新規医療イノベーションのためのシンポジウム （2014/11/10）

小型サイクロトロンによる RI製造と周辺技術

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Overview

Accelerators for Research Use

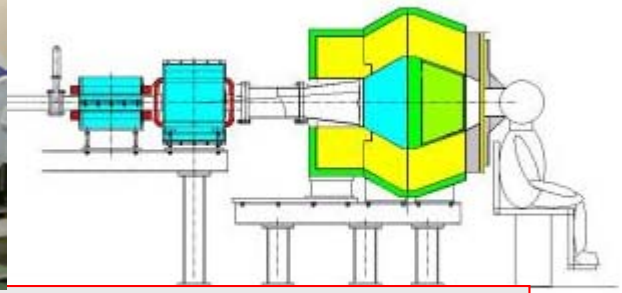
Ring Cyclotron (RCNP, Osaka)

Large Injector for Heavy Ion Therapy
(NIRS, Japan)

110MeV Cyclotron

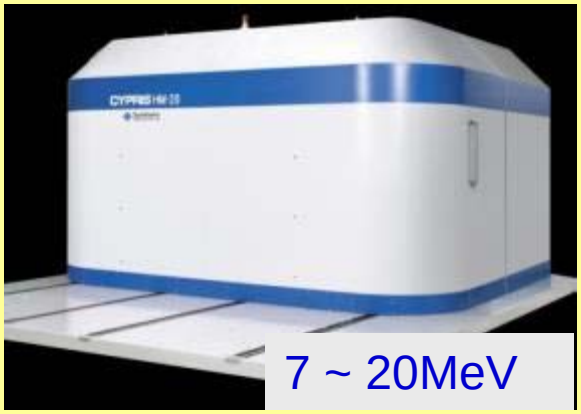
Compact Synchrotron for AURORA
(700MeV)

Cyclotrons for Medical Use



Cyclotron-based BNCT
(Boron Neutron Capture Therapy)

SPECT Cyclotron



PET Cyclotron

Proton Therapy System
(230MeV)

Cyclotrons for Radio Isotopes Production

		HM-12	HM-20	HM-30	MP-30
Proton	Energy	12 MeV	20 MeV	30 MeV	30 MeV
	Current	150 μA	150 μA	2,000 μA	100 μA
Deuteron	Energy	6 MeV	10 MeV	N/A	16 MeV
	Current	40 μA	50 μA	N/A	50 μA
Alpha	Energy	N/A	N/A	N/A	32 MeV
	Current	N/A	N/A	N/A	30 μA
Ion Source		Internal	Internal	External	External
Extraction Port		2	2	2	1
Max. Targets		8 (4/Port)	8 (4/Port)	Depend on Requirement	Depend on Requirement
Radio Isotopes		$^{18}F/^{15}O/^{13}N/^{11}C$ $^{64}Cu/^{89}Zr$ Other (p,n) reaction	+ $^{67}Ga/^{76}Br/^{99m}Tc$ $^{111}In/^{124}I$ Other (p,2n) reaction	+ $^{62}Zn/^{68}Ge/^{111}In$ $^{123}I/^{201}Pb$ Other (p,3n) reaction	+ $^{177}Lu/^{211}At$ Other (d,x), (α,x) reaction
Power		45 kW	55 kW	190 kW	150 kW
Non Shield	Room	W4.5xD4.5xH2.5	W4.5xD4.5xH2.7	W6.0xD5.5xH3.6	W6.0xD5.5xH3.6
	Weight	14 ton	25 ton	60 ton	60 ton
Self Shield	Room	W7.0xD4.8xH2.7	W7.0xD6.0xH3.3	N/A	N/A
	Weight	69 ton	155 ton	N/A	N/A

Radio Isotopes and Application

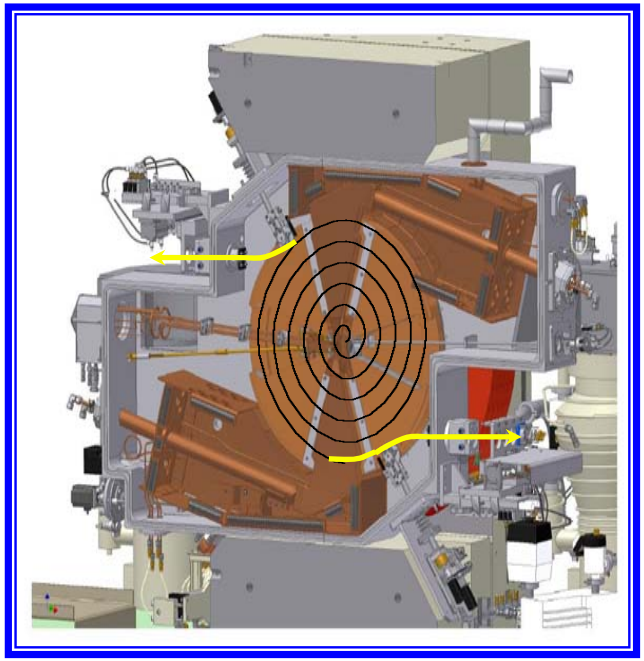
Medical

Purpose	Application	Radio Isotopes
Diagnosis	Tumor	SPECT : ^{67}Ga/^{99m}Tc/^{201}Tl PET : ^{18}F(FDG etc.)/^{11}C(MET etc.) /^{64}Cu/^{68}Ga
	Cardiac	SPECT : ^{82}Rb/^{99m}Tc/^{111}In/^{123}I/^{201}Tl PET : ^{13}N(NH3)/^{11}C (ACE etc.)/^{15}O
	Brain	SPECT : ^{99m}Tc/^{111}In/^{123}I PET : ^{18}F (Fluorbetapir etc.)/^{11}C/^{15}O/^{62}Cu/^{68}Ga
	Others (in vivo)	SPECT : ^{51}Cr//^{81m}Kr/^{123}I/^{131}I/^{133}Xe PET : ^{64}Cu/^{76}Br/^{86}Y/^{89}Zr
	in vitro	^{3}H/^{59}Fe/^{125}I
Therapy	Brachytherapy	^{60}Co/^{90}Sr/^{103}Pd/^{125}I/^{131}I/^{137}Cs/^{149}Tb/^{192}Ir/^{198}Au/^{223}Ra
	Immunotherapy	α-emitter : ^{211}At/^{213}Bi β-emitter : ^{32}P/^{47}Se/^{67}Cu/^{89}Sr/^{90}Y/^{131}I/^{153}Sm/^{166}Ho/^{169}Er/^{177}Lu/^{186}Re Auger : ^{165}Er

Industrial

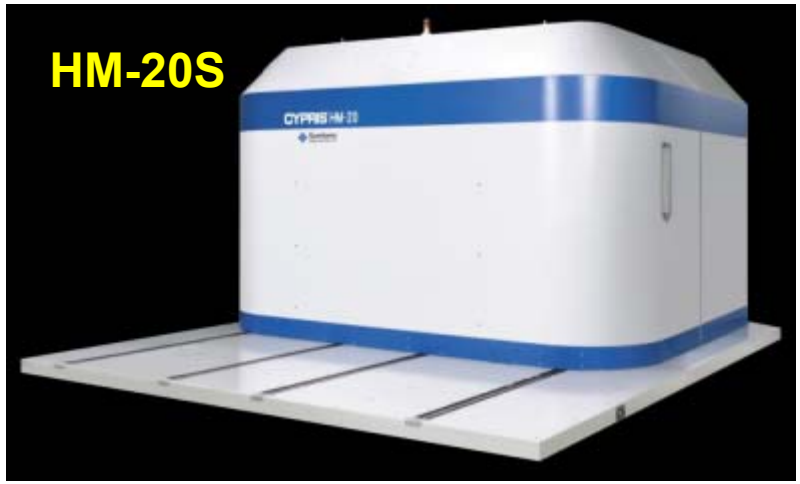
Purpose	Radio Isotopes
Radiography	^{241}Am/^{252}Cf(Neutron), ^{75}Se/^{169}Yb/^{192}Ir(Gamma)
Gauging	^{63}Ni/^{85}Kr/^{90}Sr/^{204}Tl
Tracer	^{3}H/^{14}C/^{51}Cr/^{54}Mn/^{65}Zn/^{99m}Tc/^{198}Au
Sterilization	^{60}Co/^{137}Cs

Cyclotron for Clinical Use



Dual port
Max. 8 targets
(4/port)

