THE OPERATION OF CYCLOTRONS USED FOR RADIOPHARMACEUTICAL PRODUCTION

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ABSTRACT

Amersham International and Medi+Physics have been involved in the use of cyclotrons for licensed radiopharmaceutical production for over a quarter of a century. Amersham was the first company to purchase a cyclotron for commercial radioisotope production and it is still operational after 27 years. The latest cyclotron was commissioned 2 years ago. A wealth of experience has been accumulated both on the practical aspects of cyclotron operation for the high current irradiation of targets and the associated support functions. This paper discusses the operation and scheduling of the cyclotrons for the many isotopes produced as well as our progress on machine reliability and operator dose reduction.

1. INTRODUCTION

Two years ago Amersham acquired the North American operation of Medi+Physics and now combined they operate eight cyclotrons at three sites, Amersham (UK), North Arlington Heights IL. and South Plainfield NJ. In total there are 150 people employed directly in the production of the radiopharmaceuticals. The cyclotrons operated are listed in Table 1.

Name	Installed	Energy MeV	Target
Philips	1966	25	Internal
CS22	1972	22	Internal/External
MC40-1	1979	20 - 40	Internal/External
MC40-2	1981	20 - 40	Internal/External
CP42	1984	20 - 42	External
PV70	1985	25 - 70	Internal/External
MC40-3	1986	20 - 40	Internal
Cyclone-30	1989	15 - 30	External

Table 1.

All of these machines were purchased from dedicated cyclotron manufacturers and then customized for intensive machine operation by the addition of targetry systems which differ for the various applications.

A variety of different targets are irradiated. These include:

Reaction	Uses
$^{203}Tl(p,3n)^{201}Pb \rightarrow ^{201}Tl$	Myocardial scintigraphy (Heart)
$^{112}Cd(p,2n)^{111}In$	Monoclonal antibody studies and cistern/ventriculography
$^{124}Te(p,2n)^{123}I$	} Thyroid studies
$^{127}I(p,5n)^{123}Xe \rightarrow ^{123}I$	} Thyroid studies
$^{124}Xe(p,2n)^{123}Cs \rightarrow ^{123}Xe \rightarrow ^{123}I$	} Thyroid studies
$^{68}Zn(p,2n)^{67}Ga$	Tumour location
$^{82}Kr(p,2n)^{81}Rb \rightarrow ^{81m}Kr$	Lung function studies

To be successful in the commercial production of radiopharmaceuticals, it is important to be able to deliver the product to the customer reliably day after day, all year long. The products produced have half-lives in the range of 4.8 hours (Kr) to 73 hours (Ga), and therefore it is not possible to stock these isotopes for more than a few days at most. To comply with the expiry date requirements of licensed radiopharmaceuticals the shorter lived isotopes are made to order on a daily basis, thus customer service levels are critically dependent on cyclotron reliability. To support this requirement there is a significant organizational challenge, in co-ordinating the demands of production, maintenance, development and best radiological practice.

2. ISOTOPE IRRADIATION

In order to maximize reliable isotope production sophisticated target systems are required. These systems are constrained by a number of parameters. These include the

method of positioning the target reproducibly, beam spot size on target, the requirement to dissipate several kilowatts of heat and the minimization of operator dose uptake and isotope usage. The magnitude of beam that can be used is target material dependent and requires a consistent high quality of target plating to ensure reproducible production rates. To control the usage of the enriched isotope the solid targets are normally electroplated. Current prices are \$6.15/mg for ^{68}Zn, \$3.10/mg for ^{203}Tl and \$4.35/mg for ^{112}Cd[1] making the recycling of unused material a necessity.

Irradiation performance of targets internal to the cyclotron is complicated because the vapour pressure of the solid target is decreased by several orders of magnitude by having to operate in the cyclotron tank at a pressure of about 5 microtorr. This means that short duration pulses of high intensity beam, due perhaps to ion source instability, can evaporate target material. The original cyclotron designers expertise in producing beams of low emittance further complicate the process giving high power densities (a few kilowatts/cm^2) which have to be dissipated. The size of the target is limited by the physical constraints of the vacuum tank ports but is optimized by allowing the beam to hit the target at grazing incidence, paying particular attention to the water cooling of the target backing. It is necessary to ensure there is no air in the water and that turbulent flow conditions are maintained at all times to maximise heat transfer. Increased power dissipation can be achieved by rotating the target but this complicates the design of the target handling mechanism. The opportunity for beam diagnostics is limited on internal beam machines making production control more difficult. The beam size is particularly susceptible to machine parameters such as dee phase, harmonic coil and gradient coil settings. These parameters may be detuned purposely sacrificing ion source/machine efficiency for increases in isotope productivity. The design of internal targets are often unique to each commercial cyclotron model but isotope production remains target limited.

