Development of Radioactive liquid dispensing mechanisms for exclusive applications in Radio-pharmaceutical production laboratories

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Abstract

Radio-isotopes (Mo-99, I-131, P-32, Cr-51,etc) in liquid form are popular in diagnosis and treatment of various ailments. Radiopharmaceuticals (RPhs) are stored for transportation in 10 and 15ml capacity hermetically sealed vials. RPhs are transferred to the vial inside the lead shielded tong box to comply with the regulatory requirements. Around a decade back, when the RPhs application began in small scale, dispensing of the RPh preparation in liquid form was done using the pipette mounted arrangement on the pantograph mechanism and maneuvered using the tong manipulator. This 10ml capacity pipette was connected to the 20ml capacity syringe and using the suction generated by the syringe, the RPh from the pooling vessel use to get loaded in the pipette and then dispensed into the open top vial by pushing the plunger of the syringe. To hermetically seal the vial, rubber stopper and an aluminium cap was used and further sealed using the hand operated sealing machine. This operation was causing avoidable gamma radiation dose to the operator and therefore this unsafe operation necessitate discontinuation of the traditional method by developing new method of transfer of the liquid into the sealed vial directly by using remotely operated machines. With the modern dispensing mechanisms working on the principle of vacuum transfer, various machines have been designed and deployed for transfer of the liquid to either the pooling vessel from the vial or vice versa. In one of the cases where liquid I-131 is handled, peristaltic pump is used to transfer the RPh to eliminate the associated hazard due to its volatile nature. Proposed paper discusses the chronological stages of development of the radioactive liquid transfer machines with the objective of making the operation more accurate, radiologically safe.

Keywords: Radiopharmaceuticals, pipette, vial, lead shielded tong box, peristaltic pump, negative pressure, pantograph, liquid transfer machine, nuclear medicine center (NMC).

1 Introduction

BRIT is involved in processing and supply of the various radio-isotopes (Mo-99, I-131, P-32, Cr-51,etc) in liquid form. These are called as radiopharmaceuticals (RPhs)

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and are used in diagnosis and treatment of various ailments in human body at nuclear medicine center (NMC). RPhs are processed in the shielded tong box (STB) using remotely controlled machines, tongs. STB is a hermetically sealed lead shielded cell equipped with tong manipulators, hand gloves, remotely operated gadgets, radiation shielding windows for observation etc. STB is built to be always under negative pressure to avoid spread of radioactive material's contamination. Processed radiopharmaceuticals (RPhs) are stored for transportation in 10ml and 15ml capacity hermetically sealed crimp top glass vials. RPhs are transferred to the vial inside the lead shielded tong box to comply with the regulatory requirements.

From the beginning of the last decade, when the RPhs application began gaining pace in the medical fraternity, dispensing of the RPh preparation in liquid form was done using the pipette mounted arrangement on the pantograph mechanism and maneuvered using the tong manipulator. Radiation worker or the operator would open the stock solution vial by manually operated unsealing machine and would unnecessarily get exposed to the harmful gamma radiation emitted by the radioactive material. Stock solution would then be transferred to the pooling vessel using tong manipulator directly. After chemical processing, the formed RPh solution would then be dispensed into the consignment crimp top open vial using a 10ml capacity pipette. Pipette was connected to the 20ml capacity syringe and using the suction generated by the syringe, the RPh from the pooling vessel used to get loaded in the pipette and then further dispensed into the open crimp top vial by pushing the plunger of the syringe after alignment. To hermetically seal the vial loaded with RPh, rubber stopper and an aluminium cap would be used and further sealed using the hand operated sealing machine. This operation was causing avoidable exposure to the gamma radiation and therefore this unsafe operation necessitate discontinuation of the traditional method by developing new method of transfer of the liquid into the sealed vial directly by using remotely operated machines. With increased demand from the market, dose received by the operators also increased, compelling intervention by the regulators Atomic Energy Regulatory Board (AERB). With the mounting pressure from the regulators to change or improve the method of transfer of the liquid to the vial to reduce the manrem, development of modern dispensing mechanisms working on the principle of vacuum transfer and other supporting machines took place. Various kinds of machines have been designed and deployed for transfer of the liquid to either the pooling vessel from the stock solution vial or from the pooling vessel to the consignment vials. In one of the cases where liquid I-131 is handled, peristaltic pump is used to transfer the RPh to eliminate the associated hazard due to it's volatile nature. Proposed paper discusses the chronological stages of development of the radioactive liquid handling and transfer machines with the objective of making the operation more accurate, radiologically safe.

