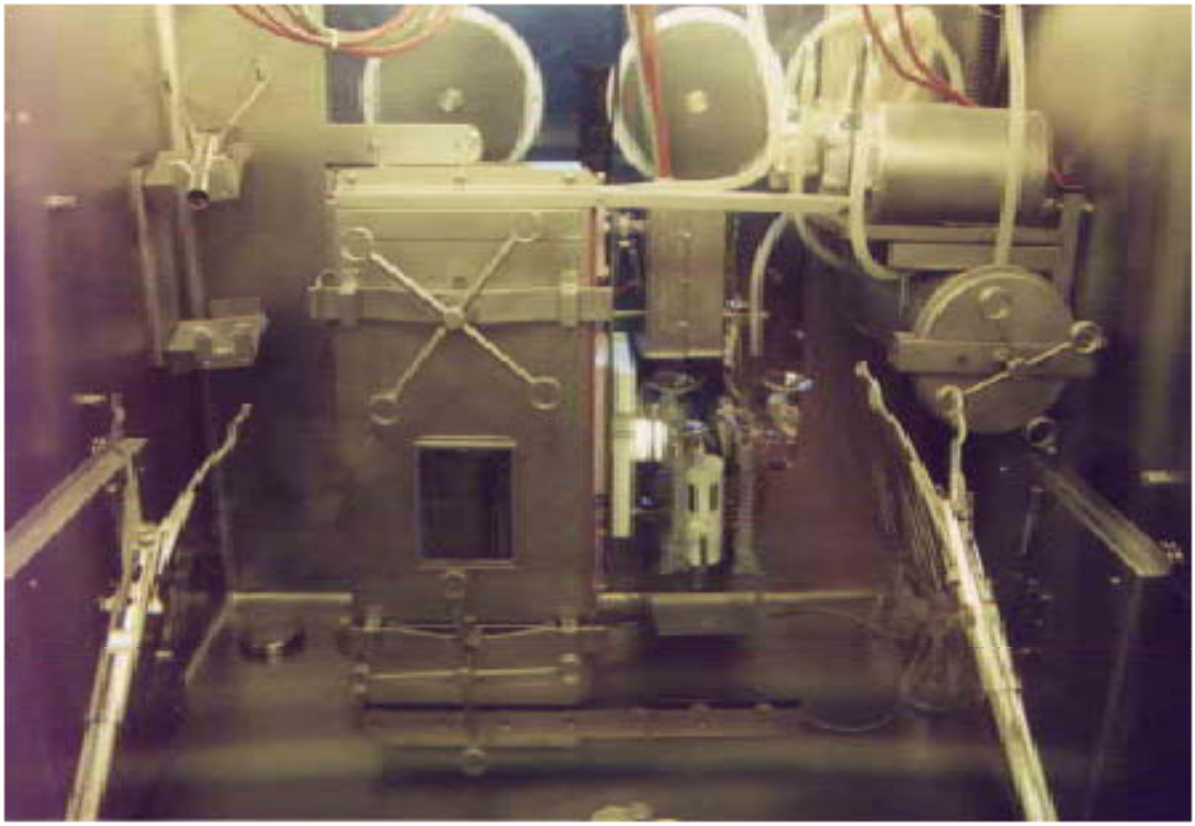

FIG. 2. $Na^{131}I$ production facility – in-cell equipment with furnace casing, separator and iodine winding trap.

The hot cells are shielded with 100 mm lead and equipped with HEPA and charcoal filters for the in-air and exhaust air. The facility has three safety barriers and safety air cycles to ensure that no radioactive iodine can be released into the environment. The 3 barriers are as follows:

— First barrier: Furnace casing, separator, iodine trap, trap pump
— Second barrier: Furnace casing with air inlet and back pressure valve, process charcoal filter, process filter pump
— Third barrier: Hermetic stainless steel hot cell with lead shielding, in-air and exhaust air filters (combination of HEPA and charcoal filter) and ventilation system of the building.

It is possible to install in the exhaust air duct an additional redundant changeable charcoal filter system on top of the cell.

FACILITY FOR PRODUCTION OF $Na^{131}I$ CAPSULES

The production facility consists of a non-shielded glove box and a hot cell shielded with 50 mm lead wall. Inside the glove box, the inactive upper and under parts of the gelatin capsules are put in special pallets (5 pieces per pallet). The under part is filled with a special salt mixture. The prepared pallets will then be transferred in the shielded production cell (Figs 3–4). $Na^{131}I$ bulk solution (in µl-range) is transferred through the bottom port into the shielded cell. The dispensing of the necessary $Na^{131}I$ solution into the capsule under part is carried out by a special Eppendorf-pipette moved vertically and horizontally by linear drivers.

After filling the capsule under parts, the pallet with the capsule upper parts are placed over the capsule pallet and the capsules are closed pneumatically by a semi automatic system. After closing the capsules, the radioactivity content of each capsule is measured and the capsules are packed in vials.