On external beam machines the control over the irradiation is enhanced by the diagnostic techniques available in the beamlines such as slits and collimators, phosphor screens or flying wires used to determine the position of the beam. The beam shape can be optimized by steering and focusing magnets making it largely independent of tuning parameters internal to the cyclotron. Again the power dissipation requirements are satisfied by inclining the target, water cooling and occasionally rotation. Another significant advantage of external beam cyclotrons is that it is possible to irradiate the target at atmospheric pressure by passing the beam through a very thin titanium or Havar foil which is force cooled with a jet of inert gas[2]. External targets can dissipate between 50-100 % more power than internal targets and thus isotope production is beam current limited.

For both internal and external target types it is useful to monitor the proton/neutron ratio during irradiation as this can aid machine diagnostics and tuning.

3. TARGET HANDLING

A number of different target handling systems are installed at our facilities. The prime function of these systems is to place the target reproducibly for irradiation by remote control minimizing the dose uptake to the operator. Conveyor systems are used to move the target through the shielding walls of the cyclotron vault. After testing for vacuum and coolant integrity the targets are mounted in their irradiation position either by the use of through-the-wall manipulators, robots or by electromechanical methods. Programmable logic controllers are used for this repetitive operation which may be automated so that unattended target changes are possible. These handling systems have to be reliable with complete backup if a full production capability is to be maintained. This is particularly important when dealing with short half-life isotopes such as ^{201}Pb that require immediate processing. This may involve the use of battery operated recovery methods or emergency generator systems for critical circuitry.

4. SCHEDULING

Scheduling the cyclotrons is a compromise between machine maintenance and production requirements. The cyclotrons are able to run unattended 24 hours/day every day of the year. A variety of shift patterns are worked by the staff so that the appropriate people are available at the required time for operational duties eg maintenance, breakdown cover, chemical processing. When scheduling irradiations the usual starting parameter is the amount of activity that is required by the customer base at a specific time. From this information it is possible to calculate when the activity must be generated allowing for chemical processing, dispensing, quality assurance, shipment and decay. As it is possible to produce several isotopes on each cyclotron a sophisticated software package has been developed to optimize the multi-isotope, multi-cyclotron utilization schedule. By iterative refinement and rapid feedback of actual yield rates dynamic scheduling is possible. A typical weekly irradiation schedule for one of our cyclotrons is shown in Fig 1.

Of particular interest are the periods during the week when the cyclotron is available but not used for production (shaded areas in Fig 1.). This reflects a high degree of efficiency so that the correct amount of radioactivity is made at the correct time. The short periods (Monday evening, Friday evening) can be used for instrumentation/calibration checks outside the vault. The longer periods of available time (Saturday) reflect production capacity that can either be exploited for development, additional production or used to

	0000	0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	0000
Sunday	→	I			Tl				Xe			I	→
Monday	→	I			Tl							I	→
Tuesday	→	I			In							I	→
Wednesday	→	I			Tl								
Thursday					MAINTENANCE							Tl	→
Friday	→		Tl				Tl				Tl		→
Saturday	→		Tl									I	→

Fig. 1. A typical weekly irradiation schedule

create a longer maintenance period on one of the other machines.

The production schedule sometimes requires that irradiation of short half-life isotopes ends before order acceptance stops that day eg the overnight iodine runs. It is vitally important that the yield information is fed-back into the scheduler to optimise the following night's production.

5. MAINTENANCE

In a multiple cyclotron operation, each machine becomes an integral part of an overall operating plan. Operations are scheduled in an eight part scenario that includes the requirements of production and maintenance on two continents.

It is easy in this industry to operate the machines until they break down and then effect emergency repairs. This is a short-sighted approach which results in increased down time, increased operator dose and low reliability. A rigorous maintenance policy supported fully by senior management is required to achieve the reliability necessary to produce short-lived radiopharmaceuticals.

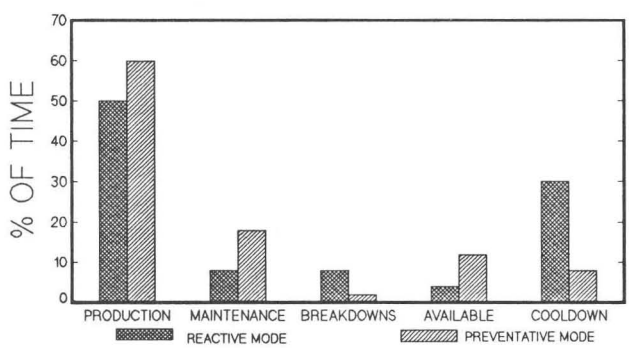

Fig. 2. Comparison of cyclotron utilization in breakdown and preventative modes

Over the last few years operations have moved gradually from the reactive to the pro-active mode. Accumulation of data during this period has enabled the step from breakdown maintenance to systematic preventative maintenance to be made. Recently it has been possible to take the next step to predictive maintenance. Figure 2. shows the utilization of the eight cyclotrons. It is clear that the reactive maintenance regime is significantly less productive requiring more unusable time as the radiation levels in the vault reduce to acceptable levels.