2 General RPh production process

Short lived medical use radio-isotopes like Mo-99, I-131, P-32, Cr-51,etc, obtained from the research reactor ‘Dhruva’of Bhabha Atomic Research Center (BARC), are redistributed, as per need of the NMCs, after chemically processing for adjusting the radioactive concentration and sometimes pH and change to useful form. Processing is carried out in the AERB approved STB using the remotely operated gadgets and tong manipulators (figure 1). STB has hand gloves for maintenance of the in-cell gadgets and general cleaning work. From the beginning of the last decade, diagnosis and treatment using radio-isotopes gained popularity and so the demand of the RPhs from the very limited market. NMCs increased from two digit number to three digit number in last 10-12 years. Today there are ~180 NMCs in India. BRIT was offering RPhs using radio-isotopes like I-131 (liquid and capsule form) for diagnosis and therapy, Mo-99 in solution for extracting Tc-99m daughter radio-isotope by using the solvent extraction technology, Cr-51 in liquid form, P-32 in liquid form. All these RPhs were in limited demand and so the scenario related to their processing was not attractive to draw attention to improve the facility due to adherence to the regulatory requirements with huge margin of safety. Therefore, the stock solution vial containing radio-isotope in liquid form arrived from the BARC would be removed from the AERB approved cask by using the long Cee-Vee tong and would then be transferred to the STB. Operator then would use the minimum time criteria to reduce the gamma radiation dose received. Further, to adjust the radioactive concentration etc of the radio-isotope for redistribution into individual vial to be sent to NMCs across the country, the operator would unseal the sealed glass vial (figure 2) using the manually operated vial unsealing tool (figure 3) by approaching it through the hand port. Thus, without lead shielding, hand of the operator would unnecessarily get exposed to the gamma/beta radiation emitted by the radio-isotope. Since the consignments of the RPhs were limited, the process of dispensing of the RPh into the individual vial was less laborious and simple using the pipette mounted on the pantograph(figure 1). For dispensing of the RPh in liquid form into the open crimp top glass vial, the operator would generate negative pressure in the pipette mounted on the tong manipulator using a syringe to suck the liquid inside it from the pooling vessel , transfer to the consignment vial, align and then dispense by pushing the plunger of the syringe. Operator then would load the rubber stopper and aluminum cap by using the tong and seal them to the vial hermetically to complete the process. In this operational step, operator would get exposed to the radiation.

Most of the above mentioned operations are common in irrespective of the product or radio-isotope the operator is handling inside the STB. General layout of the STB and the material handling equipments are same in all facilities processing RPhs.

Figure 1: Inside of the STB with in-cell gadgets and the Cee-vee tong above

Figure 2: Crimp top glass vials used for storage and transport of the RPhs

Figure 3: Vial Sealing tool, vial unsealing tool

3 Improvement in the processing facilities for production of the RPhs

As the popularity of the radio-pharmaceuticals increased, so does the demand from the limited market and operators were compelled to handle the increased quantity (in radiation standards) while the infrastructure remained the same. With increased radiation dose received by the operators, AERB made it mandatory to improve the processing set-up to reduce the dose receivable by the operators. They made it mandatory to follow the ‘As Low As Reasonably Achievable’ (ALARA) principle. To comply with the regulators requirement, in 2003-04 engineers started brainstorming discussions within the group and with the operators to mechanize the process and to improve the facilities in phased manner.

