TENMAK PROTON HIZLANDIRICISI TESİSİNDE ^{201}Tl-TlCl VE ^{123}I-NaI RADYOFARMASÖTİKLERİNİN ÜRETİMİ, SATIŞI VE RADYOİZOTOP AR-GE FAALİYETLERİ

Dr. Serdar BULUT/Proton Hızlandırıcısı Tesisi
Fizikçi

TESİS ÇALIŞIYOR MU?

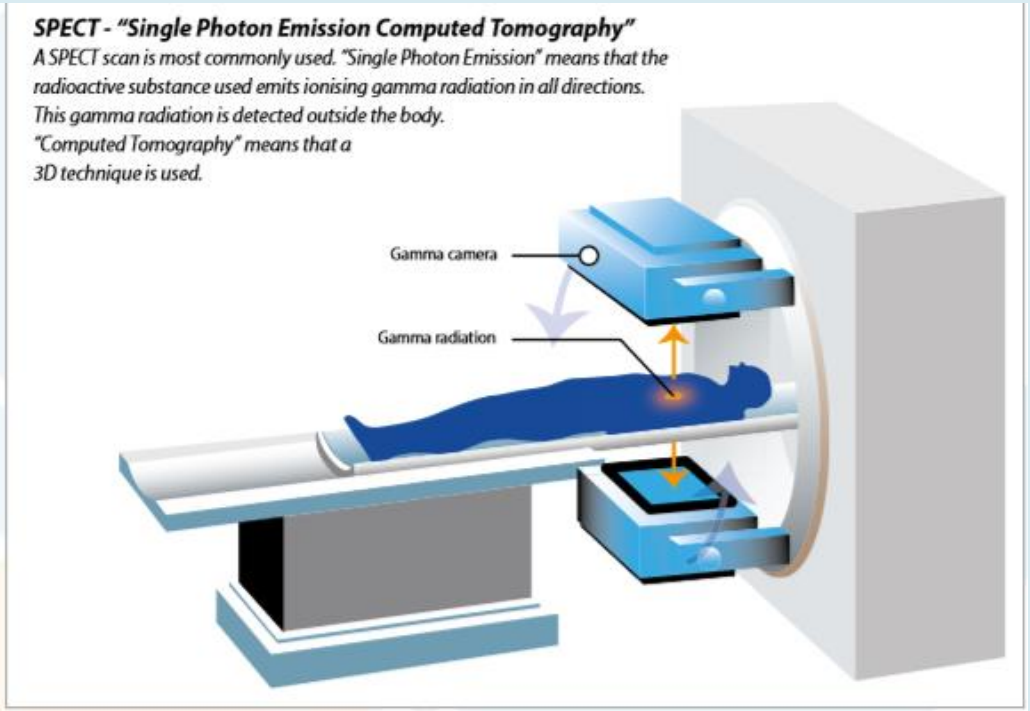
- Hızlandırıcıdan proton demeti elde ediliyor mu?
  - ✓ 2012'de gerçekleşen kabul testlerinden itibaren sorunsuz bir şekilde elde ediliyor.
- Hedef sistemleri ışınlanarak radyoizotop elde ediliyor mu?
  - ✓ 2012'de gerçekleşen kabul testlerinden itibaren sorunsuz bir şekilde elde ediliyor.
- ^{18}F-FDG, ^{201}TlCl, ^{123}I-NaI, ^{67}GaCit ve $^{111}InCl_3$ Radyofarmasötikleri üretiliyor mu?
  - ✓ 2012'de gerçekleşen kabul testlerinden itibaren sorunsuz bir şekilde elde ediliyor.
- Tesiste üretilen radyofarmasötikler ruhsatlı mı?
  - ✓ 2017 yılında ilk olarak ^{18}F-FDG ile başlayan ve devam eden, son olarak da 2019 yılında ^{201}TlCl'ün ruhsatlandırma çalışmalarının tamamlanmasıyla birlikte tüm ürünlerimiz Sağlık Bakanlığı ilaç ruhsatına sahiptir.
- Tesiste üretilen ürünler satılıyor mu?
  - ✓ 2018 yılında ^{123}I-NaI etkin madde satışı ile ürün satışı başlamış olup 2020 yılında E-Devlet ve DMO Sağlık Market üzerinden radyofarmasötik satışları yapılmaktadır.
- Hızlandırıcı sistemi ve mevcut altyapı kullanılarak Ar-Ge çalışmaları yapılıyor mu?
  - ✓ 2015 yılından beri tesiste Ar-Ge projeleri yürütülmektedir.