Extended Beam Line



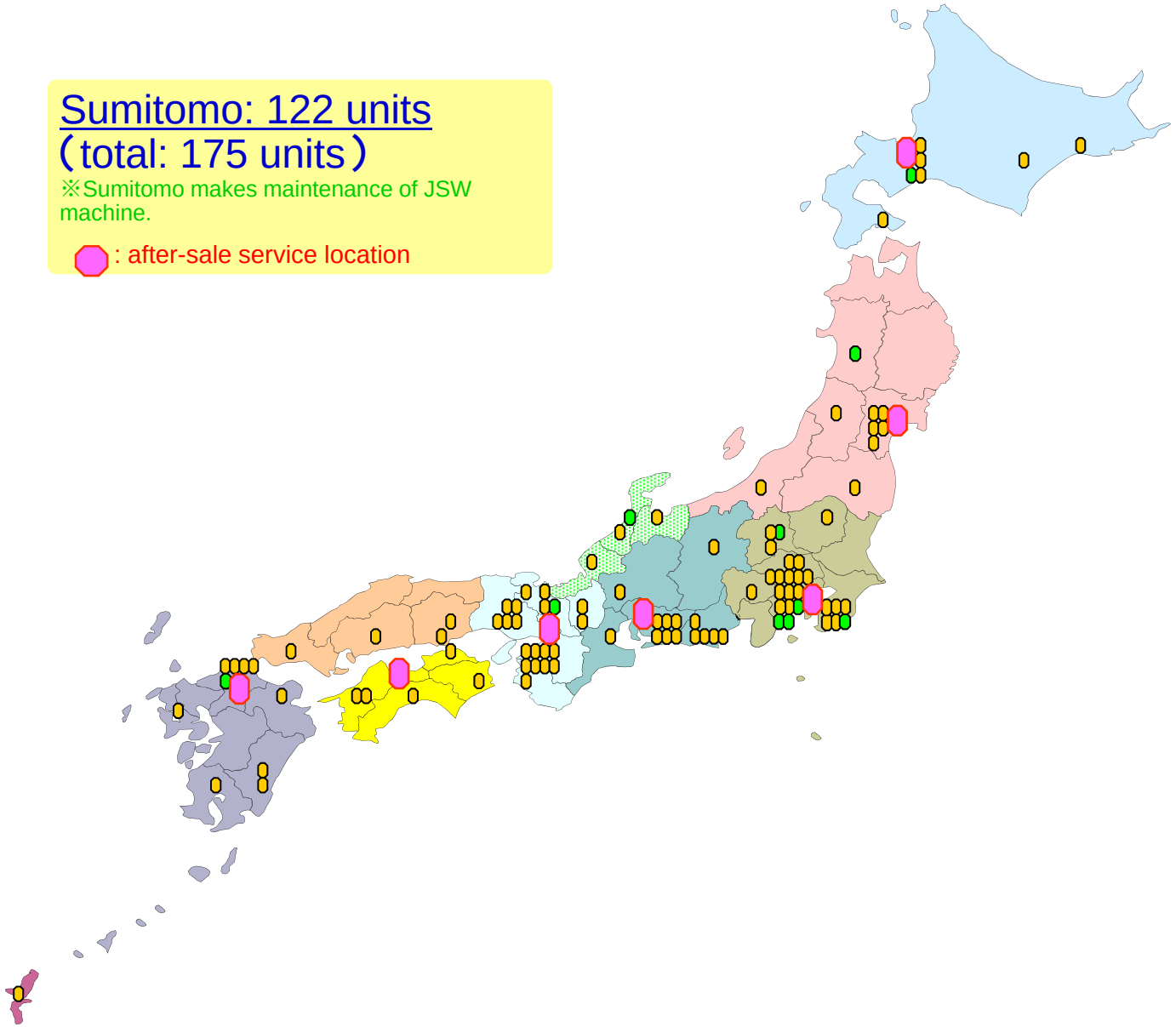
PET Cyclotrons Supplied by SHI

Japan:	122 units
China:	43 units
Hong Kong:	3 units
Korea:	4 units
Taiwan:	2 units
Malaysia:	1 unit
Thailand:	2 units
India:	1 unit
Total:	178 units

PET Cyclotrons in Japan

Sumitomo: 122 units
(total: 175 units)
※Sumitomo makes maintenance of JSW machine.

: after-sale service location



Process Overview of PET Tracer Production

^{18}O Water Purifier

Cyclotron

Target

Synthesizer

Auto QC

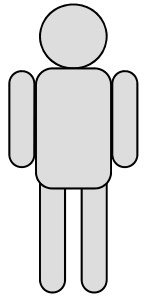
Hot Cell

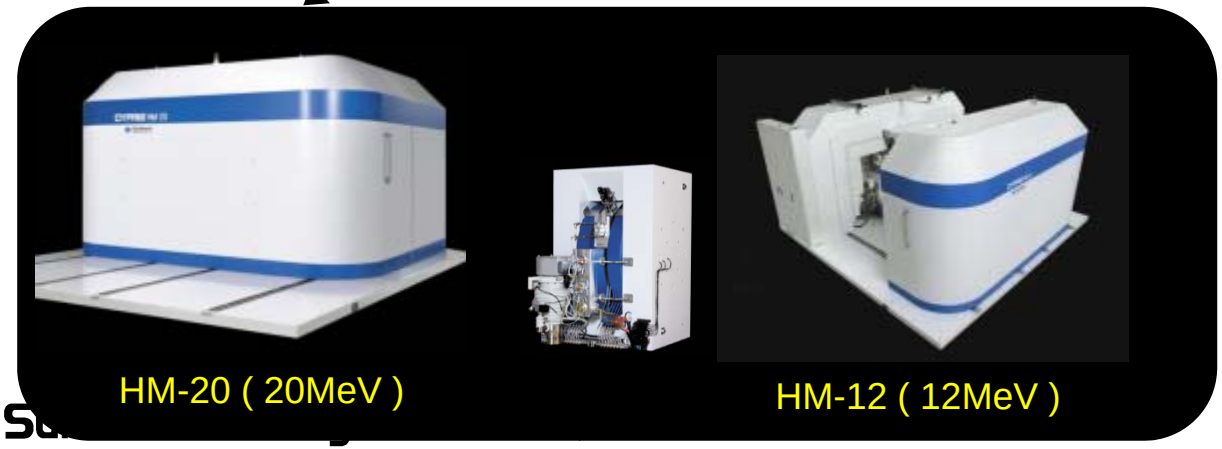
Auto Dispenser

Syringe

Vial

Auto Injector



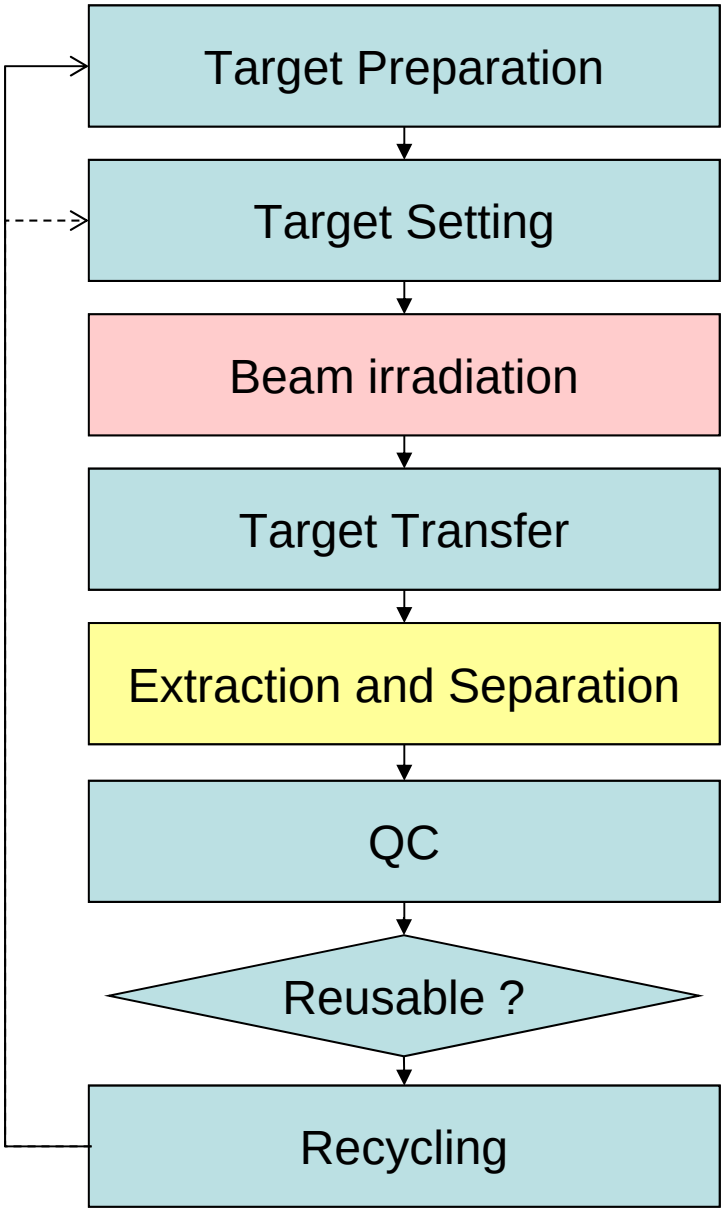


HM-20 (20MeV)