3.1 Approach

Since the dose received by the operator was maximum while handling the radio-isotope without lead shielding, designers of the gadgets and processing facility decided to mechanize following operations performed inside STB for transfer of liquid in first phase of improvement like

1. Un-sealing of the vial containing stock solution,
2. Dispensing of the liquid RPhs into the vial,
3. Sealing of the vial containing RPh,

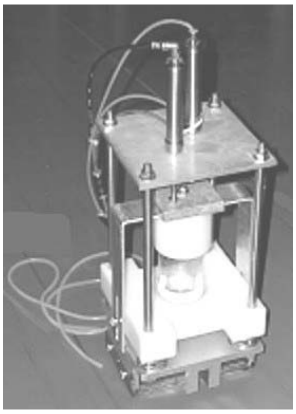
Accordingly, for completely avoiding the handling of the radioactive material without shielding inside the STB to reduce the dose due to radiation, following solutions were finalized by design and development of

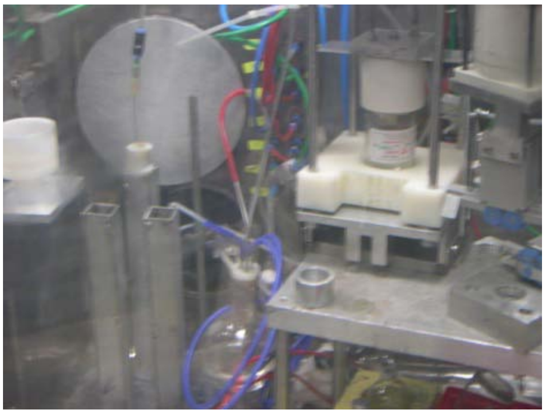
1. The vacuum aided transfer machine to transfer stock solution from the vial to the pooling vessel directly
2. The remotely operated vial sealing and unsealing machine
3. The liquid transfer machine from the pooling vessel to the consignment vial.

Engineers and operators worked persistently to conceptualise, design, fabricate and successfully install new gadgets which can be operated from behind the lead shielding as mentioned in the upcoming text.

3.2 Design and development of the vacuum aided transfer machine to transfer stock solution from the vial to the pooling vessel directly

By using the hypothesis of Bernoulli’s, flow of liquid from the stock solution vial to the pooling vessel can be instigated. Flow can also be instigated by gravity as well but the slow flow rate will delay the process. Therefore, by reducing





VALTM inside the shielded cell

Figure 4: Vacuum aided liquid transfer machine (VALTM) for 100ml capacity glass vial

the pressure inside the pooling vessel (used to collect the stock solutions before chemical processing and redistribution) and connecting it to the sealed vial carrying stock solution received from BARC by using the piercing needles (transfer needle and vent needle), the flow of liquid radio-isotope can be initiated. Using this principle, a vacuum aided liquid transfer machine was designed specifically for 100ml capacity sealed open top glass vial (figure 4) carrying Mo-99 for the Technetium Column Generator Production (TCGP) facility in the year 2005-06. Till date it has handled more than 1000 vials carrying Mo-99 in solution form. Development of this machine changed the method of handling the stock solution vials in RPh production systems. Based on the same principle, a versatile machine was designed and put to use which can handle 10ml, 15ml , 50ml and 100ml capacity crimp top vials. Vacuum inside the pooling vessel is obtained from the service line vacuum. Machine uses pneumatic actuator to move and force the needles to pierce through the Bromo Butyl rubber stoppers. This machine helped in direct transfer of the stock solution from the 100ml capacity crimp top vial to the pooling vessel without unsealing it. It was the first development in the whole process of mechanization of the radioactive liquid handling systems.