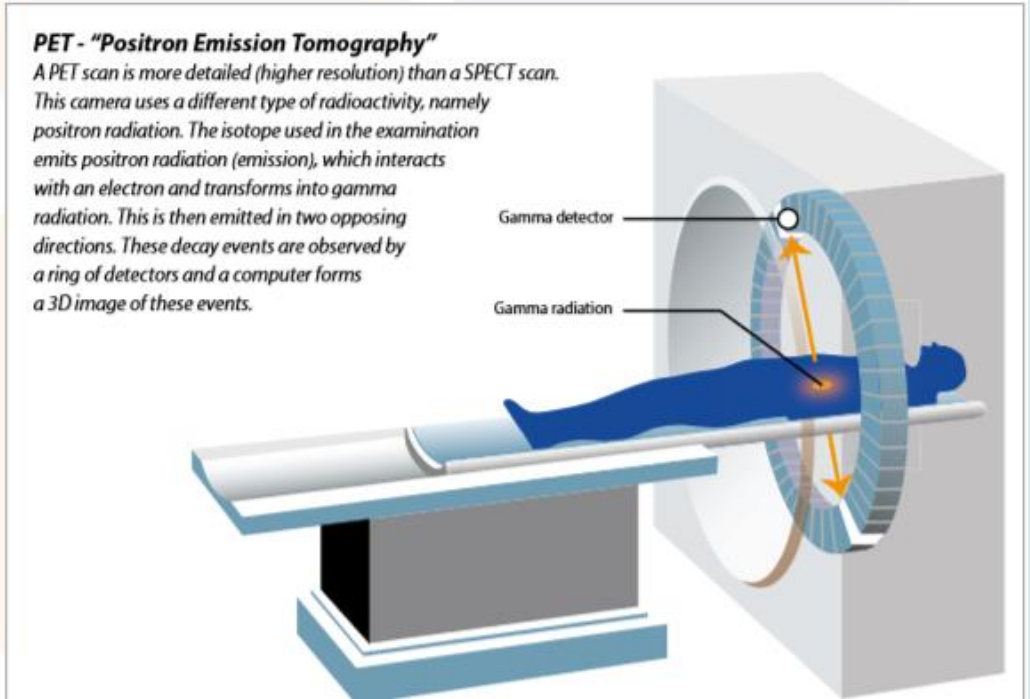
PHT'NİN KURULMA AMACI

- Nükleer Tıpta Kullanılan Radyoizotop ve Radyofarmasötiklerin üretimi
  - ✓ Flor-18 (FDG), Iyot-123 (NaI), Indiyum-111(InCl3), Galyum-67(Ga-cit), Talyum-201(TlCl)
- Gelecekte, ülkemizdeki talebe göre, diğer tıbbi radyoizotopların üretimi
  - ✓ Galyum-68, Tc-99m, Bakır-64, Paladyum-103, Iyot-124, Karbon-11, Azot-13, Oksijen-15 gibi...
- Ar-Ge faaliyetlerinin yapılması
  - ✓ Proton hızlandırıcına dayalı nükleer fizik, malzeme, tahribatsız analiz, dedektör testleri,...
  - ✓ Endüstri ve Sanayi ihtiyaçlarına cevap verecek ışınlama faaliyetlerin yürütülmesi
- Eğitim

RADIOISOTOPES IN NUCLEAR MEDICINE

- **Diagnostics,**
  - SPECT Radioisotopes,
    - Tc-99m, Tl-201, Ga-67, I-123,…
  - PET Radioisotopes,…
    - F-18, Ga-68, Zr-89,…
- **Therapeutics,**
  - Beta Emitters,
    - I-131, Sm-153, Rh-186, Y-90, Lu-177,…
  - Alpha Emitters
    - Ra-223, ^{225}Ac…
  - Brachytherapy Isotopes
    - I-125, Ir-192, Pd-103, Cs-131,…