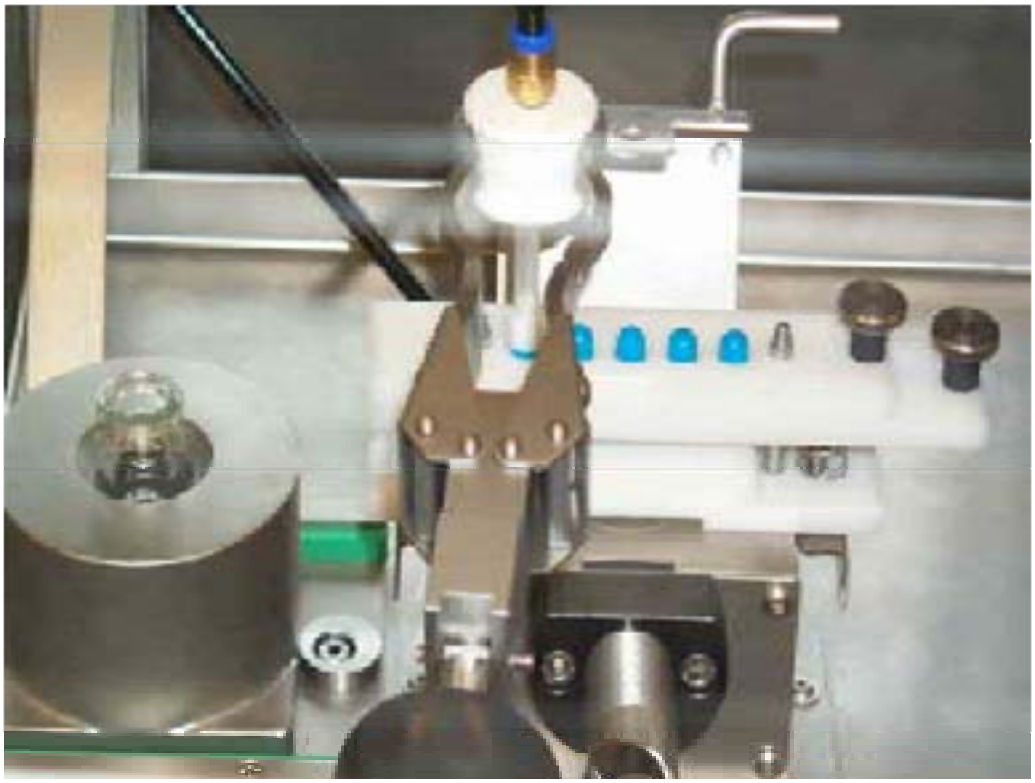

FIG. 3. In-cell equipment for $Na^{131}I$ capsule production (Capsules for diagnostic and therapeutic applications).

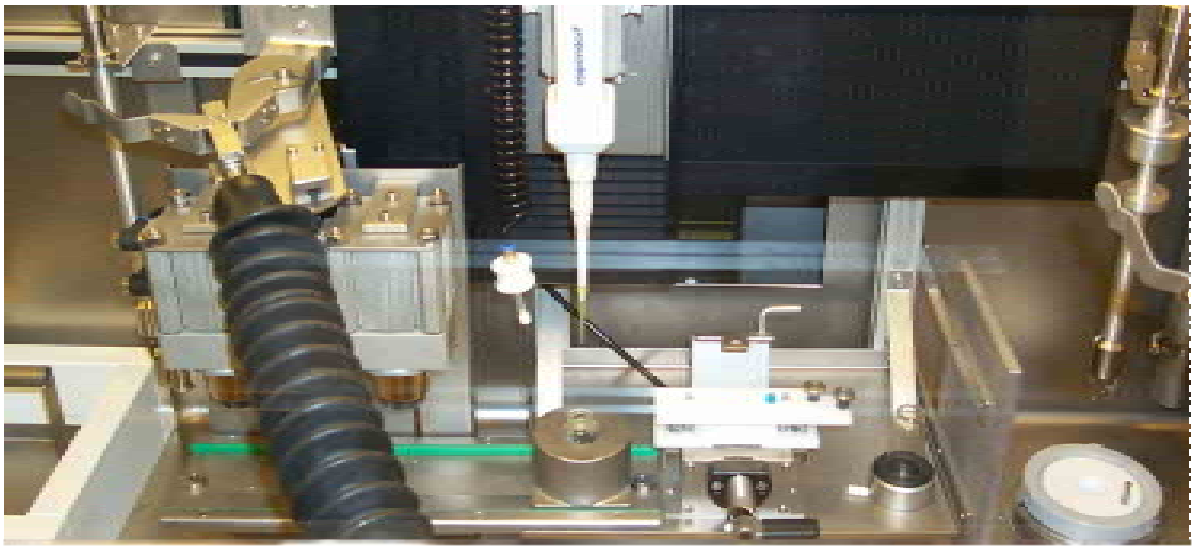

FIG. 4. In-cell equipment for $Na^{131}I$ capsule production (Capsules for diagnostic and therapeutic applications).

FACILITY FOR PRODUCTION OF ^{99}Mo-^{99m}Tc STERILE GENERATORS

The production facility for sterile generators consists of two shielded boxes, a suitable equipped clean room arrangement and a packing area. The generator is a chromatographic and dry type. The loading process with ^{99}Mo is the same as the elution process.

The production process is carried out in the following steps:

— Preparation of all generator components;
— Inactive and aseptic assembling of the generator and inactive function control;
— Preparation of the ^{99}Mo-loading solution, dispensing of the loading portion in vials, steam sterilization of the vials with the loading solution. This preparation of the loading solution will be carried out in the first shielded hot cell;
— Transport of the inactive and aseptic assembled generators to the loading hot cell by a transport conveyor, which meets the pharmaceutical requirements.

Loading the generators with vials, which contain the loading solution and saline solution for washing and evacuating vials according to the elution procedure of such a generator. The loading procedure takes place in the second shielded box which meets the requirements of a negative pressure isolator for pharmaceutical production. This loading procedure is used for production facilities with batch sizes up to 50 generators per week. For higher batch sizes it is recommended that the loading process be performed by an automatic procedure including sterile filtration.

After finishing the loading process the generator is transferred by a conventional conveyor to the packing room. The packing process is a semi - automatic process to avoid high radiation exposure to the staff and heavy manual works.

The advantages of this technology are the following:

— Aseptic assembling of the generator is carried out inactively with an inactive quality control
— Handling of the radioactivity is as simple as possible and can be carried out according to GMP-regulation
— Handling of the generator in the hospital or medical practice is simple and reliable.

HWM supplies the diverse components for the PET-technology and complete turnkey projects in this field. The supplied components for the PET-technology meet the requirements of GMP. HWM supplies PET-cells in big and small design with sufficient lead shielding and lead glass windows. The cells are equipped with or without manipulators. The incorporation of the necessary clean room class into the cells is possible. The cells can be supplied with rear or/and front walls. For special purposes the supply of so-called mini cells is offered. The mini cells are shielded but not equipped with manipulators. The mini cells are especially used in the PET-technology for the operation of PET-modules and for the dispensing of bulk solutions in patient portions in vials or syringes. HWM equips laboratories with the necessary clean room technology, ventilation systems, media supply, laboratory furniture, devices for quality control and storage of radiopharmaceuticals. In connection with other partners, HWM managed the installation of complete turnkey projects in the field of PET-technology.

