DESIGNING A RADIOISOTOPE FACILITY

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Abstract
The physics concepts and methodology of designing a radioisotope production facility based on a cyclotron is discussed with particular reference to manufacturing commercially useful isotopes known as radiopharmaceuticals. Commercially available cyclotron systems will be discussed and a conceptual facility will be described; the isotope most used in nuclear medicine, thallium 201, a heart imaging agent, will be used as a case study isotope. The requirements of Good Manufacturing Practice for the isotope products and the necessary compliance with regulatory approvals will be outlined.

1. INTRODUCTION

Cyclotron-produced radioisotopes were first developed for medical purposes at the University of California, Berkeley, in 1936. For the next 30 years cyclotron construction proliferated amongst universities and national research laboratories with increasing interest from commercial organisations for processing the isotopes as radiochemicals. However, in the early 1960's genuine medical applications for several isotopes were identified, e.g. fluorine-18, rubidium-81 etc. and the first cyclotron project totally dedicated to commercial isotopes production was established in the UK by The Radiochemical Centre (now known as Amersham International). For the period 1965-78 several 'first generation' cyclotrons were constructed, such as the early Cyclotron Corporation cyclotrons. These were essentially research cyclotrons simplified for industrial operations. However, from approximately 1975 onwards well-engineered, user-friendly or 'second generation' compact machines became available, e.g. Scanditronix MC-40 series. A significant technical leap was taken in 1988 when IBA in Belgium developed a high intensity, low cost cyclotron with negative ion acceleration, high efficiency extraction and with fully automated controls. Concurrently with the development of these 30 to 40 MeV cyclotron models, several medically useful cyclotron isotopes were also being licensed, e.g. gallium-67, iodine-123 etc.; by 1980 thallium-201 was available for cardiac imaging and has now become the most important commercial cyclotron isotope In addition to the growth in the medical applications of cyclotron isotopes, legislation for pharmaceuticals was being extended to include these cyclotron produced materials, i.e. they became radiopharmaceuticals.

Therefore, a present-day production facility will consist of a cyclotron, several beam lines and mechanical transport systems and a target arrangement which is custom built to be handled in the different chemical extraction processes for producing pure radiochemicals and then in the pharmaceutical production systems for producing sterile, injectable materials which comply with the pharmaceutical or drug licensing requirements of many countries. The underlying physics and chemistry of producing cyclotron radiopharmaceuticals will be discussed and a design of a conceptual facility will be developed within the text.

2. ISOTOPES AVAILABLE FROM CYCLOTRONS

Present-day radiopharmaceutical grade cyclotron isotopes are used for imaging and

diagnosis at nuclear medicine centres worldwide. A typical three-dimensional tomographic heart image section is shown in Fig. 1 using thallium-201. Some 2-3 million patient procedures are undertaken each year using materials produced from cyclotrons. The most common cyclotron produced isotopes are given below in Table 1.

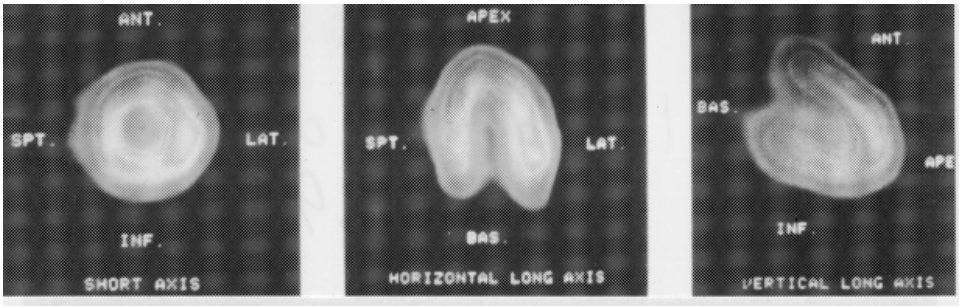

Fig. 1 Typical three-dimensional tomographic heart image

Table 1

Applications of cyclotron produced isotopes

Isotope	Half Life (Days)	Application
Kr-81m	0.25	Lung function studies
I-123	0.55	Thyroid studies
In-111	2.80	Monoclonal antibody / infection imaging etc.
Tl-201	3.05	Myocardial imaging (heart)
Ga-67	3.26	Tumour location (soft tissue)
Co-57	271.7	Calibration devices for cameras

Although even shorter-lived isotopes are also produced by a cyclotron, for the purpose of this discussion these very short lived isotope (PET or Positron Emission Tomography isotopes, Table 2) will not be discussed since their commercial usage and distribution have not yet been realised. In general most of the commercially useful radiopharmaceutical isotopes have half lives of the order of 1-7 days and their production reactions are given in Table 3.

Table 2

Common PET isotopes

Isotope	Half Life (min.)
C-11	20
N-13	10
O-15	2.1
F-18	110

Table 3

Isotope production reactions

Tl-203	(p,3n)	Pb-201 → Tl-201
Zn-68	(p,2n)	Ga-67
Cd-112	(p,2n)	In-111
Xe-124	(p,2n)	Cs-123 → Xe-123 → I-123
Kr-82	(p,2n)	Rb-81 → Kr-81m
Ni-58	(p,2n)	Co-57

The most commonly used commercial cyclotron isotope is thallium-201 which as a potassium analogue, is readily absorbed within the muscle tissue of the heart, i.e.. the myocardium. Thallium imaging is used to demonstrate blood flow within the heart muscle by imaging a patient at rest and under stress; ischaemic tissue and infarctions can be identified using 3D tomographic techniques. Thallium-201 is also one of the most complicated cyclotron isotopes to manufacture and the specification of a licensed thallium radiopharmaceutical or drug is summarised in Table 4.