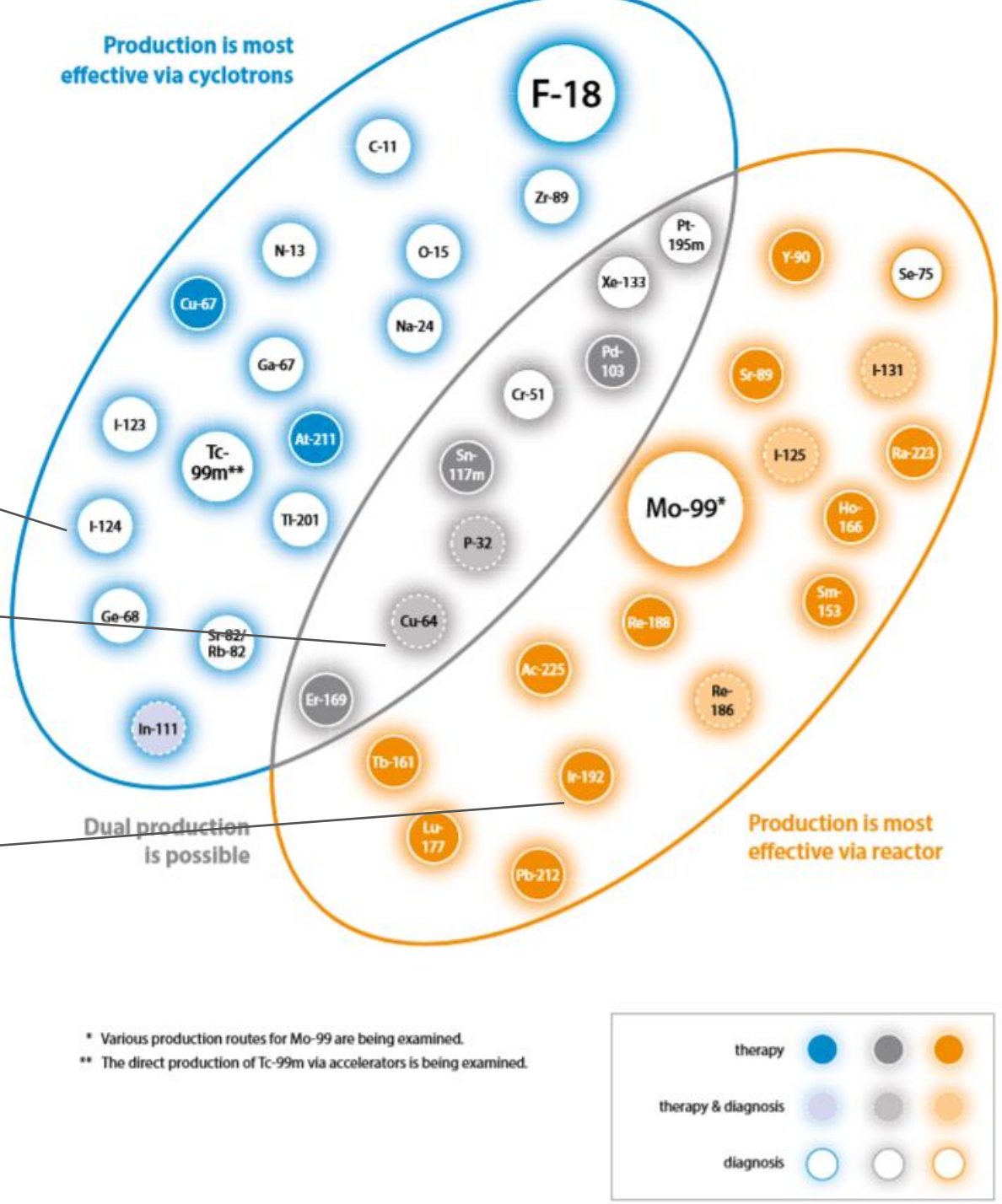


RADIOISOTOPE PRODUCTION IN CYCLOTRON AND REACTOR

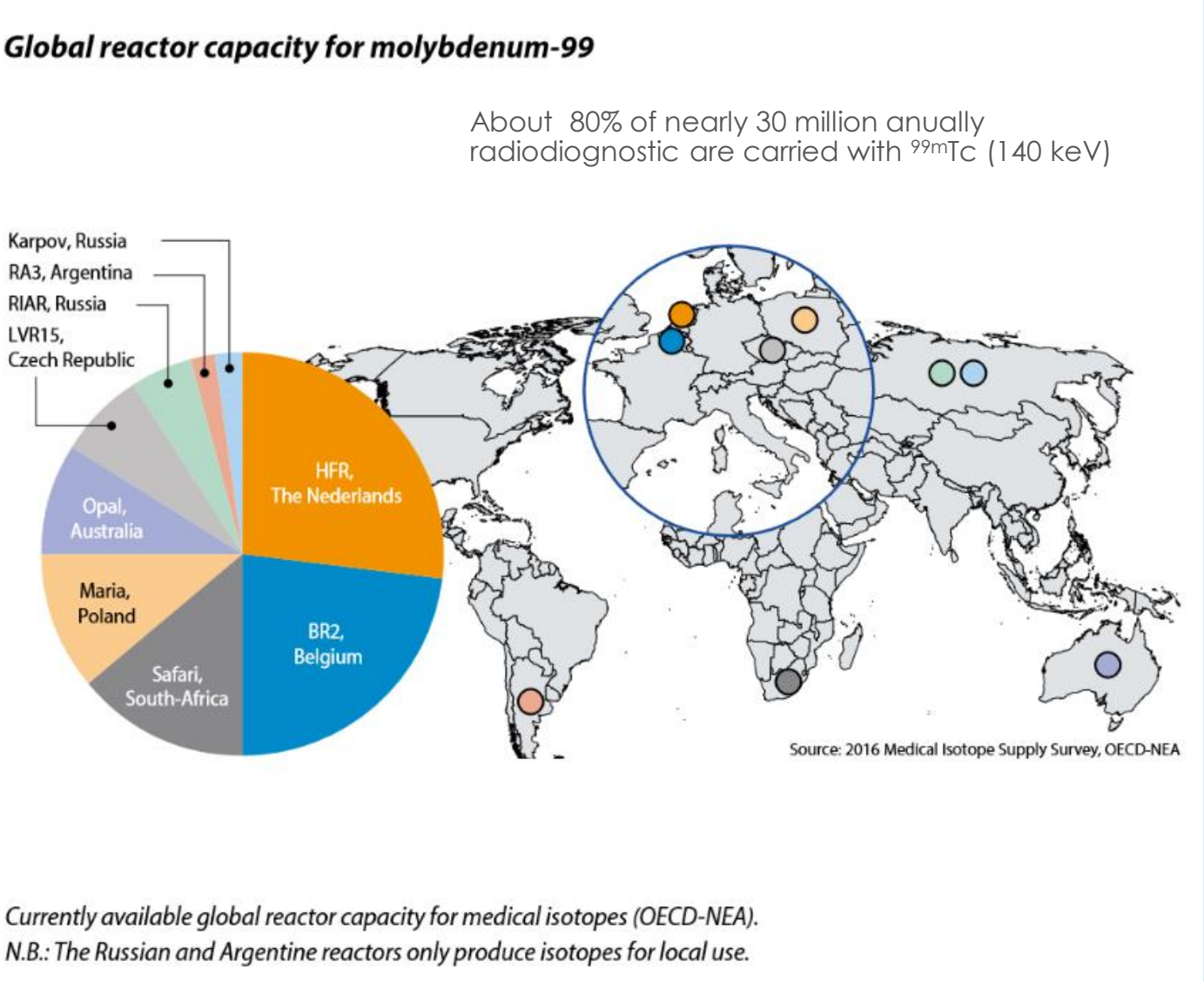