In the move from breakdown maintenance to predictive maintenance, it has been possible to halve operator exposures whilst experiencing an eightfold increase in machine activation due to product volume increases. Additionally, the unplanned breakdown time has been reduced from an average of 8 percent to less than 2 percent.

The Preventative Maintenance program relies on a sophisticated commercial software package[3]. This software maintains a large data base of machine maintenance and breakdown information. Additionally, it maintains an inventory of all spare parts. This, coupled with a bar-code system of inventory management, ensures that adequate stocks of critical spares are maintained. As spares are used, the inventory is updated and at determined levels purchase orders are produced automatically.

The powerful and flexible report writing facility of the software tracks the work orders and work completed including important task/dose information. It is possible to produce reports which indicate the maintenance by specific system allowing the determination of which systems are most liable to failure. This allows management to make informed decisions on where to invest funds for maximum benefit in reliability and safety.

6. DOSE CONTROL

Regulatory control of radiation exposure is always an important issue in a production operation. Permissible dose levels are continuously being revised downwards. In the UK the Company limit is 15mSv/year, in the US it is 25mSv/year (these limits will be reduced to 10mSv/year and 15mSv/year respectively in 1994). A benefit of the Preventive Maintenance program is that adherence to these limitations is achieved without compromising production primarily because we are able to benefit from planned machine cooldowns. It has been possible to identify those areas generating the highest dose uptake prompting engineered improvements or modification of working practises.

Figure 3. shows the total dose uptake by cyclotron operators at our UK and US facilities over the last 5 years.

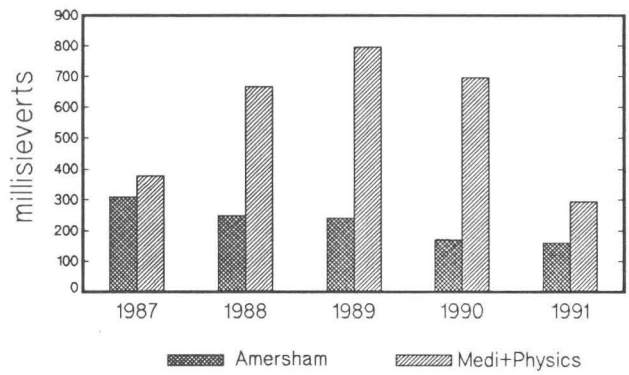

Fig. 3. Cyclotron Group Dose Uptake 1987-1991

Practical methods employed to reduce dose uptake include accurate in-vault and in-tank surveys to identify hotspots which may have dose rates of several hundred millisieverts/hour. Using this information and historic data it is possible to predict accurately the dose uptake for particular procedures. Other methods include the use of remote controlled TV cameras in the vaults to aid fault diagnosis or monitor staff; laser pointers are used to indicate equipment requiring attention without needing to enter beyond the vault door area; video recordings and photographs are used to train new operators in routine procedures without any radiation exposure. Major rebuilds are also recorded so that the information can be shared with our other facilities.

7. QUALITY

Quality, in its broadest sense, is critical to the radio-pharmaceutical business; both in terms of the efficient utilisation of expensive capital equipment and the statutory requirements of Good Manufacturing Practise (GMP)[4].

In-process control is used at all stages of production. This starts with the definition of performance criteria for the cyclotrons and the adherence to calibrated standards. Each target is checked for weight and condition prior to acceptance for bombardment. During bombardment all cyclotron operating parameters are automatically checked to be within the acceptable range. The integrated beam current, length of run and prior yield values are used to calculate the predicted yield. This is then compared with the actual yield and fed back into the scheduling program and used as a performance measure for that machine. Isotopic abundance analysis of the product is used to check that the energy of the beam was correct during irradiation. For instance, on an internal ^{203}Tl target a radial position increase of 0.5mm will increase the beam energy sufficiently to cause a non-compliance with the pharmaceutical licence due to increased ^{200}Tl content in the product.

8. CONCLUSION

Producers of licensed radiopharmaceuticals are subject to stringent controls both in terms of the regulatory compliance of the product and the legislation governing the radiation dose received by staff. Conformance with these requirements is essential for the long term viability of suppliers in this business. Operating cyclotrons is capital intensive, demanding the best possible use of the resources available. The initiatives outlined in this paper are part of an ongoing improvement programme which addresses these requirements thus ensuring reliable supplies of radiopharmaceuticals both now and in the future. This will benefit everyone in the supplier/customer chain.

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