Table 4

Specification of thallous (Tl-201) chloride injection

Half life	73.1 hours
Energy of gamma rays	0.068 to 0.082 (Hg K X rays)
Radionuclidic impurity	Tl-202 < 1.9% Tl-200 < 1.0% Pb-203 < 0.25%
Specific activity	> 3.7 GBq.μg^{-1} (or 100 mCi per μgm)
Chemical form	Sterile, isotonic, aqueous solution of thallous chloride plus 0.9% (v/v) benzyl alcohol and 0.95% (w/v) sodium chloride
Reference day	Average 6 days post bombardment
Expiry day	Reference day + 3
Administration: Normal dosage Whole body absorbed dose Upper large intestine wall	 55.5 MBq or 1.5 mCi 2.4 MBq or 0.06 rad 27.7 MBq or 0.74 rad

The features of this pharmaceutical isotope material are:

- the energy of the gamma radiation is high enough to penetrate tissue but still low enough for efficient gamma camera detection, i.e.. around 50→250 keV energy range.
- radionuclidic impurities must usually be less than 1-2% since any longer half-life isotopes contribute to increasing patient radiation dose and to blurring of images.
- half lives are approximately 3 days, which is a convenient time period for the manufacture, delivery and administration of the material to the patient.
- the specific activity of the isotope must be high enough to produce sufficient events or

counts in the required organ using a gamma camera imaging system.

– the radiopharmaceutical must be manufactured according to the protocols of "Good Manufacturing Practice".

– the specification and manufacturing protocols must comply with approved drug licence conditions issued by the appropriate Government bodies.

3. BOMBARDMENT AND ISOTOPE PRODUCTION PROCESS

For the purpose of this section the heart imaging agent thallium-201 will be used as a 'case study'; the overall production of this isotope will include the following steps:

– Preparation of a target using as a starting material the enriched isotope thallium-203,

– Bombardment by a 25-30 MeV cyclotron proton beam,

– First chemical separation process to produce the intermediate or daughter isotope lead-201,

– Secondary chemical separation of the radioactive isotope thallium-201,

– Pharmaceutical production of the sterile, radioactive, injectable thallous chloride.

Other important isotopes such as gallium-67, iodine-123 and indium-111 are produced by very similar manufacturing processes. The preferred production reaction for producing thallium-201 is shown below; in fact lead-201 is generated first.

$$\text{Thallium-203 (p,3n) Lead-201} \xrightarrow{\text{decay}} \text{Thallium-201}$$

Naturally occurring thallium consists of two main isotopes - thallium-203 (natural abundance 29.5%) and thallium-205 (natural abundance 70.5%); the initial raw material for cyclotron targets is the enriched stable isotope - thallium-203. Enriched isotopes are produced usually by large electromagnetic separators located within Government controlled establishments, producing mainly uranium-235 for fuel and weapons applications. The original 'calutron devices' at Oak Ridge are now 40 years old and are based on the concept of a 180° magnetic spectrometer and use large dipole magnets. Radioisotope production consumes a few kilograms of these materials annually worldwide and the enrichment requirements for the different isotopes are given below in Table 5.

The excitation cross sections for proton bombardment of thallium-203 are given in Fig. 2, indicating peak energies for the reactions (p,n), (p,2n) and (p,3n) etc. In addition, similar production cross sections exist for protons bombarding thallium-205 indicating that even a trace impurity level of thallium-205 within the target material thallium-203 will lead to radioactive impurity species in the final product. The competing reactions are given below in Table 6.

Table 5

Enrichment of isotopes

Isotope	Other naturally occurring isotopes	% naturally occurring	% radio-pharmaceutical specification	Electro-magnetic separator production (hours per kg)	Approx. cost (M$/kg)
Tl-203	Tl-205	29.5%	98%	20,000	2.5
Zn-68	Zn-64, Zn-66, Zn-67, Zn-68, Zn-70	18.6%	98%	65,000	4.5
Cd-112	Cd-106, Cd-108, Cd-110, Cd-114, Cd-116	24.1%	96%	55,000	3.5
Xe-124	Xe-126, Xe-128, Xe-130, Xe-132, Xe-134, Xe-136	0.095%	>20%	Gaseous diffusion	0.1 per litre

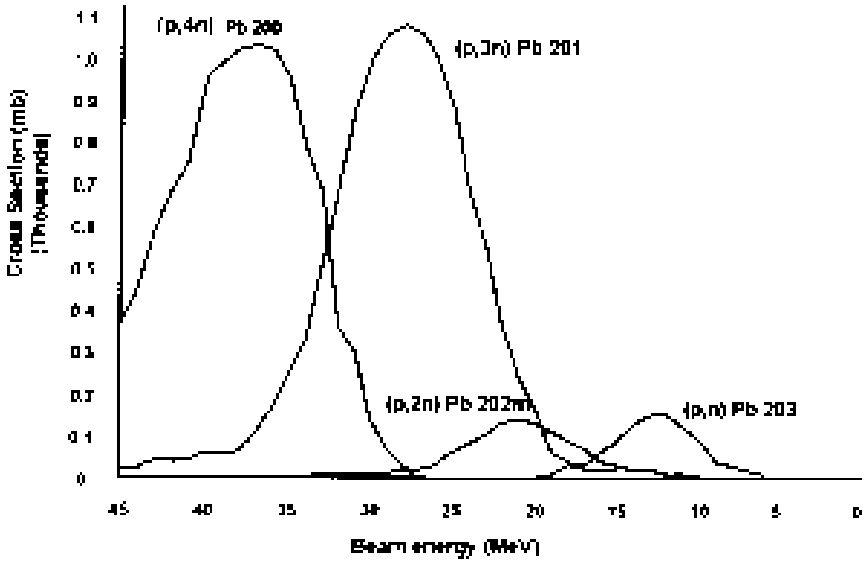

Fig. 2 Excitation cross sections for Thallium 203

From the graphs in Fig. 2 it is possible to determine:

– The maximum *bombardment energy* for the proton beam; in this case it is determined by the impurity radionuclide lead-200 created via the reaction (p,4n), resulting in a daughter product Tl-200 which has a half life of 26 hours and a high energy gamma ray. This would increase the patient dose considerably if the percentage impurity was allowed to be greater than 1%. Consequently this fixes the maximum proton energy for thallium production at 28.5 MeV.