$^{124}Te(p,n)^{124}I$

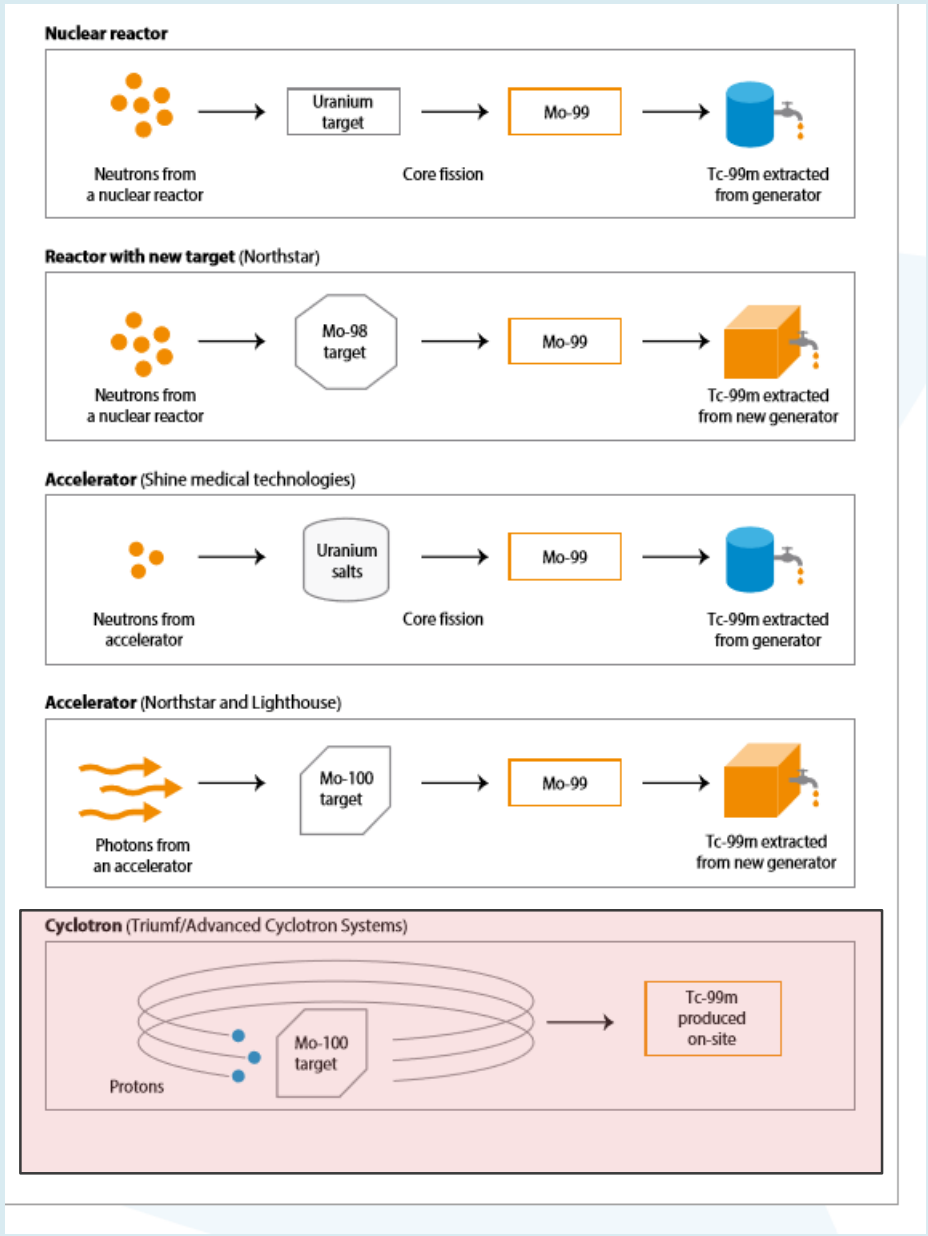
$^{68}Zn(p,an)^{64}Cu$
$^{66}Zn(d,a)^{64}Cu$
$^{64}Zn(n,p)^{64}Cu$