3.3 Design and development of the remotely operated vial sealing and unsealing machines

In the radiopharmaceuticals laboratory of BRIT, various types of storage vessels are used to store the radioactive material. It includes 20mm crimp top glass vials in capacities like 10ml , 15ml, 20ml, 50ml and 100ml (figure 2). These crimp top vials are used for transportation of the stock solution from BARC to RPh production plants in BRIT and then after processing and redistribution, some to the NMCs, some

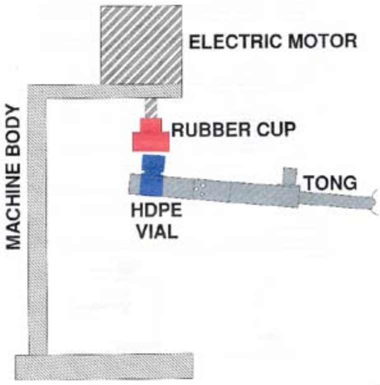


Figure 5: Schematic of the traditional set-up for unscrewing of the screwed cap type vial

Figure 6: The Unscrewing machine for 10ml capacity screwed cap type HDPE vial

for quality control checks, etc. So, these glass vials are used extensively and therefore, STB require both sealing and unsealing machines to tackle any related requirement.

Development of vacuum aided liquid transfer machine could partially solve the problems associated with the cumbersome operations of unsealing the vial to retrieve the stock solution. Sometimes, problem occurs with the supply of the BARC produced radio-isotopes due to Dhruva reactor shut-down, and in that case, required radio-isotopes are imported for keeping commitment of the production and supply of the RPhs to the NMCs. In one of such cases, Mo-99 radio-isotope is stored in screwed cap type HDPE vial for transportation. To retrieve the solution, the cap of the vial needs to be removed by unscrewing. To perform this task, traditionally, the vial is held using the tong manipulator gripper and is pressed against the rotating rough cup (figure 5). Friction between the cup and the vial cap would help in rotation of the cap, resulting in unscrewing of the same. Since the safety of the precious radio-isotope was totally depend upon the skill of the operator, operation was replaced by developing a remotely operated vial unscrewing machine. This machine has been designed to hold the main container and the cap separately by the pneumatic gripper with special shoe gripper. Once the gripper holds the vial, the motor coupled to the gripper for cap would rotate it to unscrew the cap. To grip the vial, rotary pneumatic grippers have been used (figure 6). Machine is controlled from the control panel.

Principle of redundancy is strictly followed in radiation industry where gadgets fail due to effect of gamma radiation. It is not due to poor planning but associated constraints like contamination, gamma radiation dose, un-accessibility etc. Even though the development of VALTM eased the operation of the transfer of the solution from the stock solution vial to the pooling vessel, failure of the same could not be predicted because of the lack of experience or related published data. To avoid the situation where VALTM has failed and the operator is not ready to follow the old method of unsealing the vial using hand operated unsealing tool, the unsealing tool was mechanized to be operated from the control panel. Figure 7 shows a sealed vial unsealing tool powered by the pneumatic actuator. Similarly to tackle the problem of the sealing the crimp top vial by using manual sealing tool, a machine as shown in the figure 7 has been designed. Hanging type machines don't occupy the precious floor space and are easy to handle and operate. Floor mounted machines are robust but occupy floor area. All these machines reduced the direct exposure of the operator to the gamma radiation while adding safety and reliability in operation. These machines were developed after VALT machine.