– The minimum *bombardment energy* or exit energy of the proton beam is similarly constrained by the impurity radionuclide lead-202m created by the reaction (p,2n), the resultant daughter product Tl-202 has a half life of 12 days and a γ-emission of 1.0 MeV; the minimum energy at the exit of the enriched Tl-203 material is similarly fixed at 22 MeV.

Table 6

Competing reactions - thallium bombardment

Reaction	Initial material	Radioactive products	Half life

(p,4n)	Tl-203	Pb-200 ↓ Tl-200	21.58 hours 26.1 hours
(p,3n) (p,5n)	Tl-203 Tl-205	Pb-201 ↓ Tl-201	9.4 hours 73.1 hours
(p,2n) (p,4n)	Tl-203 Tl-205	Pb-202m ↓ Tl-202	3.62 hours 12.23 days
(p,n) (p,3n)	Tl-203 Tl-205	Pb-203 ↓ Tl-203	51.9 hours stable
(p,2n)	Tl-205	Pb-204m ↓ Pb-204	1.1 hour $>1.4 \times 10^{17}$ yrs
(p,n)	Tl-205	Pb-205	1.5×10^{7} yrs

The energy of the proton beam is reduced during passage through the target and energy is lost by elastic collisions, atomic excitation and ionisation. Using the Bethe model for relativistic velocities the expression for energy loss can be shown to be:

$$\frac{dE}{dx} = -4.58 \times 10^{-12} \frac{NZ}{v^2} \ln\left(1.82 \times 10^{-30} v^2 / I\right) - \ln\left(1-\beta^2\right) - \beta^2$$

in units of MeV.mm^{-1} where:

- N the number of atoms per unit volume of target material
- Z the atomic number of the target material
- v proton velocity
- I effective ionisation potential of target material
- ß (v/c)

The stopping power in thallium is shown in Fig. 3 and the computed range of protons in thallium as a function of energy can be derived as in Fig. 4.

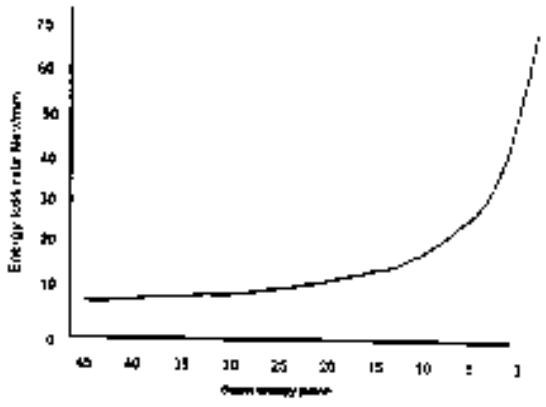

Fig. 3 Stopping power in thallium

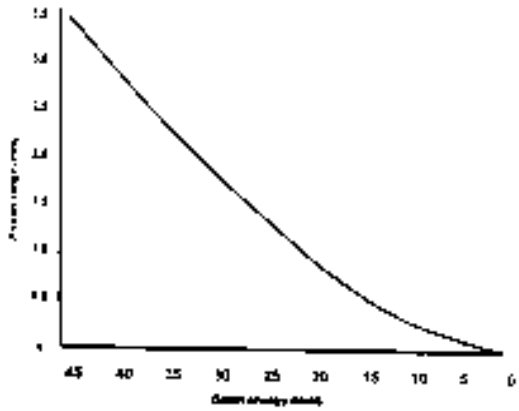

Fig. 4 Computed range of protons in thallium as a function of energy

Another parameter used in isotope production is the yield rate A_o, which represents the macro-production cross section for a particle beam with given incident and exit energies and represents the instantaneous production rate of the isotope (i.e. assuming no radioactive decay). A_o takes account of target density, molecular weight of the target material, enrichment or abundance factor of the target isotope etc. and is expressed in Curies per mA.hr. A comprehensive computer model and methodology has been developed by Forrest for any

production isotope and allows for energy loss and the reactions of all the isotopes involved. It is assumed that a thin layer of the enriched isotope i.e. Tl-203, is deposited on a thicker cooled target base (usually copper) and that the target assembly can be inclined at a given angle to the direction of the proton beam. Table 7 shows a report print out for thallium, from which the

Table 7

Summary table of yield values (A_o) – protons on thallium

Proton Energy MeV	Proton Range mm	Pb-201 Ci/mA.hr	Pb-199 Ci/mA.hr	Pb-200 Ci/mA.hr	Pb-202m1 Ci/mA.hr	Pb-203 Ci/mA.hr	Pb-204m Ci/mA.hr	Zn-65 Ci/mA.hr	
28	1.58			0.07	9.02	5.36	14.72	0.017	of Pb-200
27	1.47			0.02	8.84	5.10	14.30	0.017	
26	1.36		optimum		8.60	4.85	13.82	0.017	
25	1.29		production		8.27	4.60	13.31	0.017	
24	1.12		Pb-201		7.70	4.36	12.69	0.017	
23	1.12				7.00	4.12	11.97	0.017	
22	1.04				6.07	3.92	11.04	0.017	blockman level

design requirements for thallium bombardment can be derived. The model also predicts the impurity levels for the other radionuclides and also the production level of Zn-65 (half life 265 days) produced by the reaction which creates a waste disposal problem due to its 1.12 MeV gamma ray.

Zn-65 is produced by the reaction:

Cu-65 (p,n) Zn-65

This model assumes that the remainder of the energy is deposited within the target base; the stopping power calculation can also be used to estimate the required thickness of this copper base to ensure full proton absorption and no penetration into the cooling liquid which is usually water.

For a given set of irradiation conditions the activity produced is:

$$A_t = A_o It \; \frac{I - e^{-\lambda t}}{\lambda t}$$

where A_t is the activity in Curies at time t
I is the beam current in mA
t is the bombardment time in hours
λ is $\ln(2)/T$
T is the half life of the isotope produced

Tpical A_o values is given in Table 8.

Table 8

Table of yield rates A_o

Isotope	A_O (Ci $mA^{-1}hr^{-1}$)	E_{in} (MeV)	E_{out} (MeV)
Tl-201	21.6	28.5	22.0
Ga-67	4.3	25.5	0.0
In-111	6.3	29.0	17.0
Co-57	0.032	22.0	0.0

The design requirements for thallium-201 bombardment can then be determined and are given below in Table 9.