$^{191}Ir(n,\gamma)^{192}Ir$



$^{99}Mo/^{99m}Tc$ Generator

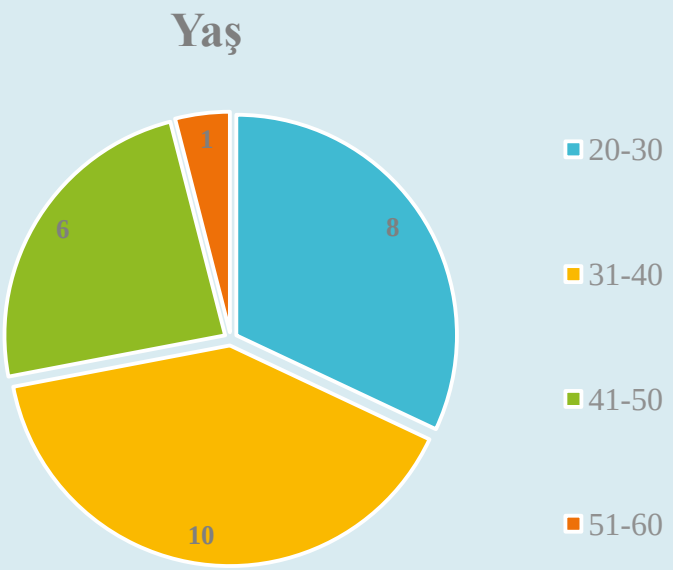


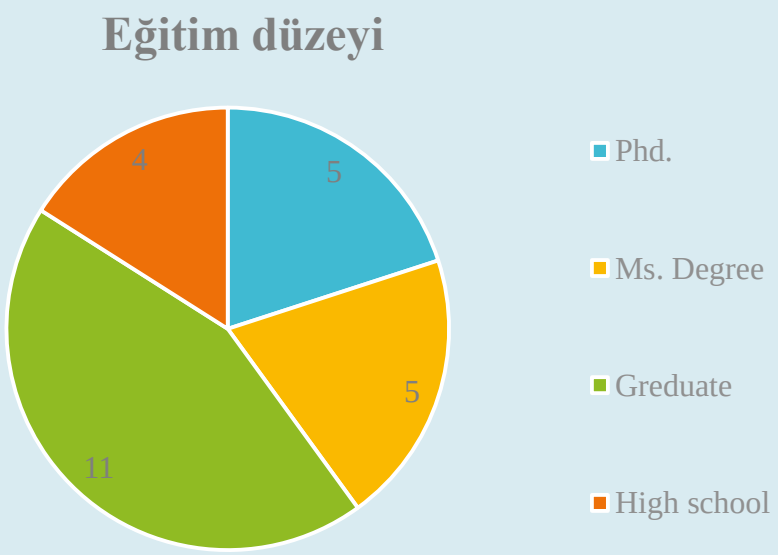


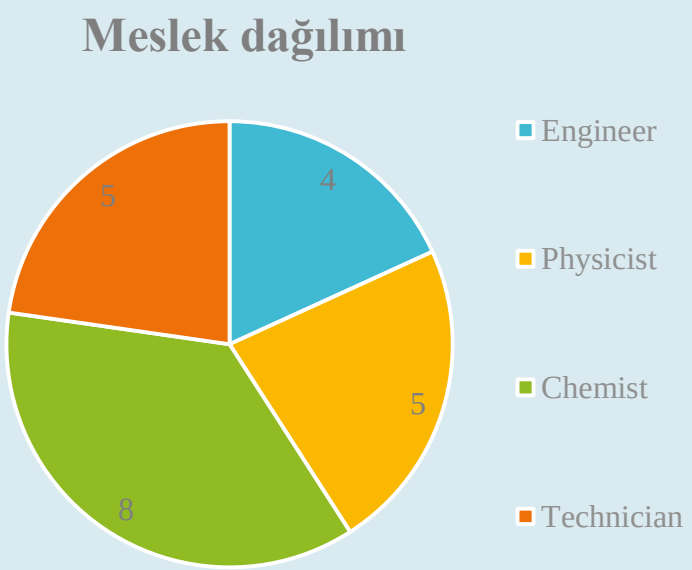
NEDEN ^{123}I-NaI ve ^{201}Tl-TlCl ?

- Sağlık Bakanlığı tarafından alım garantili 4 üründen ikisi,
- Satış öncesi hastanelerden alınan ihtiyaç tablosu dikkate alınmıştır,
- DMO Sağlık Market ve E-Devlet üzerinden satış,
- 2020 yılı ikinci yarısından itibaren pandemiye rağmen satışa başlanmıştır.