HM-12 (12MeV)

Small Animal PET

Process Overview of Solid Target



Material : Foil, Powder
Fix on disk or Insert in vessel
(Electroplating, Sintering, Deposition, Melting)

Automatic or Manual

Particle, Energy, Current, Irradiation time, Cooling
→ Yield, Impurity

Shall be Automatic
Air operated or Mechanical Transport

Dissolution → Ion exchange/Liq.-Liq. Extraction/HPLC
Sublimation → Furnace (Heat distribution control)

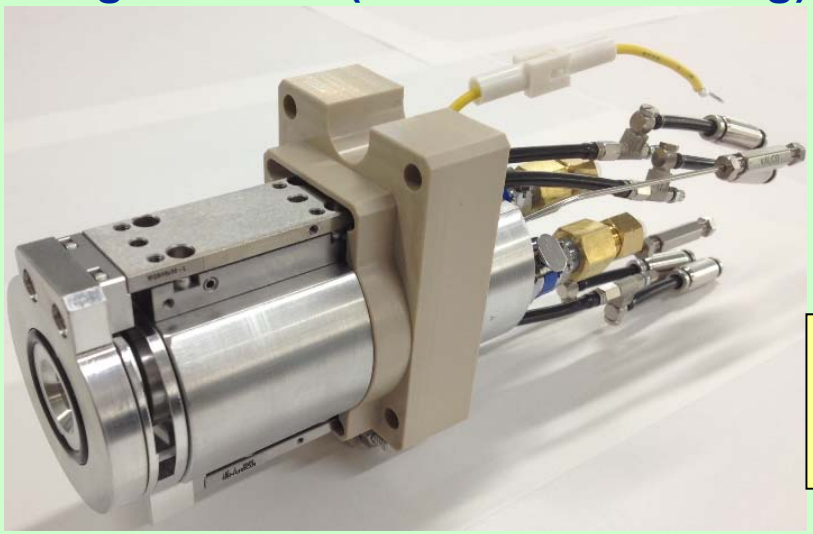
Radionuclide identification/Radiochemical purity
Radionuclidic Purity/Chemical Purity/pH/Endotoxin
Sterility/Osmolality…

Cost of Enriched target ?

No chemical treatment : ex. Te_2O_3
Purification : ex. ^{64}Ni-metal, ^{100}Mo-MoO_3

Solid Target of HM-20

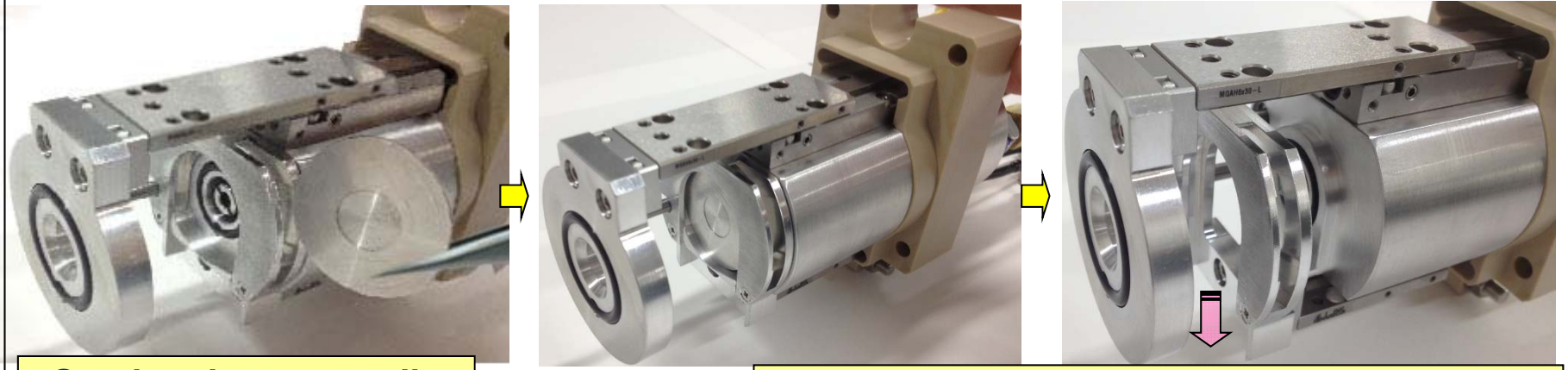
Target Holder (with Water Cooling)



Target and Base Plate

- Material (Base plate) : Au, Pt, W, Al …
- Cooling : Water (back), He gas (front)
- Motion : Manually set, Automatically ejected

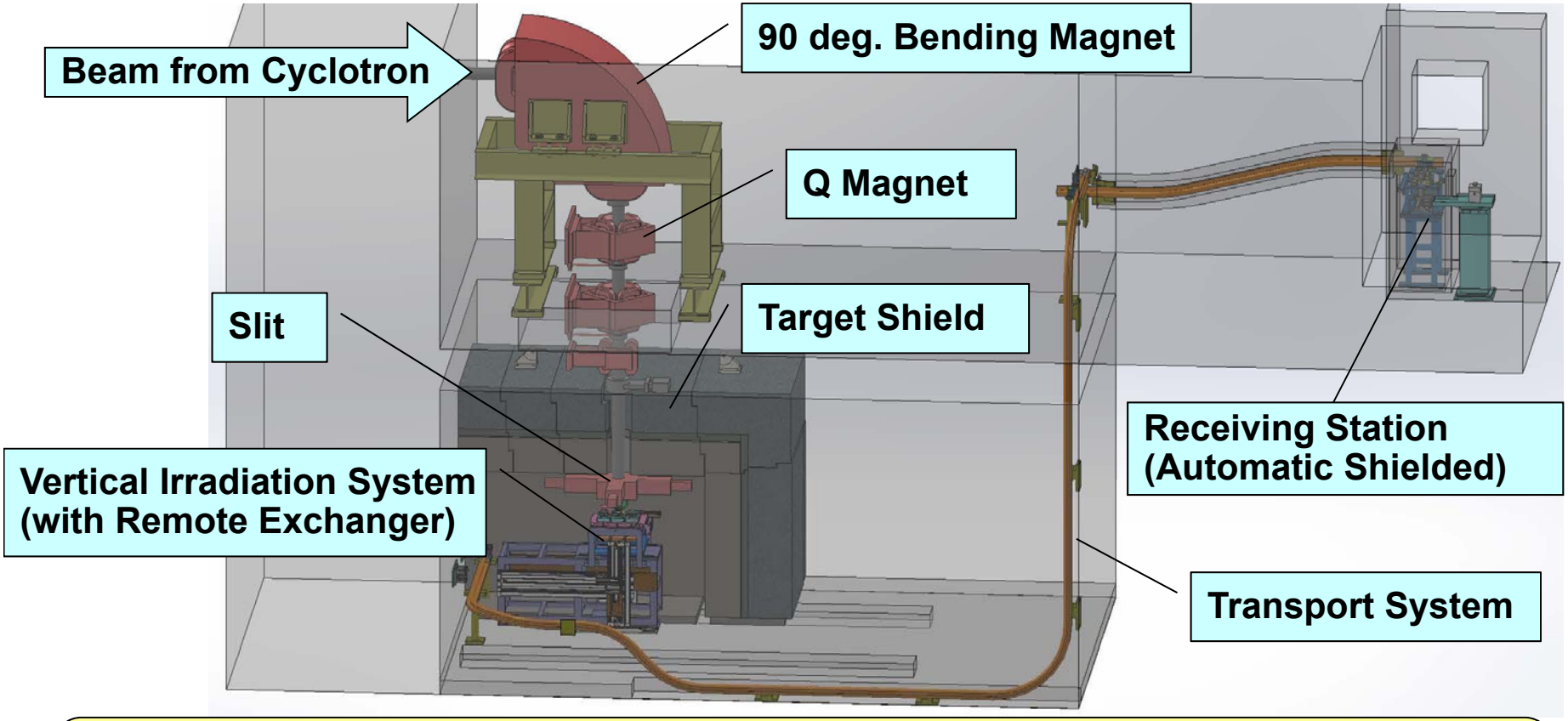
Motion



Set the plate manually

Ejected and transported into shielding box outside of self-shielding automatically