Table 9

Design requirement for thallium bombardment

Maximum energy	28.0	MeV	Pb-200 production limitation
Minimum energy	22.0	MeV	Pb-202 production limitation
dE/dx	11.9	$MeV.mm^{-1}$	Derived from 28.0 MeV incident beam energy and 22.0 MeV exit energy
Effective thickness	0.566	mm	Calculated from above
Angle of inclination	6°		Mechanical design considerations
Thickness of electroplating	0.06	mm	

In general, for solid targets the target materials are electroplated onto metal bases, usually having good conduction characteristics, such as copper, silver or aluminium and proprietary electroplating methods are often used ensuring that the starting raw materials comply with the conditions laid down in the Drug Master File, i.e. the manufacturing protocols authorised according to the drug licence. Criteria for electroplating include:

– Plating to completion of the electrolyte or otherwise,
– Electrical programming of the plating current cycle,

– Mechanical agitation of the target material,
– The addition of additives or shiners to enhance electro-mechanical deposition,
– Maintaining the minimum plating thickness consistent with the bombardment requirements.

A typical electroplating station is shown in Fig. 5.

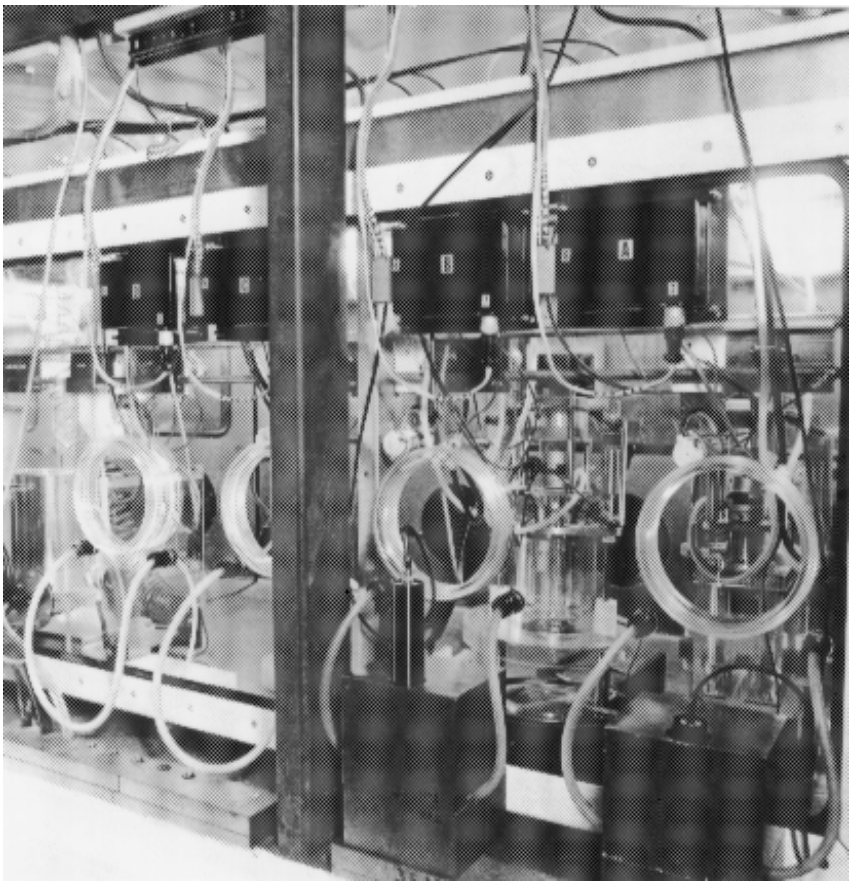

Fig. 5 A typical electroplating station

4. DESIGN CRITERIA FOR TARGETS

In commercial manufacturing of cyclotron isotopes, the key parameter for target design is the beam current acceptance. Historically, production targets have been located either inside cyclotrons as *internal*, glancing-angle targets on the external orbit of the correct energy or as *external* targets bombarded at the end of beam lines. For industrial operation, the heat transfer problem of this large energy density deposition has been addressed by either adjusting the glancing angle in the range 4°-15° for incidence on a *static* target or presenting circular

Table 10

Heating calculations for a stationary target

BEAM PARAMETERS	COPPER TO WATER HEAT TRANSFER PARAMETERS	FINAL TARGET SURFACE TEMPERATURE CALCULATION
a. 1/2 beam height(m) = 0.0094 b. 1/2 beam width(m) = 0.0009 Beam current (μA) = 150 Energy (MeV) = 29 Q. power of beam (W) = 4350 A. projected area of beam on target (m^2) = 0.0025 q(m). Mean heat flux (W/m^2) = 1710817 q. Peak heat flux (W/m^2) = 3934879	Copper/water heat transfer coefficient (W/m^2K) = 60800 cp. Specific heat of water at 20° C (J/kg K) = 4186 nb. Viscosity of water at 20° C (J/kg K) = 0.001 lb. Thermal conductivity of water at 20° C (W/m) = 0.602 Pr. Prandtl number = 6.95 d. Depth of water channel (m) = 0.00375 w. Width of water channel (m) = 0.025 M. Water flow rate (kg/s) = 1.65 m. = M/(d*w) mass flux of cooling water ($kg.m^2$ s) = 17600 Re. Reynolds Number = 2md/nb = 132000 nw. Viscosity of water at the temperature of the Cu/water surface = 0.000548 at 50°C 0.000283 at 100°C 0.000183 at 150°C	The peak surface temperature is calculated from the cooling water temperature plus three additional temperature rises. 1. Water-copper (°C) = 44.8 2. Copper (°C) = 16.5 3. Plated target layer (°C) = 6.7 Total temperature rise (°C) = 68.0 Chilled cooling water temperatur = 13.0 °C Therefore, final peak target surface temperature = 81.0 °C
TARGET PLATING PARAMETERS l3. Thermal conductivity of plating material = 44 (W/m K) = 44 X3. Plating thickness (m) = 0.00010		
COPPER BACKING PARAMETERS l. Thermal conductivity of Cu (Wm/K) = 390 x. Thickness of Cu (m) = 0.002 d. Approximate correction factor to allow for heat "spread out" in copper = 0.44		