PHT PERSONEL YAPISI

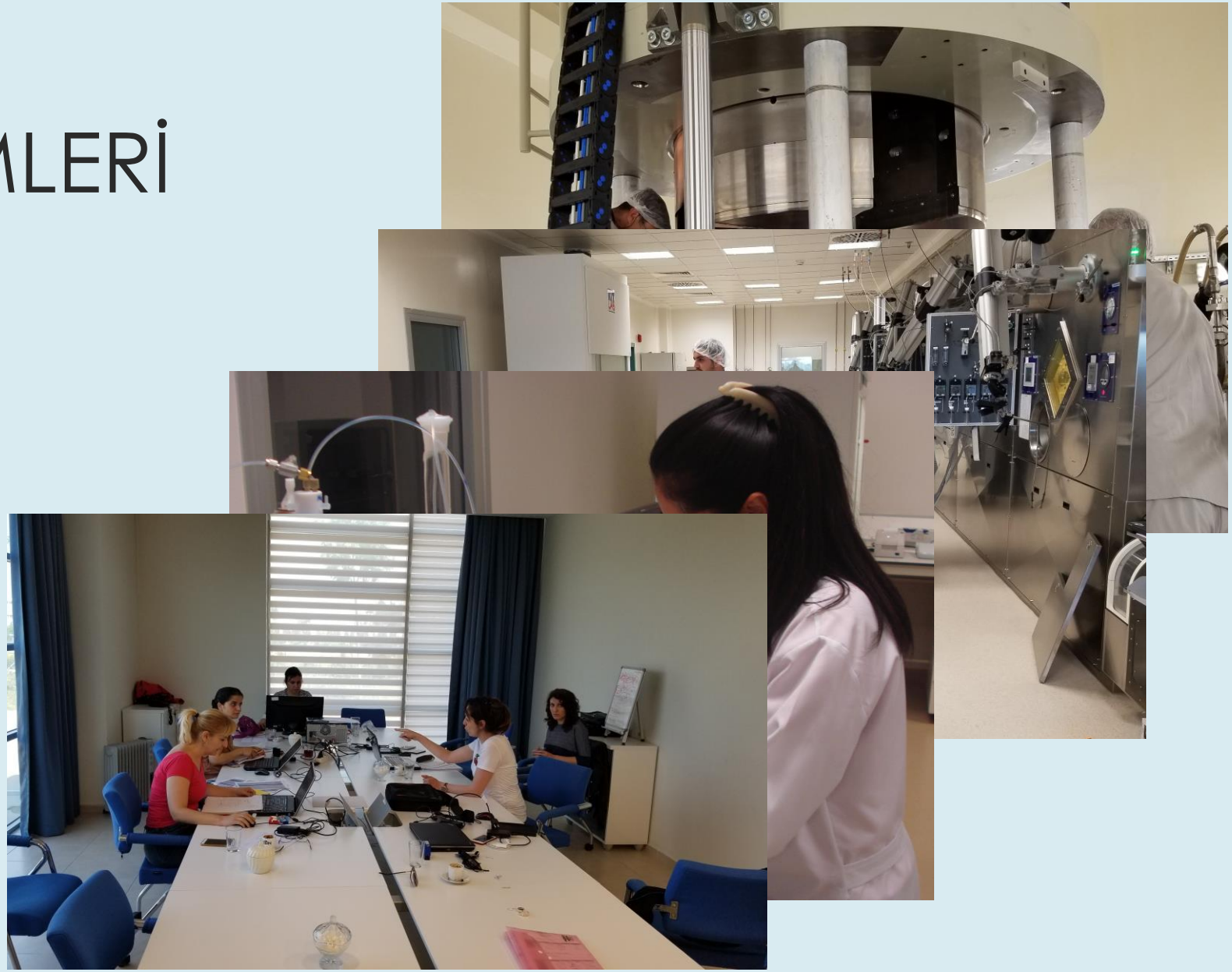






PHT'NİN BİRİMLERİ

- İşletme
- Üretim
- Kalite Kontrol
- Kalite Yönetimi



GMP AND TSE EN ISO 9001:2015 CERTIFICATED PRODUCTION FACILITY

TURKISH MINISTRY OF HEALTH

Turkish Medicines and Medical Devices Agency

Certificate Number: TR/GMP/2016/211 1.7.11.2018

Issued for Medicinal Products for human use

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

MEDICINAL PRODUCTS FOR HUMAN USE

Manufacturer's Name/Address: ***Turkish Atomic Energy Authority Saraykoy Nuclear Research and Training Centre Proton Accelerator Facility, Atom Cad. No: 27 Saray/KAZAN - ANKARA***

Activities Performed: ***^{18}F radioisotope, ^{18}F-FDG (Fluorodeocyglucose) radiopharmaceutical, ^{123}I radioisotope, ^{123}I-NaI (Sodium Iodide) radiopharmaceutical, ^{201}Tl radioisotope, ^{201}TlCl (Thallous Chloride) radiopharmaceutical, ^{67}Ga radioisotope, ^{67}GaCit (Gallium Citrate) radiopharmaceutical, ^{111}In radioisotope, ^{111}InCl$_3$ (Indium Chloride) radiopharmaceutical production.***

The company above is a manufacturer of pharmaceutical products that is subject to inspection by our Agency in regular intervals in accordance with the requirements of current "Good Manufacturing Practice (GMP)," as recommended by World Health Organization (WHO).