Option of Solid Target



Solution for unformed target

Powder and Low melting point materials

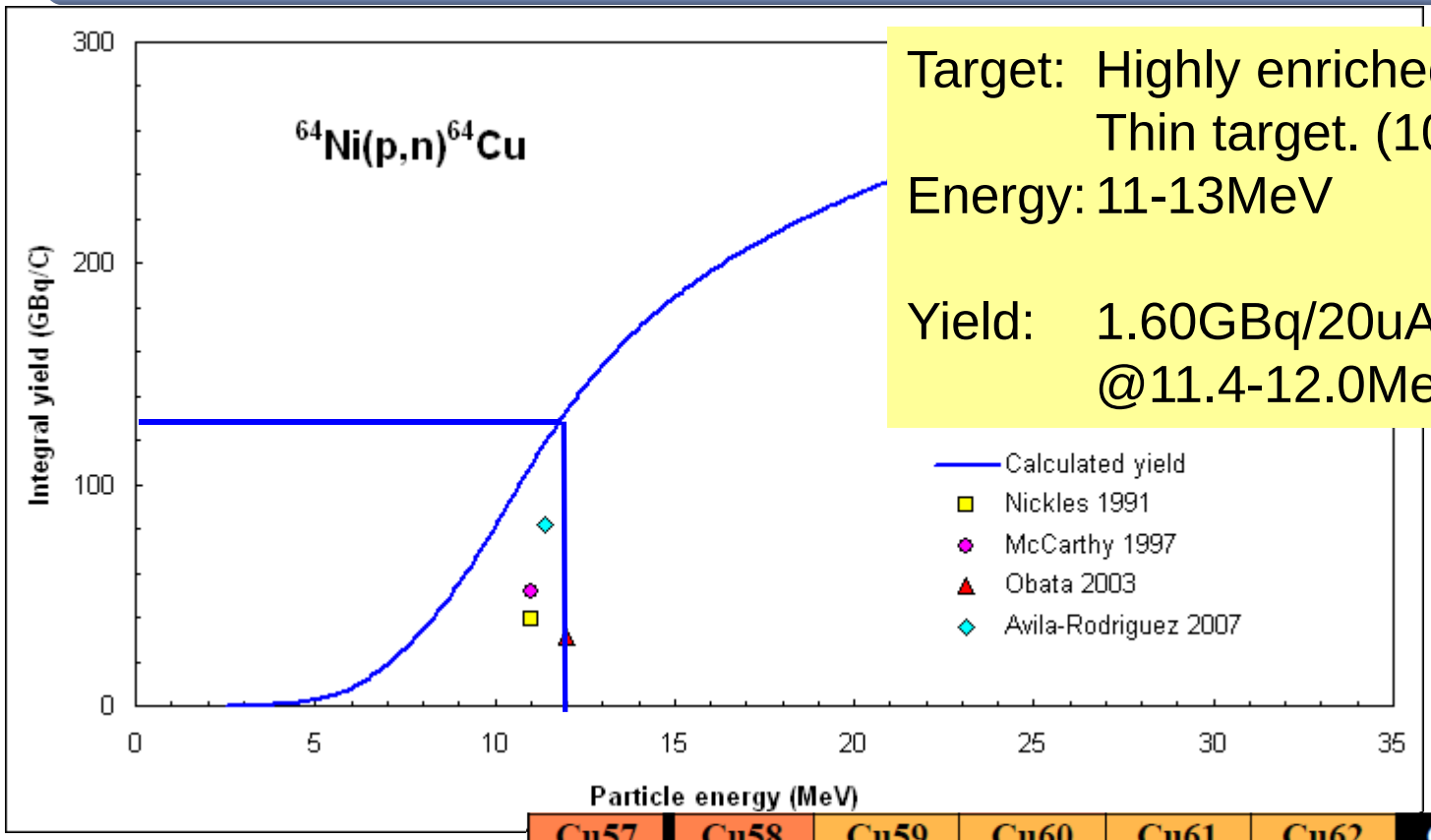
→ Vertical irradiation／Vessel type target

Solution for automatic transport

→ Air operated shuttle

^{64}Cu

^{64}Cu Reaction Yield



Target: Highly enriched ^{64}Ni
Thin target. (10 – 100 um)

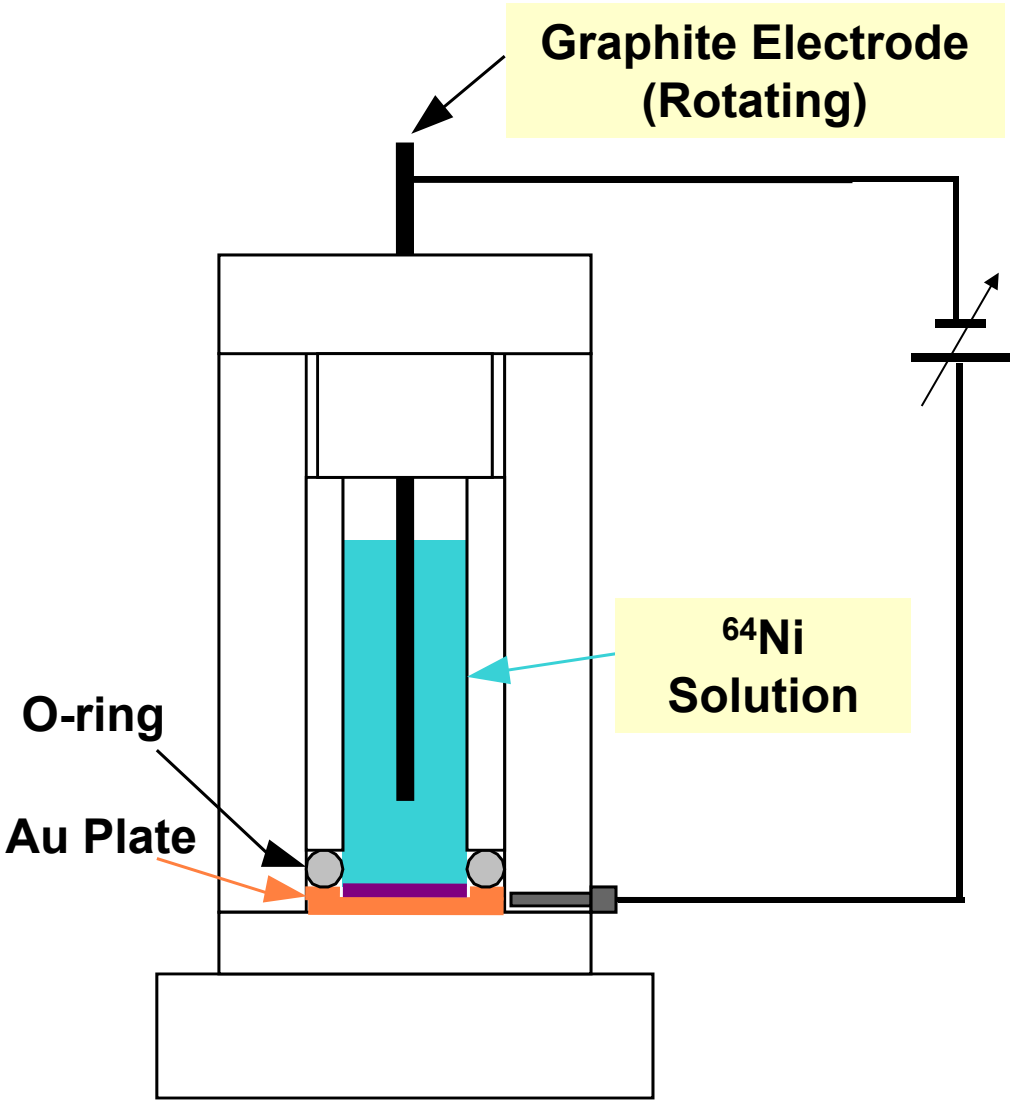
Energy: 11-13MeV

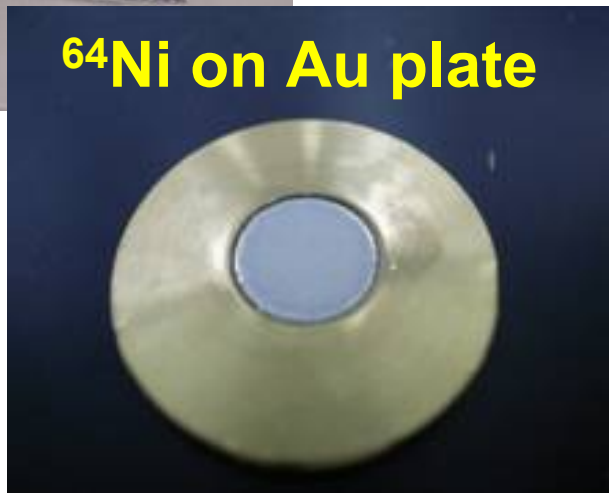
Yield: 1.60GBq/20uAx2.5H (Actual)
@11.4-12.0MeV (28um plated)