HWM also manufactures diverse shielding components such as:

— Laboratory table with table shielding and activity meter
— Laboratory furniture
— Lead shielded storage safes, refrigerators
— Compatible shielding and moveable shielding
— Tools for remote handling
— Distance tools.

ADVANCES IN RADIOISOTOPE HANDLING FACILITIES AND AUTOMATION OF RADIOISOTOPE PRODUCTION

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Abstract

Founded in 1959, the Institute of Isotopes of the Hungarian Academy of Sciences began to produce radioactive isotopes in 1964. Since then, it has become a major Hungarian centre of research, development and production relating to the application of radioisotopes. Since 1993 a part of the former Institute has been operating as the Institute of Isotopes Co., Ltd. The main advances in radioisotope handling facilities and automation of radioisotope production are presented here.

INTRODUCTION

The Institute of Isotopes is the major radioisotope producer of radiochemicals and radioipharmaceuticals in Hungary. It is divided to four business units:

- Radiopharmaceutical Business Branch
- Immunoassay Business Branch
- Molecular Biology Business Branch
- Radiation Technology Business Branch.

Beside the professional branches, the Sales and Purchase Branch distributes the Company's products and services in the domestic and export markets.

PRODUCTION OF OPEN RADIOISOTOPES

Neutron irradiation based radioisotopes (reactor isotopes) are produced in the form of radiochemicals (^{131}I, ^{125}I, ^{32}P, ^{35}S, ^{51}Cr) and radioactive pharmaceuticals (^{131}I, ^{153}Sm, ^{186}Re, ^{90}Y) depending on the processing conditions and product characteristics. Fission produced ^{99}Mo is imported in bulk form and is processed to Tc-generator.

Charged particle irradiation based radioisotopes (cyclotron isotopes) are purchased in bulk form for processing to radioactive pharmaceuticals (^{201}Tl, ^{67}Ga).

Main technological processes range from common chemical treatments to radiochemical separation techniques (e.g. ion-exchange, liquid chromatography, distillation, extraction etc.). These operations are supplemented by adjustment of the radioactive concentration with controlled dilution followed by dispensing the stock solution.

Quality control methods used for checking open radioisotopes include measurement of: radioactivity with ion-chamber based dose calibrators; radionuclidic purity by gamma ray spectroscopy, and radiochemical purity by TLC, HPLC, electrophoresis as well as control of the microbiological purity by growth on culture medium and LAL test.

The Company also produces labelled compounds (m^{131}IBG; ^{32}P and ^{35}S-nucleotides; RIA kits using ^{125}I; ^{14}C and ^{3}H-labelled organic compounds as well as undertaking custom synthesis.

TECHNETIUM GENERATOR PRODUCTION LINE

The 'workhorse' of nuclear medicine, the ^{99}Mo-^{99m}Tc elution generator based on carrier-free fission molybdenum is produced weekly under the licence of Amersham-Sorin in the form of contract manufacture. The generator provides high radioactive concentration of pertechnetate solution (over 5 GBq/ml with 8 days of pre-calibration) when eluted from a 'dry' type alumina column. Fission ^{99}Mo is imported in bulk form. Processing steps are chemical pre-treatment (oxidation) of the bulk, preparation of stock solution by dilution, adjustment and checking of the radioactive concentration, dispensing portions to alumina columns, testing elution on each generator and performing quality control of the required parameters.

Bulk processing and stock solution preparation is carried out in hot cells included in class 10000 (C category) clean room environment (as the eluted $^{99m}TcO_4^-$ solution passes through a built-in bacteria filter, it is considered a 'terminally sterilized product'). The generator assembling is performed in a local class 100 (A category) clean room environment because injection needles are unprotected here.

Peristaltic pumps are used to transfer solutions within and between the hot cells and for dispensing portions of the stock solution using a balance for precise mass measurement. Loading of ^{99}Mo in to the column is done by sucking portions of the stock solution using a vacuum system. The column and tubes are connected by nozzles.

A rolling conveyor system transfers the filled generators to the QC lab for test elutions and further on to the package area and expedition.

CYCLOTRON AND FDG MODULE

A GE PetTrace type cyclotron and an automatic FDG panel is under installation partly with IAEA support. The cyclotron is applicable for proton energy of 18 MeV with a maximum beam current of 75 μA which is suitable for producing PET radioisotopes.

The Tracer lab type automatic FDG panel (synthesis module) that is controlled by computer is used for ^{18}F-FDG synthesis. The actual steps of synthesis are displayed on a monitor.

^{18}F-FDG synthesis steps are as follows: ^{18}F separation from the irradiated target (^{18}O enriched water), introduction of the ^{18}F into organic phase through phase transfer catalyst, fluorination of the FDG precursor (mannose-triflate) by nucleophilic substitution, hydrolysis of the protecting groups by acidic or alkaline treatment, separation of the ^{18}F-FDG from the reaction mixture by a series of cartridges. A dispenser operating under aseptic conditions supplements the FDG production system.

PRODUCTION OF SEALED SOURCES

Sealed sources are produced for industrial (^{192}Ir for radiography, ^{60}Co for gamma irradiators) and medical (^{192}Ir for brachytherapy, ^{60}Co for teletherapy) applications. ^{192}Ir pellets with diameter of 2 mm and thickness of 0.3 mm are assembled with the required activity and welded into capsules for industrial sources. They have specific activity about 12 TBq/g. ^{192}Ir sources for brachytherapy are produced with pellet diameter of 0.5 mm and thickness of 0.035 mm and specific activity of 20 TBq/g. ^{60}Co sealed sources are produced with a specific activity of 0.7-0.8 TBq/g.