Figure 8: Hanging type sealing and unsealing tool powered by the pneumatic actuator installed inside the STB and a unsealing machine installed on the STB floor

3.4 Design and development of the liquid transfer machine from the pooling vessel to the consignment vial

One of the most tiresome and time consuming operations in old set-up for production and supply of the RPhs was the redistribution of the solution in the pooling vessel to the smaller capacity vials (10ml or 15ml), loading the rubber stopper and aluminum cap and sealing. Working from behind the lead shielding is ergonomically worst task as the operator has no control over the coordination between the hands and eyes due to shielding design. Maintenance or production operation is totally a blind operation and it require help of the subordinate to successfully complete the task. It is because of the design the STB in which fixing the hand port and radiation shielding windows at an ergonomic position is difficult due to physical nature of the shielding components. Due to the above, dose received by the operators was more and avoidable. Therefore it was decided to design and develop the liquid transfer machines which can be operated from behind the lead shielding and reliable to serve the intended function in radiation environment for longer period of time. Since just designing of the liquid transfer machine was not going to solve all related problems, it was decided to use the sealed vial to directly transfer the liquid RPh into it to further avoid the loading of the rubber stopper and aluminium cap on to the open crimp top vial and seal it to complete the process. This change of protocol was got approved through the regulators AERB. With changed scenario, objective lead to the design and development of the two machines, based on the method of powering the needle to pierce the rubber stopper, namely

1. Dispensing machine: using power screw and the electric motor
2. Dispensing machine: using pneumatic actuator to pierce a set of needle.

Both types of machines were developed with one objective of 'Dispensing of the liquid RPh into the sealed crimp top vial (10ml or 15ml capacity) using a set of twin needles and under relative negative pressure inside the sealed vial obtained using either vacuum pump or service line vacuum'. Of the two needles, one acts as a vent connected to the vacuum source and the other one the liquid transfer needle. Liquid dispensing machine is typically a set-up to

1. Locate the sealed vial to be in line with the needle set
2. Receive the RPh in liquid form into the syringe receiver from the pooling vessel mounted on the machine. Liquid transfer to the syringe to be done by using peristaltic pump.
3. Movement of the needles towards the sealed end of the vial and pierce the rubber stopper of the vial so that the vial gets evacuated due to the connection of the vent needle with the vacuum source and liquid is transferred to the vial.
4. On completion of the liquid transfer operation, retract the pierced needles from the rubber stopper of the vial without moving the vial

To achieve the above, two separate machines were designed: in first case using the power screw and the motor to drive (figure 9) and in the second case (Figure 10) the pneumatic actuator to move and push the needles into the rubber stopper. Figure 10 also shows various gadgets like tong mounted pipette (stand-by), peristaltic pump, vial unsealing machine and the tongs, radiation shielding windows, etc.

Liquid transfer machines are operation and maintenance friendly. Needles, being delicate, are prone to failure due to buckling due to resistance from the seal to pierce due to misalignment and sometimes chocking due to accumulation of the solid

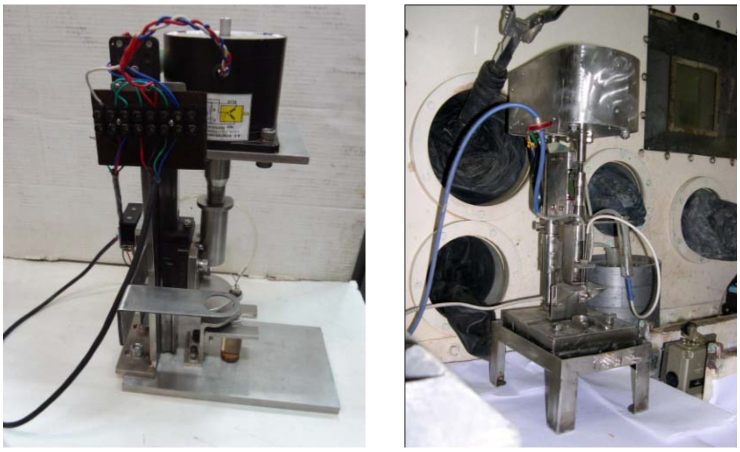


Figure 9: Liquid Dispenser

Figure 10: Liquid transfer machine and other accessories inside the STB.

particles. So, the adopter of the needles has been designed to be able to remove with ease and installation the new pair with accuracy. Additionally, the silicone tube, which is used for transfer of the liquid RPh from the pooling vessel to the syringe using the peristaltic pump, as a preventive maintenance protocol, is laid to be able to replace with the new one using the hand ports of the STB during preventive maintenance. Machines can be easily lifted and shifted out of STB to tackle the unmanageable problems and therefore are designed ergonomically.