geometry *rotating* targets at high speed to ensure optimum heat transfer. Current commercially available cyclotrons are capable of producing external beams with good emittance control for the current range 150 - 400 μA per beam on target. For the purposes of this 'case study' it will be assumed that a beam current of up to 200 μA external beam will be incident on a static target at a glancing angle. Typical beam emittance is of the order of 5 to 10π mm.mrad which translates to available beam spot dimensions of the order of 3 - 20 mm in either dimension. Early experimental measurement and heat conduction calculations published by Pinto (Table 10) indicated that a temperature rise of 150°C would occur with an incident proton beam of 30 MeV, 200 μA on a target with no electroplated material but designed for optimum cooling. He concluded that for production targets, temperature rises could be limited to about 150°C even with electroplated target material; this temperature is lower than the melting point of thallium metal and would guarantee integrity of the targetry and retention of the expensive raw material on the target surface. This calculation was substantially improved by Forrest to allow for the heat transfer across the interface between the electroplated layer and the base material for several different materials. The model also allowed for defining the optimum target inclination angle for a given beam spot size and Table 11 indicates computed surface temperature increases for different glancing angles based on the following assumptions:

– Optimum target mechanical design to stimulate turbulent flow with water cooling,

– Uniform electroplated material,

Table 11

Target Heating calculations for different metals and beam incident angles

Static Target Heating Calculations

Data :-

Water Temp	=	293	C
Mass in Copper	=	30	C
Beam Current	=	400	µA
Beam Energy	=	30	MeV
Beam Power	=	12000	J/s
Beam X	=	20	mm
Beam Y	=	6	mm
Target backing	=	2800	µm

Metal: Cu, Ni, Ti

Metal	Conductivity (W/mK)	Specific Heat (J/kgK)	Density (g/cm³)
Cu	401	385	8.939
Ni	94	445	8.908
Ti	122	338	7.206
Cu	104	231	8.631
Ta	57.5	130	11.784

New machine stationary target

All operational data as calculated

Target Plate Dimensions:-
Width = 42 mm
Depth = 6 mm
Target Plate Area = 4864 mm²

1 - Beam is across target plate surface
1 - Beam is across target plate surface

Resultant surface temperatures for the incident angles shown

Target Metal	Reaction path (mm)	← Beam Incident Angle (degrees)													
		5	14	15	12	11	14	4	3	2	6	8	3	2	1
Cu	—	179	171	162	154	146	137	128	119	111	102	93	85	76	67	59	50
Ni	0.95	247	230	213	197	180	163	145	129	113	129	101	90	79	69	59	50
Ti	1.46	281	260	239	220	200	180	161	143	125	139	105	92	80	69	59	51
Cu	1.60	282	261	240	220	200	181	162	144	126	139	105	92	80	69	59	51
Ta	1.07	257	238	219	201	183	165	148	132	116	128	96	84	73	63	54	46

dimensions of approximately 6 mm high by 20 mm wide,

– Nominal beam energy 30 MeV,
– A maximum possible proton beam current of 400 μA.

The computed surface temperatures for different incidence angles are given for typical initial raw materials used in radiopharmaceutical production with the requirement that the surface temperature never exceeds the melting point of the material at the reduced vapour pressure within the target enclosure. In general, optimisation of computed models and practical experimentation result in the 'typical' target specification, shown in Table 12.

Table 12

Target specification

Beam current	400 μA, 30 MeV
Beam size	20 mm x 6 mm
Target inclination	6°
Maximum power density deposition	12 kW
Maximum temperature rise of Tl-203	128°C

Due to the relatively high radioactivity activation levels of production targets, well designed, remote controlled mechanical transport systems are necessary to ensure that target integrity is maintained otherwise local contamination of radioactivity and loss of valuable enriched isotopes could occur. Two approaches are now used:

– Compact target transfer by pneumatically operated rabbit systems – the system designed by TRIUMF is shown in Fig. 6.

– Railway transfer systems which remove the target assembly from the cyclotron into a demounting station.

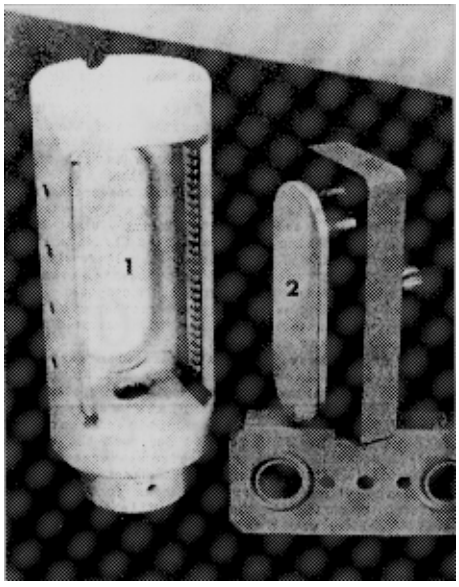

Fig 6 Target transfer showing rabbit (1) and target (2)

5. CYCLOTRON SPECIFICATION

Requirements of cyclotrons for commercial isotope production are:

- Proton beams as indicated in Table 3; the large majority of useful isotopes can be produced by proton reactions (p,xn).
- High beam currents, since the isotope production rate is proportional to beam current.-
- Variable energy is required to accommodate all the reactions in Table 3.
- Extracted beams are preferred to allow optimisation of target design and ease of handling
- High reliability operation is essential for the production of these short-lived isotopes which have to be delivered several times a week.
- Low radiation activation levels are essential at the cyclotron and around the target system to allow for regular maintenance, equipment upgrades etc.
- Low operating costs are desirable for a viable, competitive commercial operation.

The present day 'third generation' compact cyclotrons have been designed specifically for this type of commercial operation and satisfy the above requirements. Two excellent models are available as off-the-shelf packages, viz

IBA, Cyclone-30 designed by Yves Jongen, Louvain La Neuve, Belgium and

EBCO, TRS-30 designed by TRIUMF for EBCO Industries, Vancouver, Canada.