Contract irradiation of Ir pellets is carried out in high flux reactors ($2x10^{15}$ n.cm^{-2}.sec^{-1}) abroad while long-term Co irradiations are executed in special irradiation channels of the national nuclear power plant.

^{192}Ir sealed sources are produced in the hot cell line for sealed sources of the Company. ^{60}Co sealed sources are produced in the hot cells of the gamma irradiation facility.

Electric arc welding machine (welding current 14-20 A, welding speed 4-6 mm/s, rotation speed of 20 RPM, electrode distance 0.75 mm) is used for sealing industrial sources and a laser welding machine (Plazmafix 50E model, welding current 1.5 A, plasma gas flow 0.3 l/min, protecting gas flow 8 l/min, welding time 0.8 s) is used for sealing brachytherapy sources. An automatic tool is used for clamping and rotating the source under welding. Activity measurement is carried out in an ionisation chamber. Leakage tests are performed after sealing in ultrasonic bath using nitric acid.

RADIOISOTOPE HANDLING FACILITY

The radioisotope production building licensed to nuclear 'A' level allowing processing of high-levels of radioisotopes is located nearby the nuclear research reactor that have power of 20 MW and neutron flux of $1x10^{14}$ $n.cm^{-2}.s^{-1}$. Irradiated targets from the research reactor are transported to the radioisotope production building in big lead containers by truck. The truck can enter into the ground-level of the production building from where the containers are lifted up to the production level by means of cranes.

Cranes with the container run through the receipt area and stop above the first hot cell of the line. The container is placed into the first (called opening cell) where the target is taken out by means of manipulators. Then the target is placed onto the trolley for transporting to the processing hot cell.

The production building includes five hot cell lines (consisting altogether of 34 hot cells) for processing irradiated targets, producing radiochemicals, bulks for radioactive pharmaceuticals, injectable radioactive pharmaceuticals, ^{99m}Tc generators and radioactive sealed sources.

Hot cells are supplied with exhaust system leading to the reactor chimney through filters. A trolley, the position and running of which is controlled electronically, runs behind the hot cells and carries the targets and accessories from the input cell to the individual processing cells and also the products to the output. The governing principle is that each technology is installed in separate hot cells in order to avoid cross-contamination. However, the hot cells are connected to each other through the trolley tunnel so potential cross-contamination can occur through the air. Rate of the cross-contamination is checked and evaluated by validation and is negligible.

Radiopharmaceutical and Tc generator processing hot cells are placed in clean rooms. Cold kits are prepared in separate clean rooms supplied by air through a HVAC systems and are also exhausted by fans forwarding the air into the reactor chimney.

Radioisotope products leave the processing hot cell lines through the outlet door located at end of the line. Filled up vials are placed into product containers and after tinning they are transferred to the expedition area. From this, the packed products are transferred to the radioisotope warehouse located in the ground floor of the building and are transported to customers.

The radioisotope production area can be entered and left through a radiation monitored gate which checks potential radioactive contamination of the operators.

HOT CELL DEVICES

Equipment and devices operating in the hot cells have been designed for manipulator operation. Matching to the limited space within the hot cells they are compact in size. Each hot cell equipment and device is designed locally and prepared by the Company's workshop.

The personnel of the workshop carry out the maintenance of the hot cells. Several of these type of hot cells are provided to other countries through the IAEA.

Equipment and devices designed specifically for hot cell operations are described below:

Target crushing device

It is a pneumatically operated crusher to disintegrate the irradiated target materials (e.g. tellurium dioxide) to granules within the aluminium irradiation capsule. The capsule is placed under the plug and then it is operated pneumatically beating the aluminium capsule mechanically.

Target cutting device

It consists of two cylinders rotated by an electric motor and a cutting disc. Aluminium capsule is laid on the cylinders and the cutting disc is pushed to the aluminium capsule while rotating.

Ampoule capping device

A pneumatically operated crimper, the ampoule with its cap is placed on its holder by manipulator and then the pneumatic sealing head is operated.

^{125}I dry distillation equipment

It consists of a compact electric oven for heating up the irradiated aluminium capsule, acid scrubber and alkaline absorbers. The oven is temperature controlled and values are displayed.

^{131}I-dry distillation equipment

A compact electric oven for heating the irradiated tellurium oxide granules contained in a silicium-carbide ceramic pot, followed by an acidic scrubber and alkaline absorbers. Temperature controlled and supplied with a built-in activity meter.

Autoclave

A small-sized, manipulator-operated sterilisation chamber with two trays for vials, the temperature and pressure of which can be controlled. Operating data are displayed on a screen. Qualified for test bacteria.

Welding machine

Operable in hot cell and have welding seam control optical system for manufacturing and quality control of sealed sources.

CLEAN ROOMS AND ISOLATORS

Natural environment is highly infected with microorganisms (its magnitude is around 10^6 cfu/surface unit). At the same time injectable pharmaceuticals must be sterile. Microorganisms contaminating the product can be eliminated by autoclaving (product sterilisation) but metabolic

products of bacteria and killed bacteria (pyrogens) remain in the product and cause temperature elevation in patients. To eliminate this, operations must be performed in spaces with low microbiological contamination (10^{-3} cfu/surface unit), called aseptic surrounding (cfu = colony forming units).

According to the latest requirements relating to the pharmaceutical industry injectable pharmaceuticals must be produced in aseptic space in order to protect products from bacterial and pyrogen contamination. Clean rooms (large aseptic spaces) and isolators (local aseptic spaces) continuously supplied with filtered air flow are used for this purpose. For radioactive products (radioactive pharmaceuticals) prevention from radioactive contamination as well as radiation protection aspects must also be taken into consideration. As mechanism of the biological and the radioactive contamination is opposite to each other (biological contamination spreads from the natural surrounding towards the product while the radioactive contamination spreads from the product towards the surrounding) and radiation protection aspects often crosses these – harmonisation of the three aspects and requirements is not easy.