3.5 Liquid dispenser for I-131 capsule production set-up

BRIT offers I-131 capsules to the NMCs for diagnosis (product code IOM-2) and therapeutic (product code IOM-5) purpose. I-131 in the sodium Iodide liquid form is dispensed on the sodium sulphate powder stored in the open gelatin capsule. Since the capacity of the capsule is very less, sodium Iodide solution is dispensed in micro-liter volume (a drop of liquid through the 22gauge hypodermic needle). To get desired capsule specification required by the hospitals, radioactive concentration of the I-131 for the therapeutic application is maintained higher. To dispense a drop of liquid, peristaltic pump is used. Flow rate is controlled by selecting proper size of silicone tubing and rotational speed of the pump through the controller. Figure 11 shows the inside view of the facility consisting of peristaltic pump, needle assembly, vial sealing machine etc for production of the I-131 loaded gelatin capsule.

Photograph of the facility for IOM-2 production

Photograph of the facility for IOM-5 production

Figure 11: Photographs of the facilities handling I-131

4 Effect of increased demand and dose received by the operators before mechanization

As the demand for the RPhs increased, radioactive material handled by the operators inside the STB also increased. Table -1 shows the increase in the processing quantity of Mo-99 radio-isotope (expressed in radiation standard unit, Curie (Ci)) by BRIT affected by the demand from the market. Increased demand also increased the dose received by the operators and it compelled regulators to impose ALARA principle to reduce the personal dose. After implementing the ALARA, the processing gadgets, as discussed in previous sections, for RPh production became remotely controlled. This reduced the dose received by the operators.

As it can be seen from the tabulated data (table-1 and table-2) and figure 12, there is continuous increase in the processing of the Mo-99 and I-131 to be sent to NMCs. Handling of increased quantity of the RPhs also increases the dose received by the operators handling it. Table-2 also shows the data obtained from the health physicists (H.P) about the dose received by the operators. H.P's are responsible for implementation of the ALARA and maintenance/implementation of the procedures approved and laid in handling of the radioactive material. Data obtained is from the analysis of thermo-luminescent detector (TLD) that the operators wear while handling the radioactive material. It is clear from the data that the dose received is increasing till year 2006 and then it reduces dramatically because of the introduction of the remotely operated machines which helped in reducing handling of the radioactive material without shielding.