It is also worth mentioning Scanditronix's MC-32 NE which is a negative ion cyclotron but does have a lower output level. For the purposes of this paper, the Cyclone-30 is assumed. The performance specification of the Cyclone-30 is shown in Table 13 and a drawing of the Cyclone-30 cyclotron is shown in Fig. 7.

Table 13

IBA Cyclone-30 specification

Beam current	350-500 μA
Energy range	15-30 MeV
Extraction beam	2
Beam emittance	5-10 mm mrad
Power consumption	150 kW
Ion source	External
Base vacuum	3×10^{-7} torr

Clearly the above requirements for commercial isotope production are well met by the general system specifications of the Cyclone-30, viz

- Proton or deuteron beams can be produced efficiently.
- High extracted beam currents of 350 to 500 μA which are significantly higher than previous 'second generation' cyclotrons, cf. 60 to 100 μA.
- The extraction foil mechanism together with a 'combination' magnet provide an adequate range of extraction energies.
- High reliability operation is achieved by simple yet elegant magnet and RF design, well-engineered extraction equipment, high reliability sub systems, comprehensive diagnostic facilities and stable high beam extraction performance.
- Low radiation levels are maintained by efficient (negative ion) extraction, selection of low activation material for construction of the cyclotron vacuum chamber etc., and low neutral beam activation by high vacuum operation by using an external ion source.
- Low operating costs are achieved by very efficient power consumption of the main

magnet and RF systems, a high reliability operation as well as good maintainability and access.

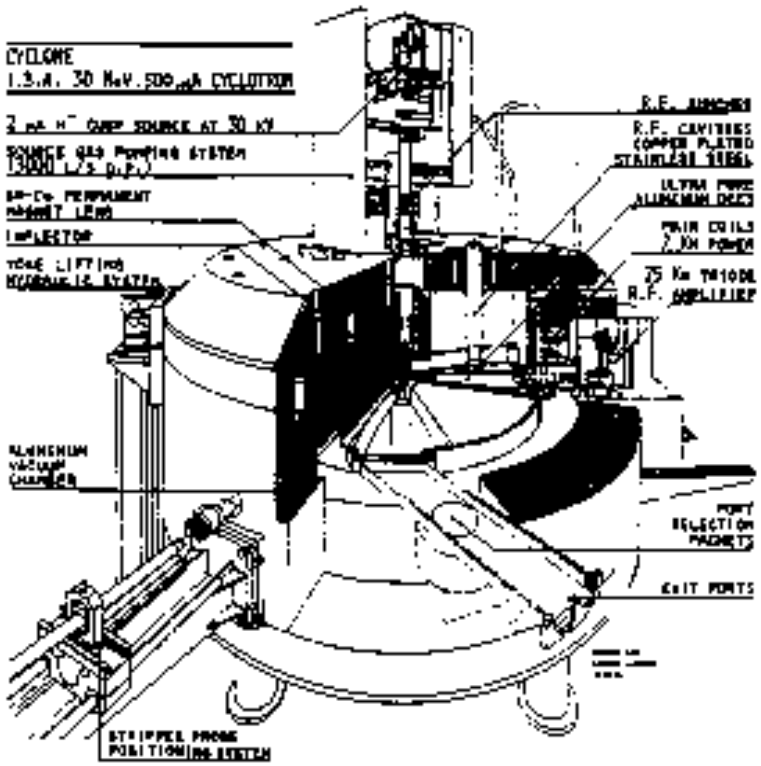

Fig. 7 Cyclone-30 cyclotron

The analysis in Section 4 indicated the following target demands for the extracted beam:

- stable, high current extraction
- low beam loss at extraction
- accurate reproducible extraction energy with low dispersion
- low emittance in both planes, preferably with balanced divergence.

Again, the Cyclone-30 performance meets these requirements although it is essential to ensure that the beam size at the target location can be controlled within the "footprint" of the material on the target thereby minimising the usage of the expensive enriched isotope material. Figure 8 shows a typical TRANSPORT generated computer calculation of beam line optimisation for a possible Cyclone-30 beam to give a minimum 'image' size of 20 mm x 4 mm onto an inclined target footprint of 20 mm x 40 mm, and using the minimum length of beam line yet allowing sufficient space for shielding between cyclotron vault and target vault. For this particular example the beam optics show a very large vertical beam dimension. Beam line design for commercial operation has to satisfy two conflicting demands:

– a small beam size at the target to minimise the usage of expensive enriched isotopes
– a short beam line length to limit the construction costs of the facility.

The final design is a compromise ensuring that beam loss in the beam lines does not lead to excessive radiation and activation of equipment.

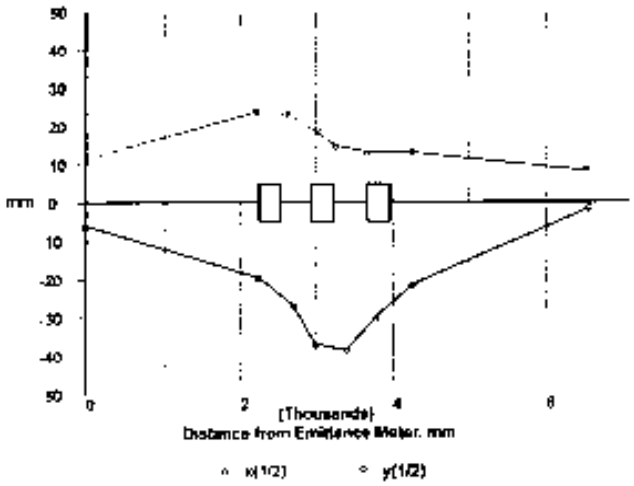

Fig. 8 Cyclone-30 beam optics calculated with the TRANSPORT program

6 . RADIOCHEMISTRY

In cyclotron systems, the amount of isotope generated in the targets is determined by the sum effect of the physical processes described earlier. Extraction of the radioisotope from the targets is achieved by chemical or radiochemical methods. For example, in order to achieve the correct radiochemical formulation for thallium-201, the following processes are required:

First chemical separation: Acid extraction of the primary product lead-201 from the initial thallium-203 and the target base material, e.g. copper.