Protection of the surrounding from radioactive contamination needs depression in the production space while that from biological contamination needs continuous air flow around the product. The latter is provided in the pharmaceutical industry in clean rooms where overpressure is maintained. Combination of the two systems for radioactive products can be solved in two ways:

Either exhausted hot cells are placed into clean room (double space system) or negative pressure isolators (single space system) are used. Negative pressure isolators are hermetically sealed aseptic chambers that are exhausted while the inlet air is filtered. Shielded isolators provide protection against radiation, radioisotope contamination of the surrounding and bacterial contamination of the product within one space and are much cheaper than clean rooms.

As radioactive pharmaceuticals are generally ‘terminally sterilized products’ (they are autoclaved), clean rooms or isolators of class 10 000 can satisfy pharmaceutical requirements. (Clean room classes with limits of suspended particles and microorganisms in the air are found in GMP guidelines.) However, in critical places (e.g. open injection needles at Tc-generator production) class 100 is needed.

Air circulation is provided by HVAC systems using HEPA filters for eliminating fine particles and microorganisms from the air. Recirculation for radioactive products is not recommended. Forced air exchange (>20 per hour) is required for the effective rinsing because in stagnating air microorganisms would grow. Linear velocity of the introduced air is limited to the laminar range (0.3-0.45 m/s) because turbulence would cause contamination. Temperature and air humidity are also prescribed for clean rooms.

In addition to the clean room operation parameters many aspects relating to the design and construction materials must be taken into consideration when designing and installing clean rooms.

As human beings also represent high risk of bacterial contamination to the product, total body coverage (dress, mask, boot) must be worn. While operators stay in the clean room during production, they are excluded from isolators so isolators are more beneficial from this point of view.

Surfaces of the aseptic spaces (clean rooms and isolators) must be regularly sanitized. Because sealed spaces are difficult to clean and sanitize, application of evaporated agents (e.g. hydrogen peroxide gas generators) have high potential in isolators and hot cells operated according to the isolator principle. Hydrogen peroxide gas is not only very effective sanitizing agent but can penetrate into hidden spaces not accessible for mechanical cleaning. Clean spaces must be kept under permanent particle and microbiological control.

For smaller companies producing radioactive pharmaceuticals with low or medium capacity, the hot cells constructed and operated according to the negative pressure isolator principle (as local clean

rooms) seems to be a cost saving solution. They must be totally leak-tight and supplied with air locks for the inlet and outlet. However, their independent operation is questioned by the latest guidelines requiring class 100 000 environment for isolators.

The Institute of Isotopes Co., Ltd. has made considerable investments to provide aseptic environment for the preparation of radiopharmaceutical solutions (in class 10 000 clean room) with isolator-like hot cells, Tc-generators (in class 10 000 clean room with class 100 local space) and cold kits (in class 100 clean room).

SHARING TECHNOLOGIES TO ASEPTIC AND NON-ASEPTIC OPERATIONS

Radioisotope handling facilities consist of generally big spaces having 'dirty' machines (e.g. cranes) and tons of lead containers and operating heavy hot cells serving for radiation protection. Such systems basically differ from pharmaceutical ampoule-filling plants for which pharmaceutical requirements have been primarily developed.

Also construction of clean rooms with continuous air flow circulation and filtering system is very costly. Contrary to the conventional pharmaceutical industry recirculation of the filtered air is not recommended for radioactive products, consequently much higher air flow rates need to be filtered and conditioned increasing the operating cost. As additional drawback lead containers ('packaging materials') need to be introduced into aseptic spaces increasing the risk of microbiological contamination and the cost of protection against it.

For the above reasons small and medium sized radioisotope production companies should carefully select critical operations which need aseptic clean spaces and plan to reduce the space of clean rooms in order to reduce the cost of construction and operation. They should also need to compromise several arrangements in order to harmonize nuclear (protection against radioactive contamination and radiation of the surrounding) and pharmaceutical (protection against microbiological contamination of the product) requirements. Also careful selection of the clean room category (classes A, B, C, D) is important because the cost difference in differences in their construction is not significant, but the operation and quality control costs are significantly different e.g. according to the latest guidelines class 100 spaces need continuous particle number monitoring.

Production of radioisotopes has some further features that are not in harmony with conventional pharmaceutical schemes. For instance the yielded activity after irradiation cannot be predicted with high precision that would be needed for describing precise composition of the components. Also operations such as target processing need 'dirty' mechanical operations and devices (e.g. capsule crushing, cutting) as well as technological steps consisting of rough chemical and physical operations (dry distillation of granules, dissolution of solid target materials in acids, etc.) compared to the injection ampoule filling operation in conventional pharmaceutical industry. Due to the short half-life of radioisotopes frequently retrospective quality control must be allowed.

Considering all these factors and constraints, the Institute of Isotopes Co. Ltd. found a compromised solution of sharing the radiopharmaceutical production technologies to non-aseptic target processing operations executed in traditional hot cells resulting in low volume 'bulk' solutions and to aseptic bulk diluting and dispensing operations executed in clean room.

Bulk solutions are autoclaved prior to entering into the clean room. With this living microorganisms are eliminated but pyrogen concentration can exceed the limit. However, the subsequent dilution carried out in the aseptic clean room decreases pyrogen concentration considerably because of the high dilution rate (>100 times) and because sterile and pyrogen-free distilled water is used for dilution. The resultant radioactive solution is bacteria-free and its pyrogen concentration is below the acceptance limit for injectable radioactive pharmaceuticals.

Based on this compromise a relatively small sized aseptic laboratory (class 10 000 clean room) with small hot cells has been installed for dilution and dispensing operations for production of radioactive pharmaceuticals.

GMP COMPLIANCE IN THE PRODUCTION OF RADIOACTIVE PHARMACEUTICALS

While clean rooms and isolators provide technical conditions for the aseptic production of radioactive pharmaceuticals, regulations governing production conditions of medicinal products, i.e. GMP, require further arrangements to be complied with for licensing such production technologies and products.