Ref: IAEA-TechDoc1211

Cu57 199.4 ms 3/2- EC	Cu58 3.204 s 1+ EC	Cu59 81.5 s 3/2- EC	Cu60 23.7 m 2+ EC	Cu61 3.333 h 3/2- EC	Cu62 9.74 m 1+ EC	Cu63 3/2- 69.17	Cu64 12.700 h 1+ EC,β-	Cu65 3/2- 30.83
Ni56 6.077 d 0+ EC	Ni57 35.60 h 3/2-	Ni58 0+ 68.077	Ni59 7.6E+4 y 3/2- EC	Ni60 0+ 26.223	Ni61 3/2- 1.140	Ni62 0+ 3.634	Ni63 100.1 y 1/2- β-	Ni64 0+ 0.926
Co55 17.53 h 7/2- EC	Co56 77.27 d 4+ EC	Co57 271.79 d 7/2- EC	Co58 70.82 d 2+ * EC	Co59 7/2- 100	Co60 5.2714 y 5+ *	Co61 1.650 h 7/2- β-	Co62 1.50 m 2+ * β-	Co63 27.4 s (7/2)- β-

Solid Target for ^{64}Cu

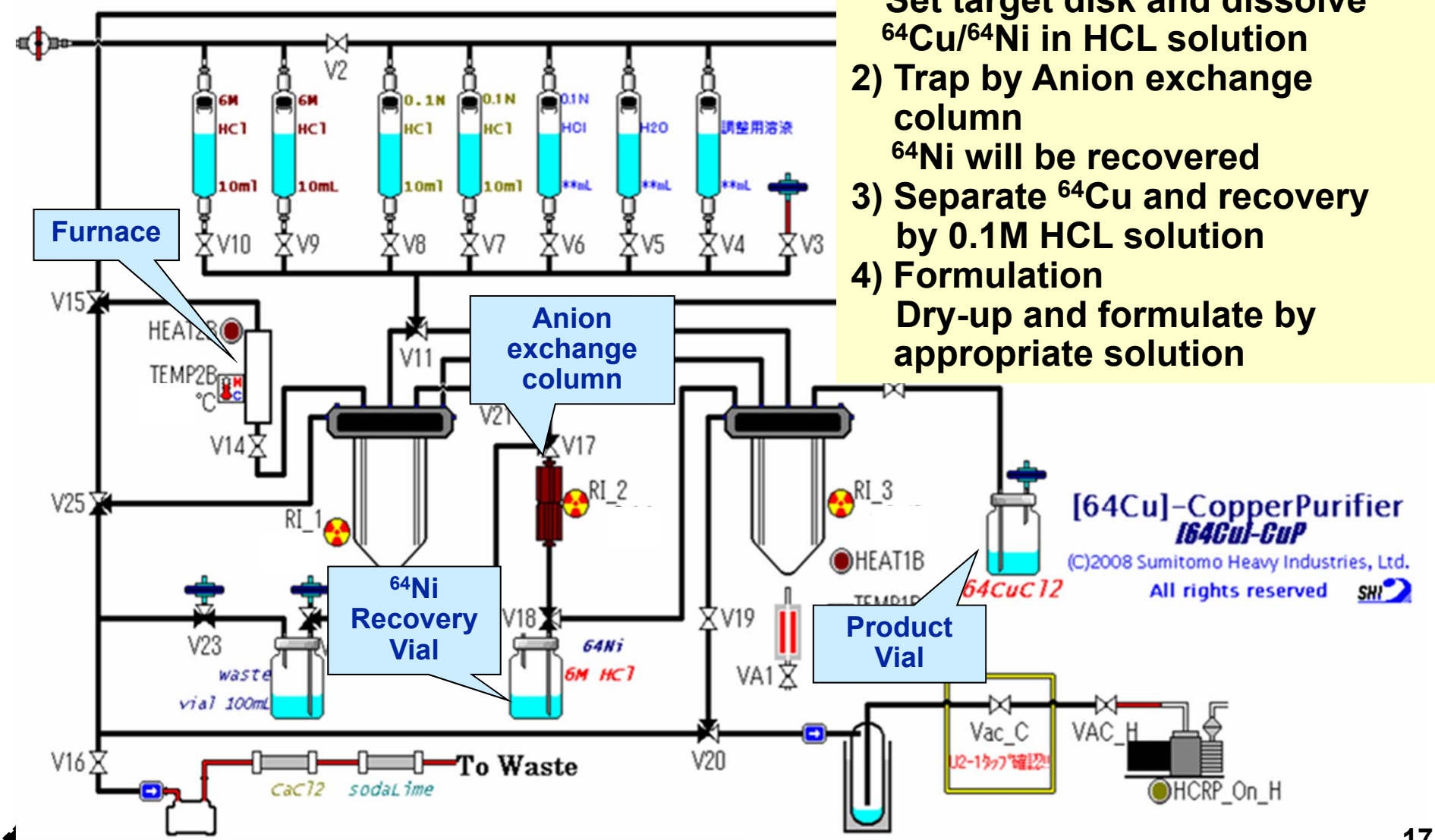




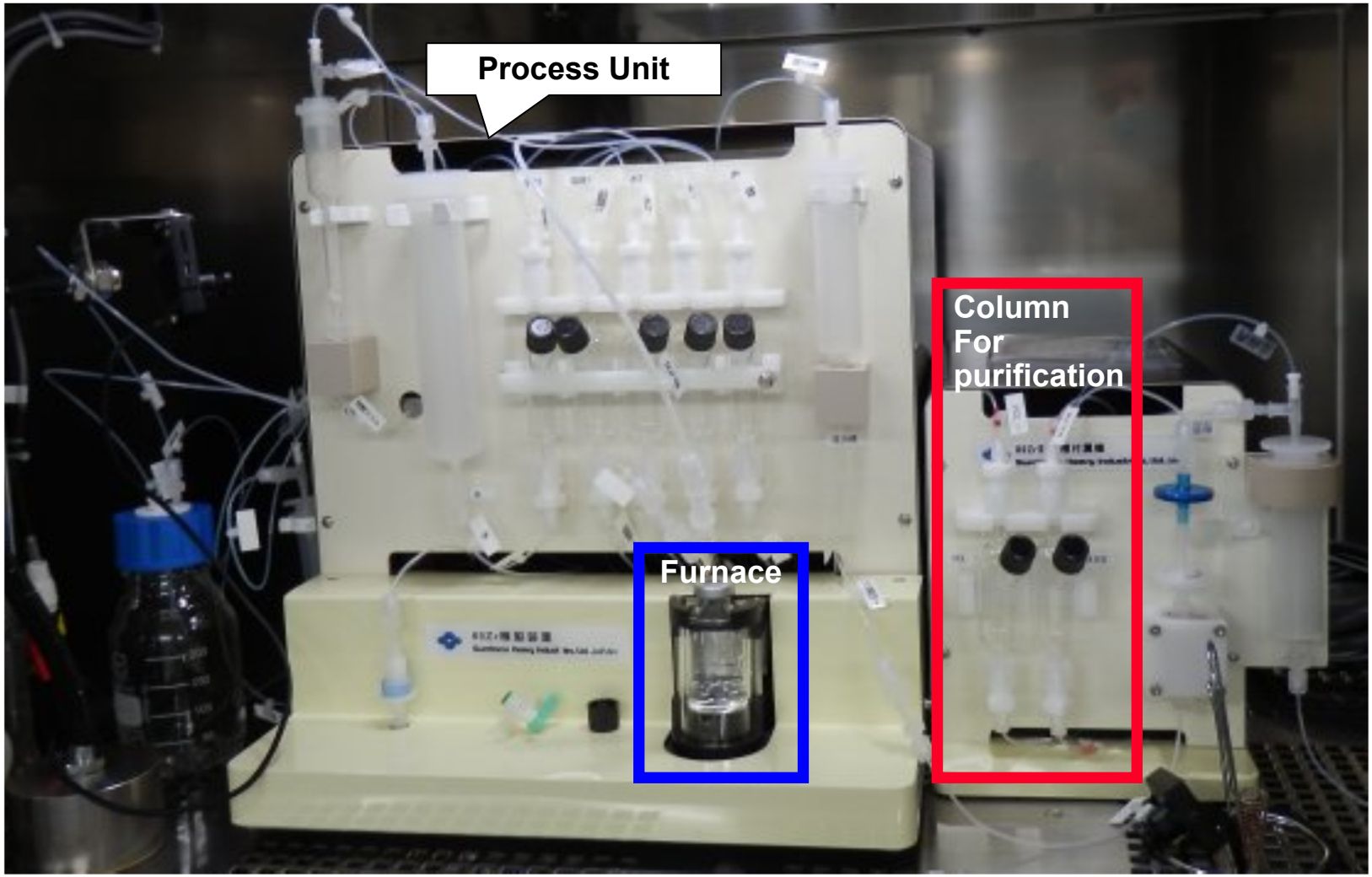
Dissolution and Separation of ^{64}Cu

< Process>

1) Extract from Gold substrate
   Set target disk and dissolve
   $^{64}Cu/^{64}Ni$ in HCL solution
2) Trap by Anion exchange column
   ^{64}Ni will be recovered
3) Separate ^{64}Cu and recovery by 0.1M HCL solution
4) Formulation
   Dry-up and formulate by appropriate solution