Second chemical separation: Ion exchange to remove the secondary product thallium-201 from the primary product lead-201.

– Chemical recovery of the original thallium-203 from the aliquot of lead and thallium isotopes as well as the copper impurities.
– Possible removal of the radioactive zinc-65 from the copper material in the target base since this radionuclide constitutes a severe radioactive waste disposal issue.

The graph of Fig. 9 shows the change in radioactivity during the manufacture of Tl-201 during bombardment, the first and second chemical separations, pharmaceutical production, the decay of Tl-201 to the reference date of the product and to the expiry date of the material.

The majority of other isotopes using solid targets, e.g. Ga-67, In-111, etc. are produced by similar techniques although some processes may employ organic solvent extraction chemistry. The main exception is I-123 which is usually produced by dedicated bombardment and processing equipment such as the gas system using Xe-124 as developed at KF Karlsruhe.

These chemical processes are performed within a facility dedicated for the production of radiochemicals and containing heavily shielded production plant or cells with shielding equivalent to 10 or 20 cm lead. Each plant is usually equipped with:

- a set of manipulators,
- leaded-glass window,
- in-plant chemical equipment,
- front-panel controls for electrics and pneumatics,
- transfer ports for product flow, waste materials,
- air flow into filtered air handling unit.

The radiochemical produced has the correct chemical ingredients but not necessarily the correct concentration, and is not sterile enough for drug purposes.

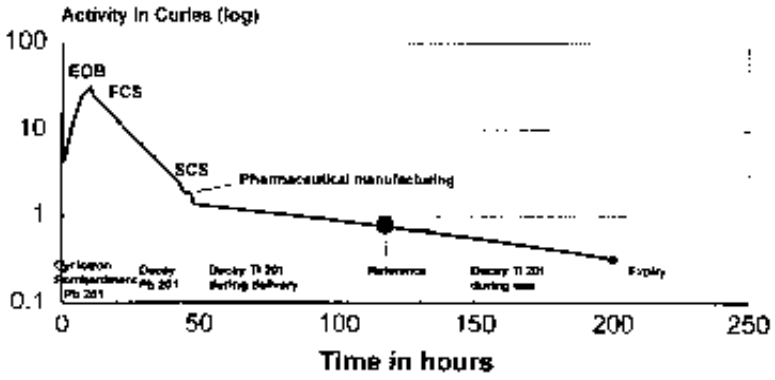

Fig. 9 Activity of thallium-201 during production, delivery and use

7. RADIOPHARMACEUTICAL PRODUCTION

As the usage of cyclotron isotopes increased, pharmaceutical licensing requirements for manufacturing became more demanding. Today, cyclotron isotopes used in nuclear medicine are not just radiochemicals with medical applications but genuine pharmaceutical materials incorporating a radioisotope component. These isotope products are usually supplied in a shielded vial container or syringe ready for injection.

The manufacture of radiopharmaceuticals include the following steps:

- container preparation and cleaning, i.e. for vials or syringes
- transfer of the radiochemical material to a pharmaceutical grade 'clean room',
- quality control of parameters such as chemical purity, radionuclidic purity, specific activity,
- sterile dispensing of the radiochemical into its final container,
- terminal sterilisation of the final product,
- batch release of the product by the Qualified Person,
- labelling, packing, distribution, etc.

The detailed steps in this manufacturing procedure have to comply with the principles of "Good Manufacturing Practice" (GMP). All steps are defined in extensive documented procedures within a Drug Master File. This is the legal document binding the manufacturers' operations to the conditions of the pharmaceutical licence which is awarded by Government Regulatory bodies such as CPMP (Europe), FDA (USA). In this way Regulatory Authorities strive to guarantee the safety of the product and the reproducibility of the manufacturing operation.

In order to comply with the regulatory requirements for these small volume 'parenterals', special attention must be paid to ensure that the products are:

- pyrogen free,
- sterile,
- free of particulate material etc.

To achieve this careful control is required of:

- the manufacturing environment,
- the manufacturing processes,
- the product containers.

In addition there is also a requirement that manufacturing operations are performed in a manner that minimises the risk of:

- cross contamination of one product by another,
- incorrect labelling of product containers etc.

A system of Quality Assurance must be in place to ensure that all processes are documented, validated and performed repeatably in accordance with written instructions. All batches of materials used in processes must be tested to ensure conformance with specification; traceability of materials through to the finished product must be maintained and batches of final product for sale must be tested/inspected to demonstrate conformance with specification. All production facilities must be regularly monitored to ensure continuing performance to specification, e.g.

- water quality in purified supplies
- air quality in clean rooms
- performance of sterilisers
- integrity of air filters
- calibration of measuring instruments

During the development phase of a new product, all processes must be systematically validated to show that the process will produce the specified output for all inputs at the upper and lower limits of their specification ranges. This will include a demonstration that the product remains stable throughout its shelf life for specified storage conditions. All experimental and test data must be retained and is liable to inspection by the Regulatory Authority. The finished product must be stored and shipped in a manner that ensures that product deterioration does not occur. Finally, the selection and training of staff is vital to the maintenance of GMP.

8. DESIGN OF THE FACILITY

For the purpose of this discussion, the construction of a complete radiopharmaceutical grade facility is assumed on a green field site.

According to the principles described in Section 5, a cyclotron and associated beam lines are selected and purchased from a specialist vendor. Design features of the facility for accommodating this accelerator hardware should include:

- construction of a solid base or plinth,
- construction of a complete radiological shield or vault for the cyclotron, beam lines and target system,
- subterranean access to the cyclotron for maintenance,
- adequate headroom for access to the ion source and for lifting the upper pole of the magnet for maintenance.

The design of a conventional radiological shield or vault should allow for:

- attenuation of the neutron flux (produced at the isotope target) to a level of $< 5\ \mu Sv.hr^{-1}$ at the external surface of the shield
- selection of appropriate material (concrete) to ensure correct shielding efficiency without voids and without high Z materials which result in high activation levels,
- correct design to avoid neutron (and gamma) short paths in access ducts and channels
- correct design of the movable access doors,
- fail safe interlock system for access to each vault
- adequate shielding and protection around the beamline penetrations into target vaults.