In GMP guidelines a separate section entitled 'Manufacture of Radioactive Pharmaceuticals' deals with radioactive materials declaring that they are potentially hazardous, radiation protection is needed, they have the risk of radioactive contamination, small batch sizes are generally applied, early release is necessary due to short half-life, attention must be paid to cross-contamination and retention of radionuclide contaminants as well as to waste disposal. At the same time injectable radioactive pharmaceuticals must meet requirements relating to the 'Manufacture of Sterile Medicinal Products'.

GMP guidelines relating to radioactive pharmaceuticals require self-contained facilities, lower air pressure than surrounding to prevent radioactive contamination, product protection from environmental contamination and air extraction without re-circulation. They emphasize importance of process validation, equipment qualification, control and monitoring, require product release based on written procedures and retention of reference samples.

The Institute of Isotopes Co., Ltd. devoted in the last decade considerable efforts in developing GMP conformity and gaining production licence and registration for its radiopharmaceutical products.

Full documentation system providing traceability have been developed including site master file, drug master files for the individual products, validation master file, specifications for materials, manufacturing formulas and processing instructions, packaging instructions, batch processing records, batch packaging records and several other instructions and records for such operations as receipt, sampling, testing, release, rejection, recall, calibration, maintenance, cleaning, sanitation, treatment of complaints, behaviour of personnel, and environmental monitoring.

Based on the technical arrangements and investments (aseptic production in clean rooms and isolators), organisational arrangements and development of the required documentation of the Company has reached compliance with the GMP guidelines and preconditions of licensing of the production of injectable medicinal products. As a result of these efforts the pharmaceutical production line and the Tc-generator production line (as well as the cold Tc-kit production laboratory) have been accepted as complying with the GMP requirements by the national pharmaceutical authority and production licence has been granted.

THE PRESENT STATUS OF HOT CELL DESIGNS AT NECSA

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Abstract

The radioisotope production group of the South African Nuclear Energy Corporation has manufactured a range of radioisotopes since 1967. A 20 MW nuclear reactor is used for radioisotope production. It has modern hot cells and an efficient waste handling facility. There are two sections dealing with radioisotope and radiopharmaceutical production and quality control. The Radiochemical Section produces radioactive bulk products such as ^{99}Mo, ^{32}P, ^{35}S and ^{131}I, whereas another section manufactures final products such as ^{131}I diagnostic and therapeutic capsules, ^{192}Ir radiography sources, ^{137}Cs and ^{60}Co sealed sources, ^{85}Kr glass tubes for smoke detectors. The ^{99}Mo-^{99}Tc generators produced from ^{99}Mo and the complimentary kits are largely used as radiopharmaceuticals for nuclear medicine.

INTRODUCTION

The Nuclear Energy Corporation of South Africa (NECSA) is well equipped for producing radioisotopes. The on-site workshop, which was built to accommodate the size and requirements of the enrichment of uranium plant, are able to produce hot cells, isotope production equipment, irradiation rigs and transport containers. The last mentioned is helped by the plentiful supply of depleted uranium, which is casted and machined to the required shapes.

The design of the hot cells is based on the principles of radiation protection which envisages radiation levels below 2.5 μSvh^{-1}, a free standing box within the lead-brick biological shield, the La-Calhene DPTE transfer system for waste and sample transfers and in-cell equipment that is able to be maintained and replaced using only the existing handling equipment. This is achieved without the integrity of either the ventilation or shielding of the facility being compromised.

The radiation level of 2.5 μSvh^{-1} or less is to be seen as the maximum level when the activity is up against the front wall of the cell and the reading is taken on the closest point on the outside. The effect of this decision has been that no significant exposure has ever been received at the front of the cells. All exposures can be traced to the packing and transport of the product. The shielding is generally in the form of 50 mm and 100 mm lead bricks, which are covered by easy washable and replaceable plastic-coated wallpaper. A single slate of steel, which is easily removed for cell access, constructs the roof. Although steel slabs had been used for walls, this practice has been discontinued due to its design inflexibility and eventual resultant cost.

PRODUCTION HOT CELL FOR FISSION PRODUCED ^{99}Mo

The fission produced ^{99}Mo is the major irradiated target for producing ^{99m}Tc generator. In most cases, the amount of activity in a cell is cyclic in that raw material is introduced which is then processed and dispatched. The production of ^{99}Mo is an exception to this as only a small percentage of the total activity leaves the cell after production; the remainder being waste which is stored for later treatment. The radiation levels stay high, therefore, especially in the first cell where the initial separation of the fission products occurs and the effects of this radiation on the manipulator booting and lead glass window are unacceptable. To minimize the problem, the first cell has been built with a shielded cavity under the containment box into which the waste tanks and reaction vessels have been placed (see sketch). The cell is built with 250 mm lead brick walls but the cavity has an effective 350 mm lead to the outside and 100 mm to the box (and windows, booting) (Fig. 1).