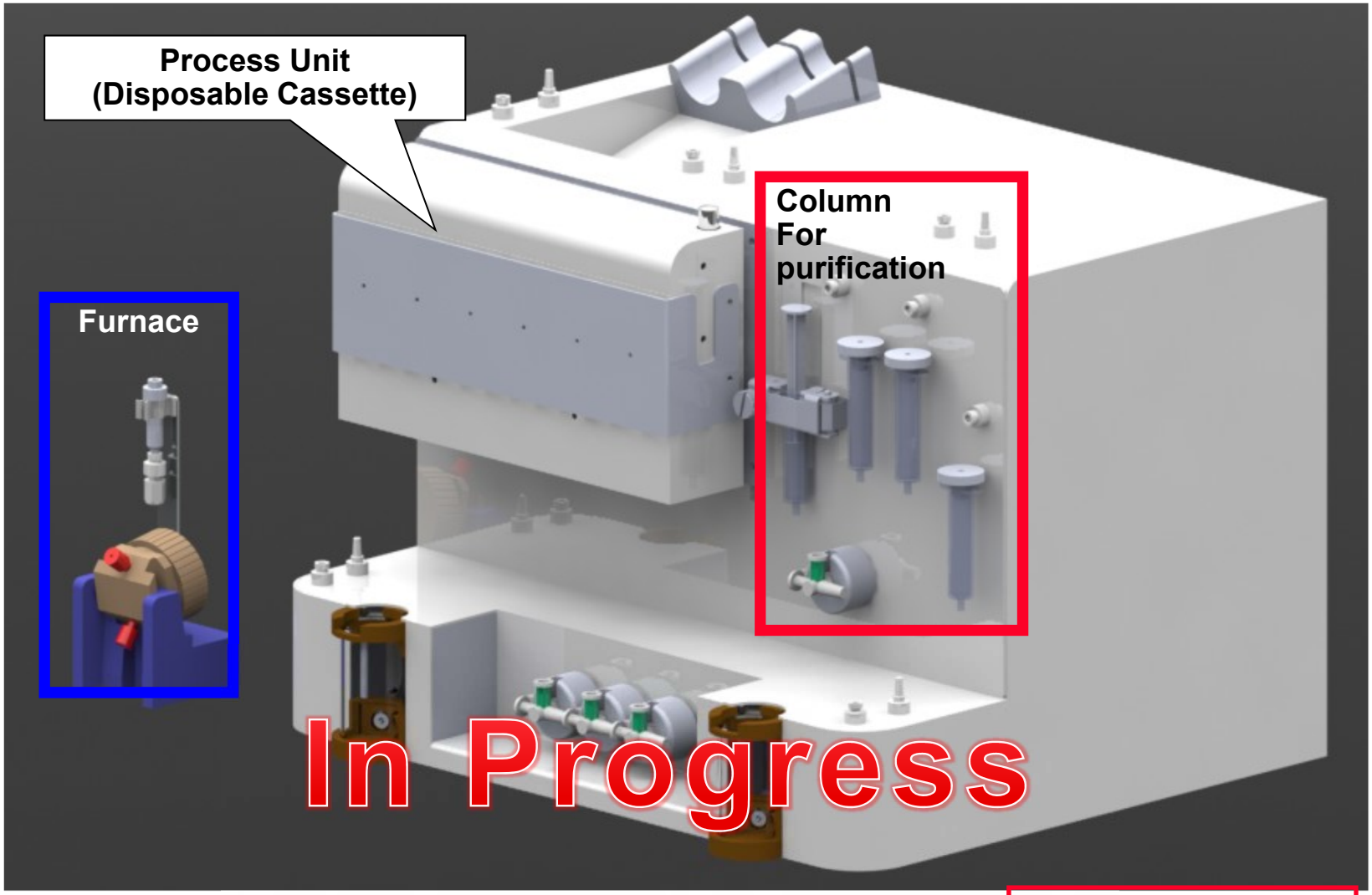


Automatic Separation Unit for ^{64}Cu



Multi-purpose Separation Unit

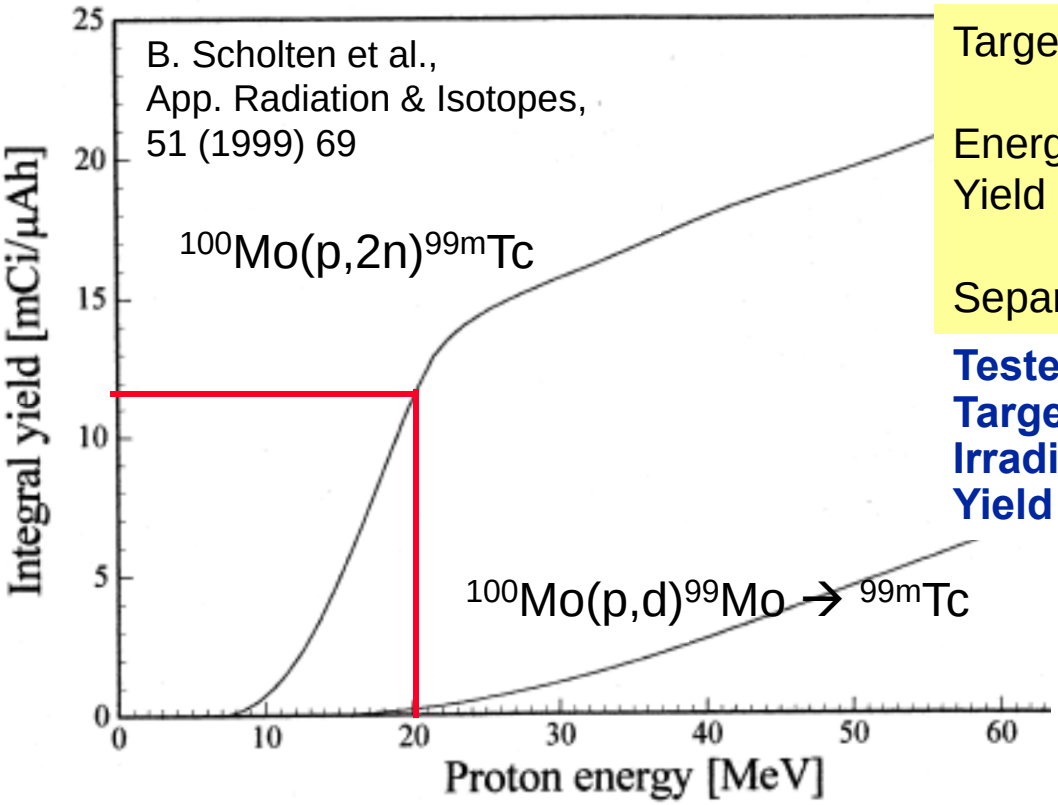
Separation of ^{62}Zn, ^{64}Cu, ^{89}Zr, ^{99m}Tc, etc are available in ONE unit.



Patent pending

^{99m}Tc

^{99m}Tc Production



Target : Highly enriched ^{100}Mo-Metal or Oxide
MoO_3 is better for dissolve and reuse
Energy : 15-20MeV
Yield : 11.7GBq/20uAx3H@20MeV
(Extrapolated from test result)
Separation: Ion exchange or Sublimation

Tested (SHI)
Target Mo×t0.5mm（nat-Mo：100Mo=9.6%）
Irradiation 17MeV×5μA×10min
Yield（EOB） 12MBq

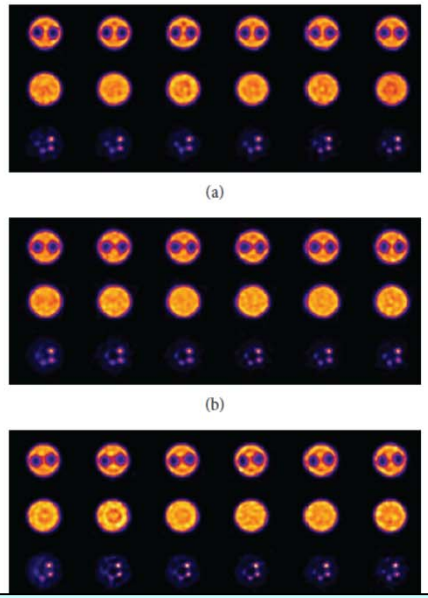
Extrapolated
Target 100Mo（99%）×t0.7mm
Irradiation 20MeV×20μA×3H
Yield（EOB） 11.7GBq