Target station design should allow for:

- remote mechanical control of the target load/unload function,

- diagnostic and monitoring of target performance parameters,
- protection against loose material contamination from the target assembler,
- installation of pneumatic controlled rabbit systems (or equivalent) with shielding to transfer targets to their respective handling stations,
- mechanical back-up for systems 'disaster' recovery of radioactive targets,
- material specification for radiation hard materials, low-Z materials and wherever possible, the absence of semiconductor control devices.

Support services for the accelerator/cyclotron system are:

- correctly fused, interference-free, electrical power supplies including uninterruptible power supplies for key equipment, i.e. computers, safety systems,
- high pressure, de-ionized water supply for cooling of the targets and the cyclotron system,
- air handling of cool, filtered air to avoid humidity and the accumulation of gaseous radionuclides such as argon 41 with appropriate ? cycles,

- compressed air for servicing much of the mechanical (pneumatic) controls,
- mechanical engineering shop capable of machining radioactive components.

A validated waste disposal system with facility monitoring for unacceptable levels of background radiation and contamination is necessary which includes:

- solid waste disposal and compaction of target and ancillary cyclotron components
- removal of effluent generated in the radiochemical and pharmaceutical areas

An overall facility design is shown in Fig. 10 with

- segregated areas for cyclotron operations,
- high level radioactive radiochemical processing area,
- clean room environment for radiopharmaceutical finishing operations,
- ground floor laboratories for quality control etc.,
- appropriate personnel change rooms and environmental monitoring support services
- upper storey accommodation for mechanical and electrical plant, non-radioactive workshops, offices, etc.
- warehouse, packing and product despatch areas for the final product.

9. CONCLUSION

The design principles of a cyclotron facility for the commercial production of radiopharmaceuticals has been described, explaining the underlying physical principles of design, the requirements of radiochemical production and final pharmaceutical finishing. The design of a "green field" facility with all the support functions at today's prices would cost approximately £8M sterling. However, in order to generate an adequate return on this financial investment, sales of cyclotron isotope products of the order of £4M to £5M per year are necessary. This can only be achieved by:

– The large manufacturers who have existing approved drug licences and large sales organisations capable of distributing the products too numerous hospitals and medical centres, or
– Government sponsored laboratories who usually have their capital expenditure covered by central funds, and are allowed to operate on a cost recovery basis by producing small volume niche products or radiochemical materials which are used by the larger commercial manufacturers.

Although cyclotron isotopes production is essentially a commercial operation, the total manufacturing process encompasses fundamental accelerator physics, radiochemistry and industrial pharmaceutical technology. This presents a very rewarding occupation to the people working in the industry producing very valuable materials which are used by clinicians to diagnose illness and to alleviate the suffering of many millions of people every year.

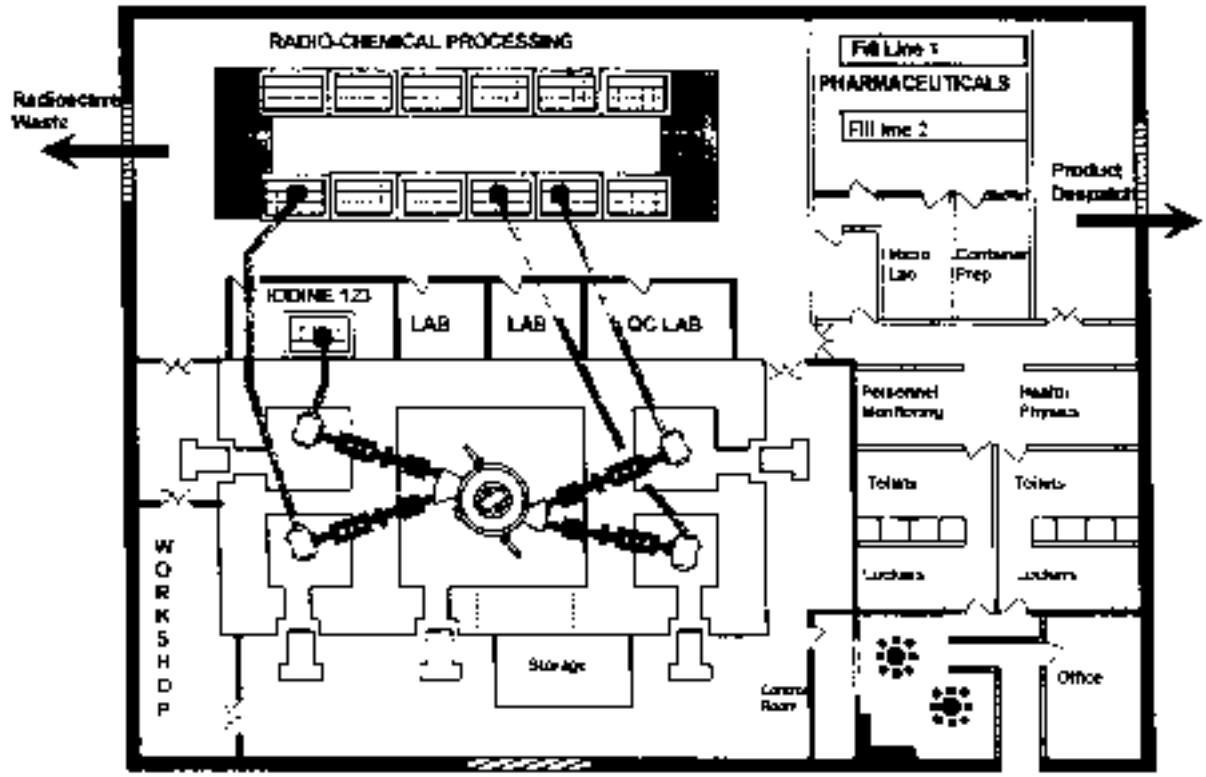

Fig. 10 Conceptual cyclotron facility

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