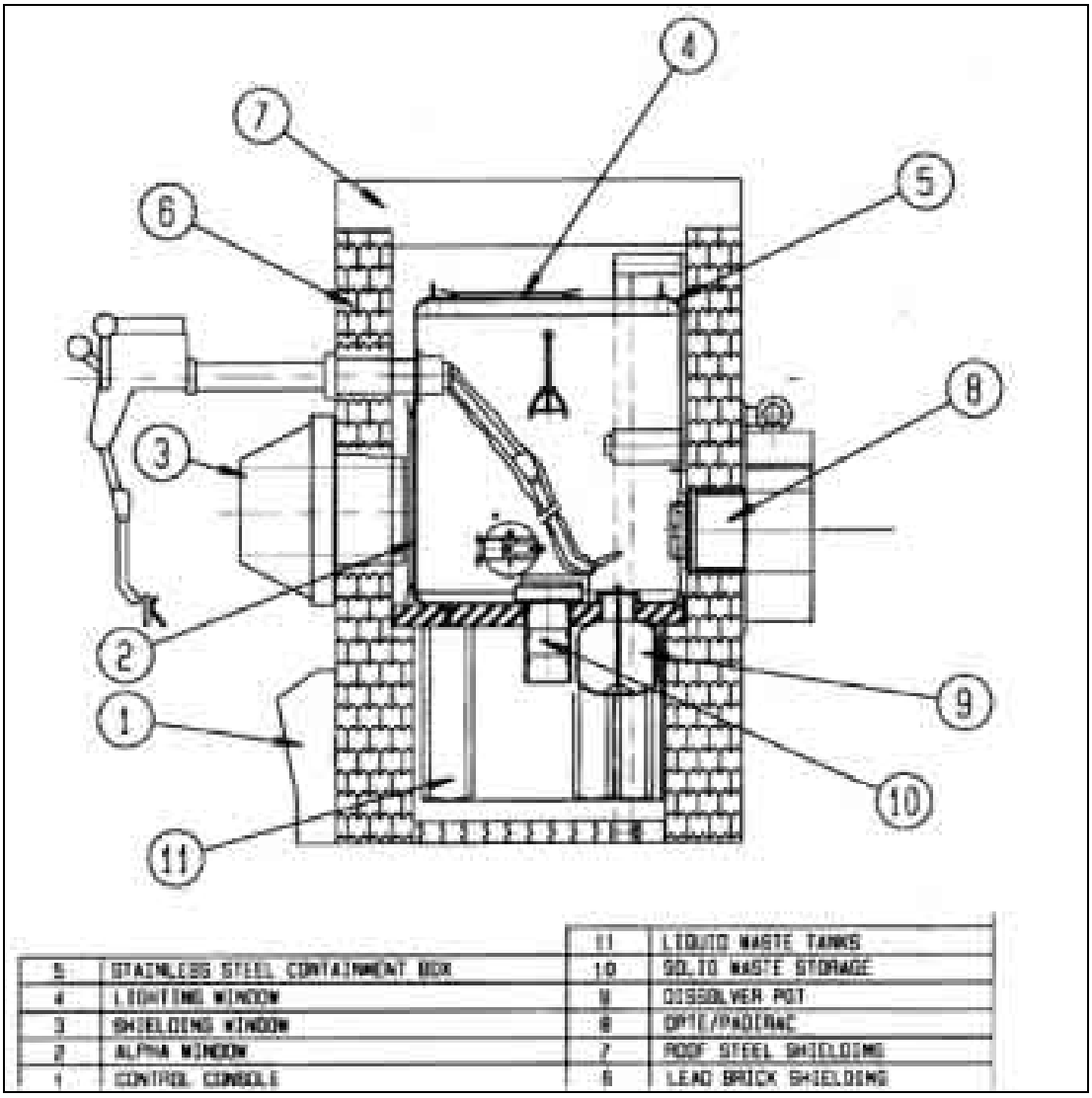

FIG. 1. Cross-section of fission produced ^{99}Mo production hot cell.

The freestanding boxes are constructed either with a stainless steel frame with polycarbonate panels or with a 6 mm welded stainless steel construction and stabilized glass for viewing and lighting. The latter is preferred for the handling of higher activities. These boxes are lowered into position through the open roof after the walls have been built and services are introduced by access from either side “quick disconnect” feed through.

Should a box therefore require replacement either because of maintenance reasons or to introduce a new product facility, the radiation is reduced to an acceptable level by cleaning or decay, the roof is removed and the box is lifted out.

The boxes are designed so that cleaning is facilitated. It has been found, however, that although corners have been rounded and made accessible, fittings such as doors, window frames, etc, do not receive the same attention and often form contamination traps. Improvements for this are been continually sought.

The DPTE system from La-Calhene is extensively used in virtually all cells; in most cases the double system is employed, which consists of concentric doors, the smaller of which is used for sample handling and the larger for waste removal. A locally designed SARIE has been added that allows the essentially closed DPTE system to be used to remove the product (Fig. 2).

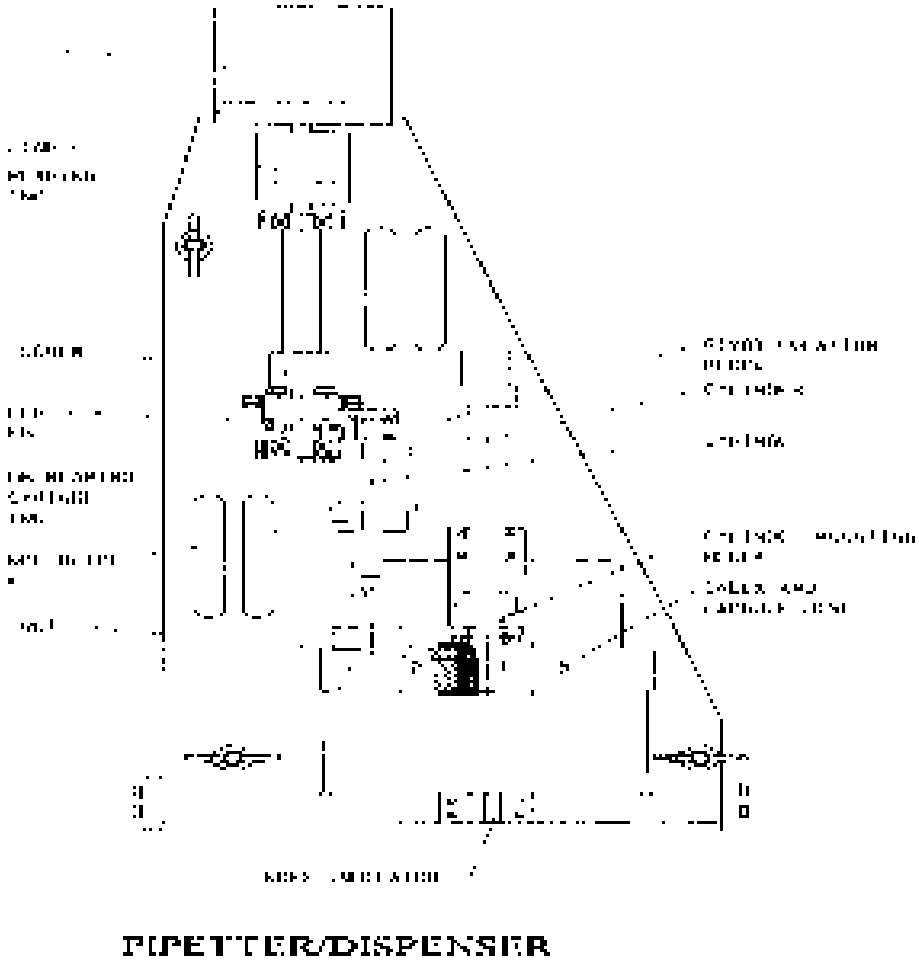

FIG. 2. Pipetter/dispenser.