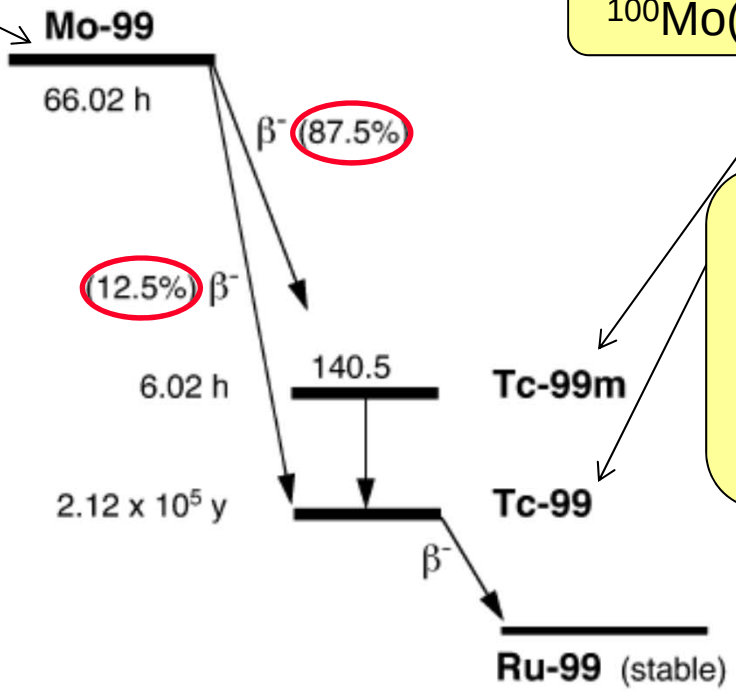
Tc91 3.14 m (9/2)+ * EC	Tc92 4.23 m (8)+ EC	Tc93 2.75 h 9/2+ * EC	Tc94 293 m 7+ * EC	Tc95 20.0 h 9/2+ * EC	Tc96 4.28 d 7+ * EC	Tc97 2.6E6 y 9/2+ * EC	Tc98 4.2E+6 y (6)+ β-	Tc99 2.111E+5 y 9/2+ * β-	Tc100 15.8 s 1+ β-	Tc101 14.22 m (9/2)+ β-
Mo90 5.67 h 0+ EC	Mo91 15.49 m 9/2+ * EC	Mo92 0+ 14.84	Mo93 4.0E+3 y 5/2+ * EC	Mo94 0+ 9.25	Mo95 5/2+ 15.92	Mo96 0+ 16.68	Mo97 5/2+ 9.55	Mo98 0+ 24.13	Mo99 65.94 h 1/2+ β-	Mo100 1.2E19 y 0+ β-β- 9.63
Nb89 1.9 h (9/2+) * EC	Nb90 14.60 h 8+ * EC	Nb91 680 y 9/2+ * EC	Nb92 3.47E+7 y (7)+ * EC,β-	Nb93 9/2+ * 100	Nb94 2.03E+4 y (6)+ * β-	Nb95 34.975 d 9/2+ * β-	Nb96 23.35 h 6+ β-	Nb97 72.1 m 9/2+ * β-	Nb98 2.86 s 1+ * β-	Nb99 15.0 s 9/2+ * β-

Quality of Cyclotron Produced ^{99m}Tc

Reactor
$^{235}U(n,f)^{99}Mo$
$^{98}Mo(n,\gamma)^{99}Mo$

Cyclotron
$^{100}Mo(p,2n)^{99x}Tc$





Ratio of $^{99g}Tc/^{99m}Tc$
depend on …
ex. Proton energy: 20MeV
Irradiation time: 3H
Time after EOB: 6H
→ R~11.8

Almost equivalent

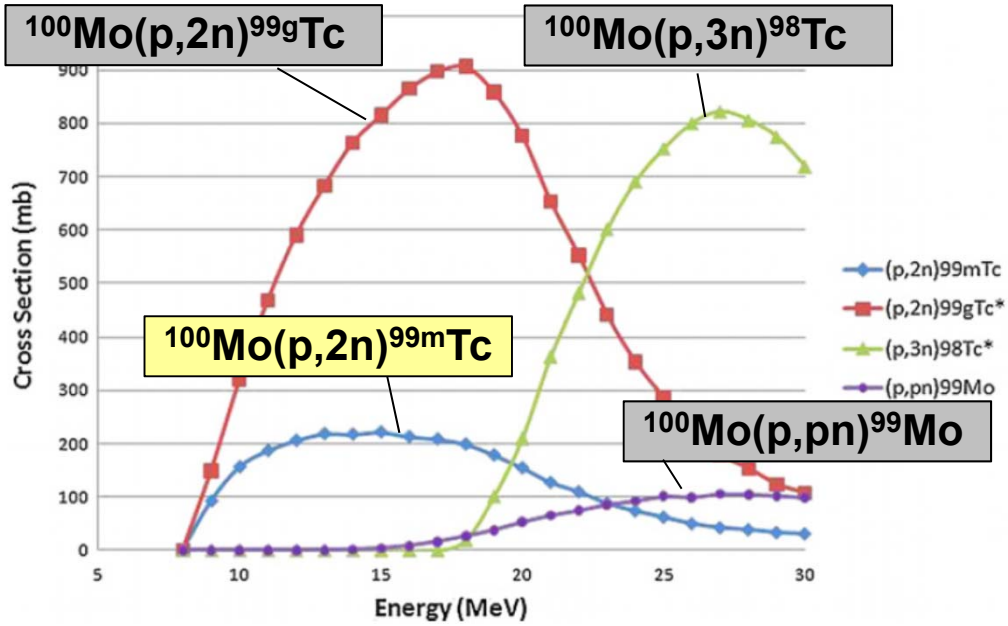
Ratio of $^{99g}Tc/^{99m}Tc$
depend on frequency of elution
ex. 24H~R=3.2, 48H~6.7, 72H~11.8
→ Fulfilled all QC tests
NEMA phantom confirmed
No variations in images
up to R=15.2

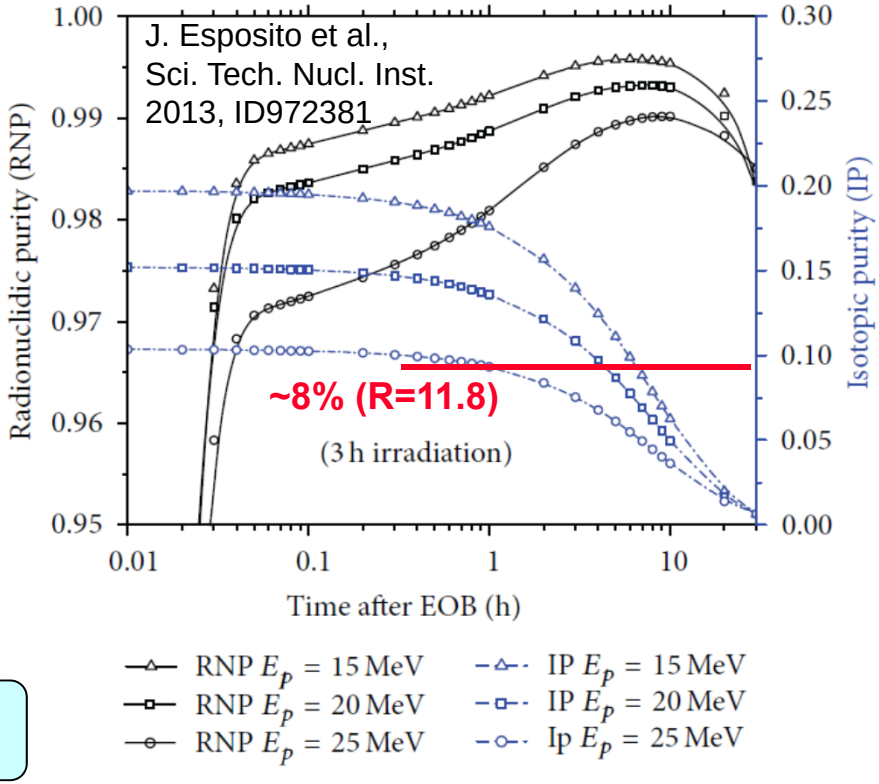
To be specified

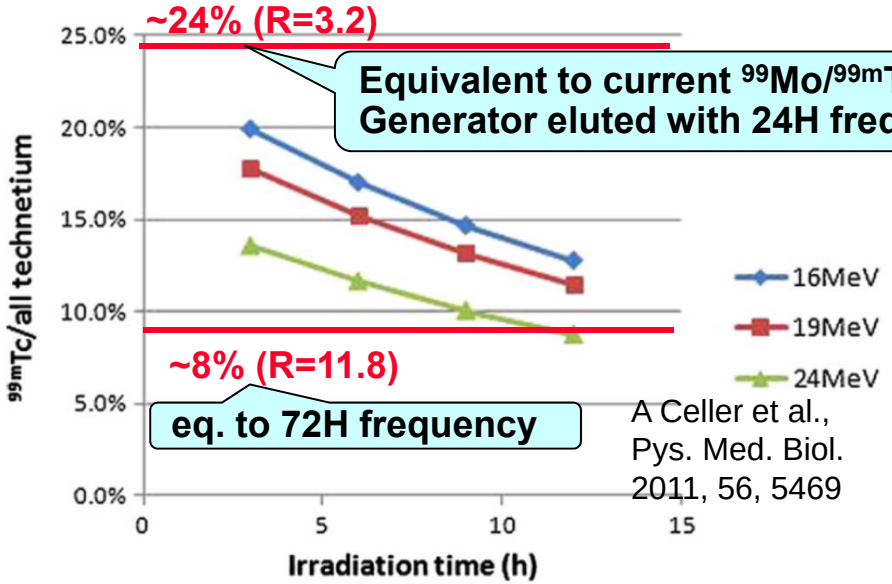
- **Regulatory requirement : Quality, Safety**
- **Logistics : Shelf-life, Transport**
- **Economics : Production cost**