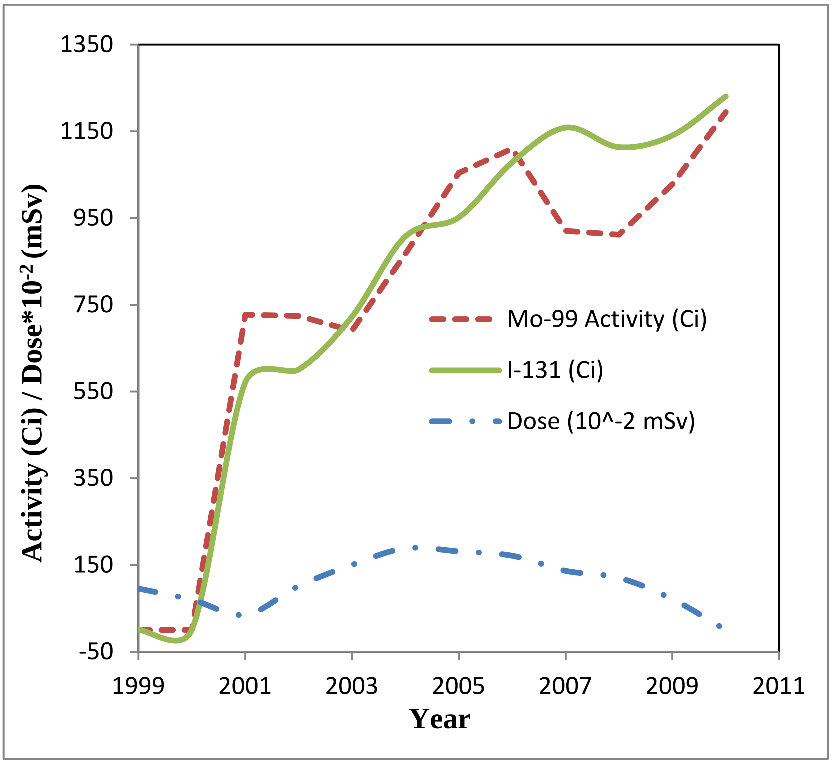


Figure 12: Plot of activity handled and dose received by the operator from year 1999 – 2010

Table-1: Trend of radioactive material handled in processing lab in RPL, BRIT*

Year	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Mo-99 Activity, Ci	727	724	690	867	1054	1110	920	911	1027	1194
I-131 activity, Ci	570	600	722	907	951	1078	1158	1113	1140	1230
*- received from BARC, excluding imported radio-isotope										

Table-2: Dose received by the operators handling radioactive material

Year	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Total Occupational Exposure, Person-mSv	115.4	66.3	35.4	104.1	143.25	179.45	170.9	165.95	149.8	126.19	96.1
No. of Persons exposed	121	94	100	103	103	95	94	97	110	104	135
Per capita dose, mSv	0.953	0.698	0.35	1.01	1.5	1.88	1.81	1.71	1.362	1.2	0.71

- AERB dose limit for civilians is 1 mSv per year.
- AERB dose limit for radiation workers is a maximum upto 30 mSv per year or 20 mSv averaged per year over a period of 5 consecutive years, and must not exceed a total value of 100 mSv in 5 years.

5 Conclusion

At the beginning of the last decade, when the market demand for the RPhs was limited, handling and processing of the radio-isotopes was laborious and manrem extensive. As the market demand rose due to popularity of the nuclear medicines in diagnosis and treatment of various ailments, quantity of the medical use radio-isotopes handled by the operators also increased. Increased quantity of the radio-isotopes directly increased the dose received by the operators due to poor practices and lack of remotely operated gadgets and was noted by the regulators who in turn asked the designers of the STB and gadgets to improve the production set-up by following the ALARA principle linked to radiation dose. To achieve the target set-up by AERB, technology development team, through discussions with the users and brain storming, targeted critical operations like unsealing and sealing of the vial carrying stock solution, transfer of the RPh into the vial as the area for improvement. Process of production set-up improvement started in the year 2003 in which gadgets like vial unsealing machine, unscrewing machine, sealing machine, liquid transfer machine from the stock solution vial (100ml capacity) to the pooling vessel and from pooling vessel to the consignment vials (10ml and 15ml capacity) were designed, fabricated and commissioned. By the year 2006-07, almost all RPh processing facilities were equipped with remote handling gadgets and improvement continued. While the liquid transfer from the stock solution vial to the pooling vessel is safely done using the vacuum, the transfer from the pooling vessel to the consignment vial is safely and accurately done using the peristaltic pump. Peristaltic pump is highly accurate, safe and reliable machine used for transfer of the RPh from the pooling vessel to the intermediate stop i.e. the syringe (through the silicone tubing) mounted on the liquid dispenser.

Handling RPh under vacuum is found to be safe.

Post first phase of implementation, data collected on the dose received by the operators showed that even-though the annual requirement of the radioactive material has increased, dose received by the operator has decreased. Improvement in the situation was due to improved material handling facilities/practices and extensive use of remotely operated gadgets for transfer of liquid radio-isotopes.

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