The maintenance of in-cell equipment is problematic as the manipulator/tong is limited in its mechanical capability and at times high contamination and/or radiation levels preclude access to the box. The only safe entry is via the DPTE and a policy was adopted that all equipment be so designed as to be removed and replaced via this system. The policy is therefore one of replacement and not of service and repair. To this end, a storage facility was built to safely accommodate a number of the DPTE containers, the contents of which are allowed to decay to the shape when open handling is feasible (Fig. 3). The equipment is sent directly to the waste section should a long-lived isotope contaminate the equipment where storage decay is impractical (Fig. 4).

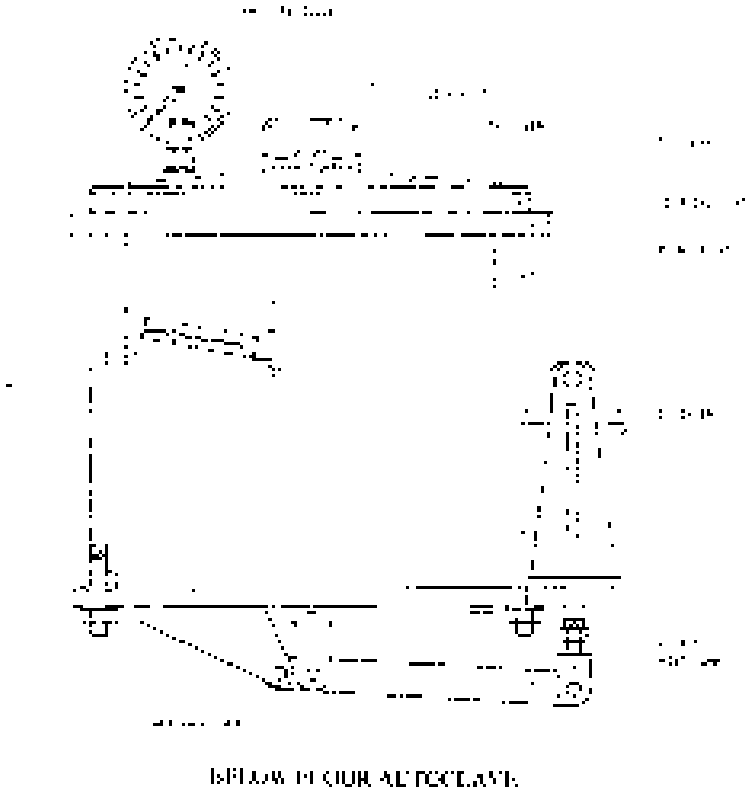

FIG. 3. Below floor autoclave

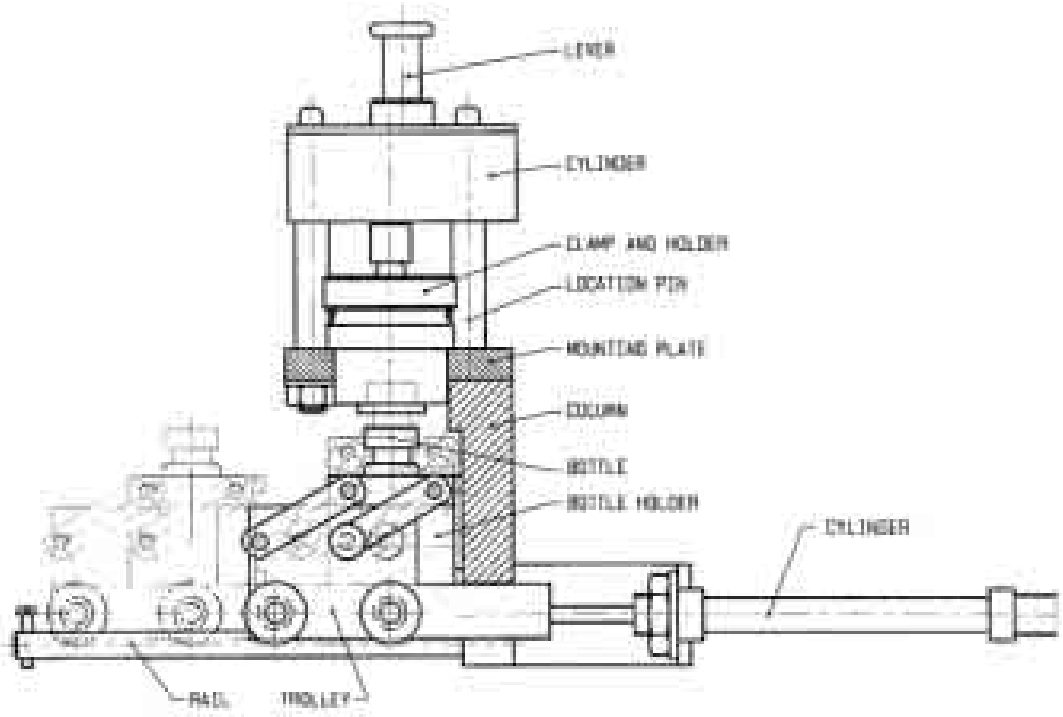

FIG. 4. Vial capper.

Although the design of hot cells has not shown much innovation over the years, it is felt that future facilities be built around the process and not, as in the past, the process fitted into a standard facility. In-cell equipment is being made simpler and easier to remove and replace. Further development will also concentrate more on the requirements of pharmaceutical production.

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