L. Uccelli et al.,
Science and Technology of Nuclear Installations, 2013, ID379283

Energy and Irradiation Time





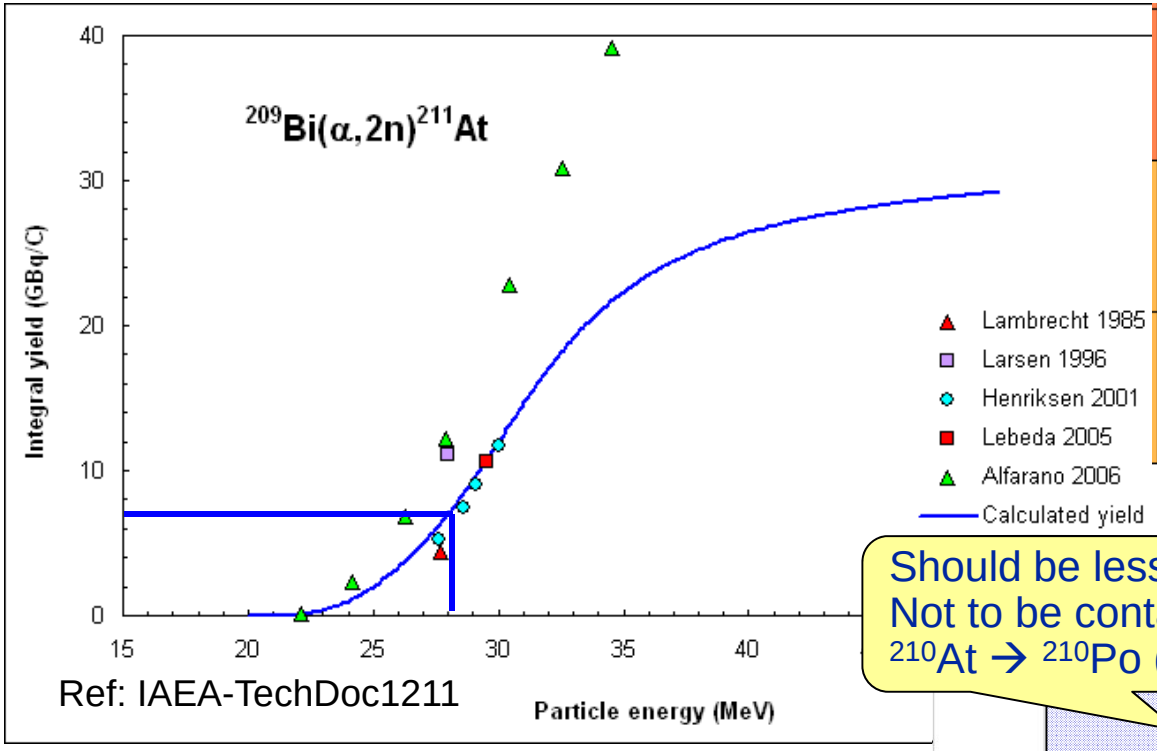


A Celler et al.,
Pys. Med. Biol.
2011, 56, 5469

Recommended
Proton energy: 15-20MeV
Irradiation time: 1-3H
→ Useful time window ~10H
(Isotopic purity > 8%)

^{211}At

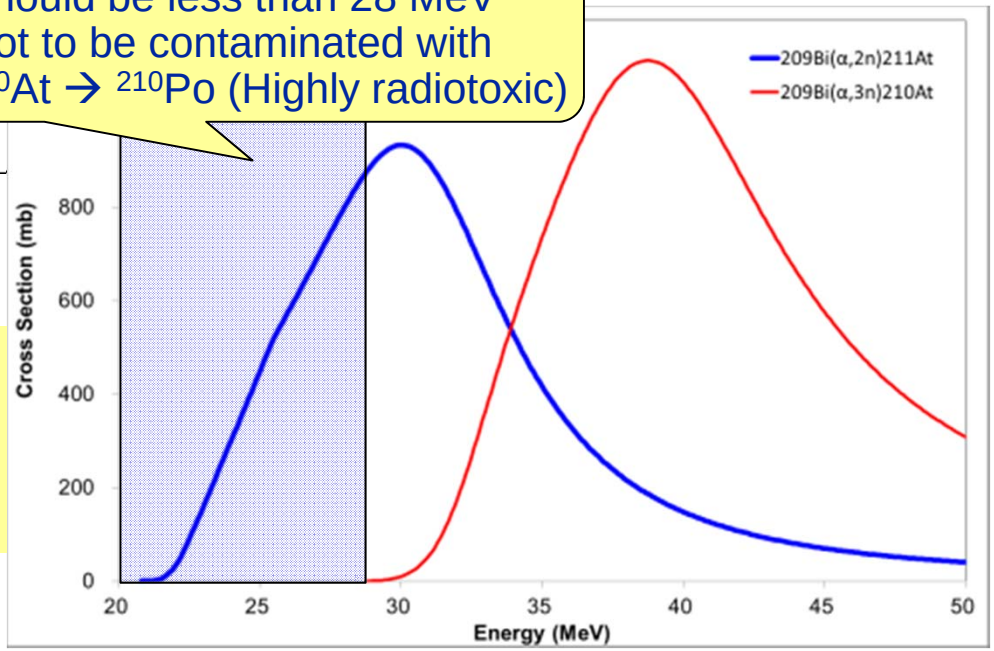
^{211}At Reaction Yield



Ref: IAEA-TechDoc1211

At209 5.41 h 9/2- EC,α	At210 8.1 h (5)+ EC,α	At211 7.214 h 9/2- EC,α	At212 0.314 s (1-) * EC,β-,α,...	At213 125 Ns 9/2- α
Po208 2.898 y 0+ EC,α	Po209 102 y 1/2- EC,α	Po210 138.376 d 0+ α	Po211 0.516 s 9/2+ * α	Po212 0.299 Us 0+ * α
Bi207 31.55 y 9/2- EC	Bi208 3.68E+5 y (5)+ * EC	Bi209 9/2- 100	Bi210 5.013 d 1- * β-,α	Bi211 2.14 m 9/2- β-,α

Should be less than 28 MeV
Not to be contaminated with
^{210}At → ^{210}Po (Highly radiotoxic)



Target : nat-^{209}Bi foil or powder
Energy : Should be less than 28 MeV
Yield : 23.4MBq/uAH@28MeV(Theoritical)
Separation: Sublimation (Dry distillation)

Summary

Summary

【既存製品群】

短寿命PETトレーサー製造のための小型サイクロトロンシステム

- 7 ～ 30 MeV
- $^{11}C/^{13}N/^{15}O/^{18}F$ ターゲットシステム
- 合成装置、分注装置、ホットセル、自動品質検定、自動投与器

(p,n) 反応を用いた金属ターゲット、自動分離装置

- ^{64}Cu, ^{89}Zr, ^{123}I, ^{124}I
- 自動分離装置 (イオン交換、昇華)

【現在の取り組み】

30 MeVクラスの多目的サイクロトロンと金属ターゲットシステム

- Proton 30MeV, Deuteron 16MeV, Alpha 32MeV
- 外部ビームライン(垂直照射)、ターゲット自動交換／自動搬送

(p,2n), (d,x), (α,x) 反応を用いた金属ターゲット、自動分離装置

- ^{62}Zn, ^{68}Ge, ^{99m}Tc(テスト済), ^{177}Lu, ^{211}At etc.
- カセット式多目的自動分離装置 (イオン交換)
- 他分離法による自動分離装置 (液-液抽出, 液クロ)