ACTIVE SUBSTANCE(S)*

Manufacturer's Name/Address: ***Turkish Atomic Energy Authority Saraykoy Nuclear Research and Training Centre Proton Accelerator Facility, Atom Cad. No: 27 Saray/KAZAN - ANKARA***

Active Substance(s) Manufacture: ***^{18}F-FDG (Fluorodeocyglucose), ^{123}I-NaI (Sodium Iodide), ^{201}TlCl (Thallous Chloride), ^{67}GaCit (Gallium Citrate), ^{111}InCl$_3$ (Indium Chloride)***

Chemical Name: ***2-deoxy-2-[^{18}F]fluoroglucose, [^{123}I] Sodium Iodide, Thallous [^{201}Tl] Chloride, Gallium [^{67}Ga] Citrate, Indium [^{111}In] Chloride***

Commercial Name: ***TAEK-PHT FDG, TAEK-PHT NaI, TAEK-PHT TlCl, TAEK-PHT GaCit, TAEK-PHT InCl$_3$***

(The company above is a manufacturer of active substance(s) that is subject to inspection by our Agency in regular intervals in accordance with the requirements of current "Good Manufacturing Practice (GMP)," as recommended by World Health Organization (WHO) for the commercialization or distribution of acitve substance(s) in the country of manufacture or import.

*This section is only for API Manufacturers.

Fatih TA...
Kurum ...
Yardım...

This certificate is valid until 31.03.2019

Turkish Medicines and Medical Devices Agency

IAF

TÜRKAK

KALİTE YÖNETİM SİSTEMİ BELGESİ

QUALITY MANAGEMENT SYSTEM CERTIFICATE

EK / APPENDIX

Partner of IQNet

Belge No / Certificate No: KY-7327/17-R15

Belge Tarihi / Date of Certificate: 05.06.2018

Belgeli Kuruluş Adı, Adresi:

Name and Address of the Certified Organization:

TÜRKİYE ATOM ENERJİSİ KURUMU RADYASYON VE HIZLANDIRICI TEKNOLOJİLERİ DAİRESİ BAŞKANLIĞI PROTON HIZLANDIRICISI TESİSİ SARAY MAH. ATOM CAD. NO:27 KAHRAMANKAZAN - ANKARA / TÜRKİYE

K - Q TSE-ISO-EN 9000

Belge Kapsamı:

TS EN ISO 9001:2015

- RADYOİZOTOP
- RADYOFARMASÖTİK

ÜRETİMİ

Scope of the Certificate:

TS EN ISO 9001:2015

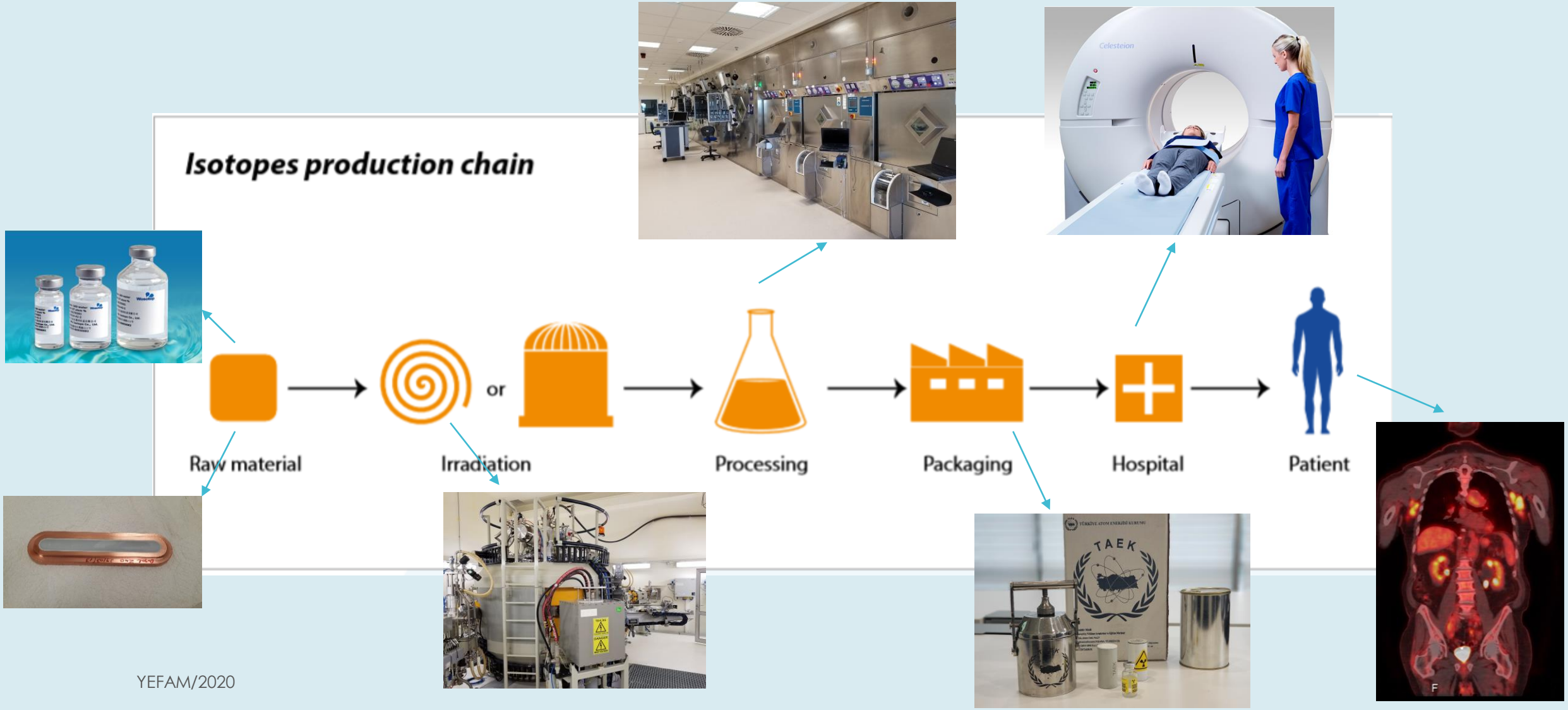
PRODUCTION OF

- RADIOISOTOPE
- RADIOPHARMACEUTICALS

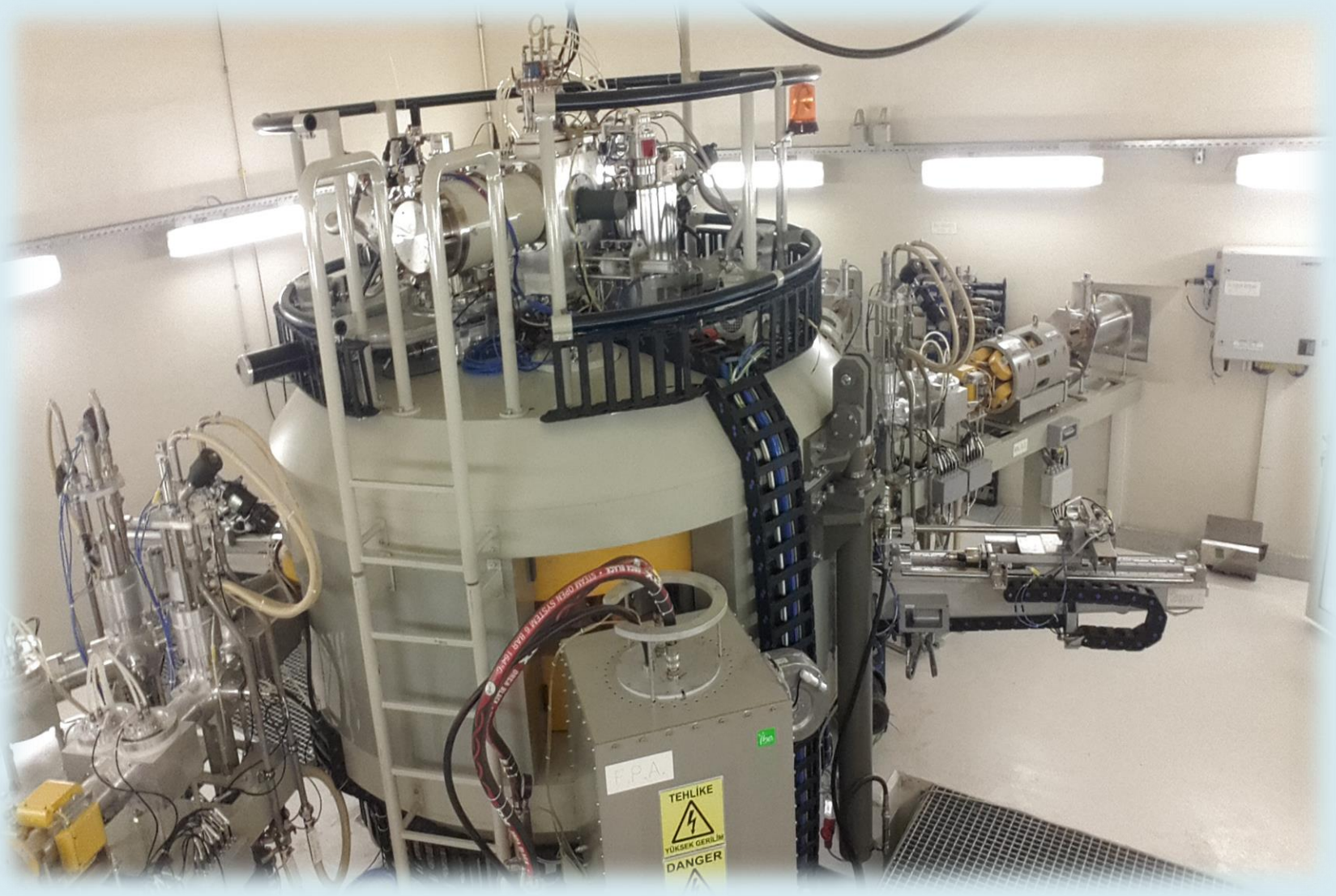
0631020180259000 1

Good manufacturing practice (GMP) is a concept that ensures products are consistently produced and controlled according to quality standards. It is designed to minimize the risks to the patient involved in any pharmaceutical production.

ÜRETİM


Isotopes production chain
Raw material
Irradiation
or
Processing
Packaging
Hospital
Patient
Celesteion
TAEK

SİKLOTRON



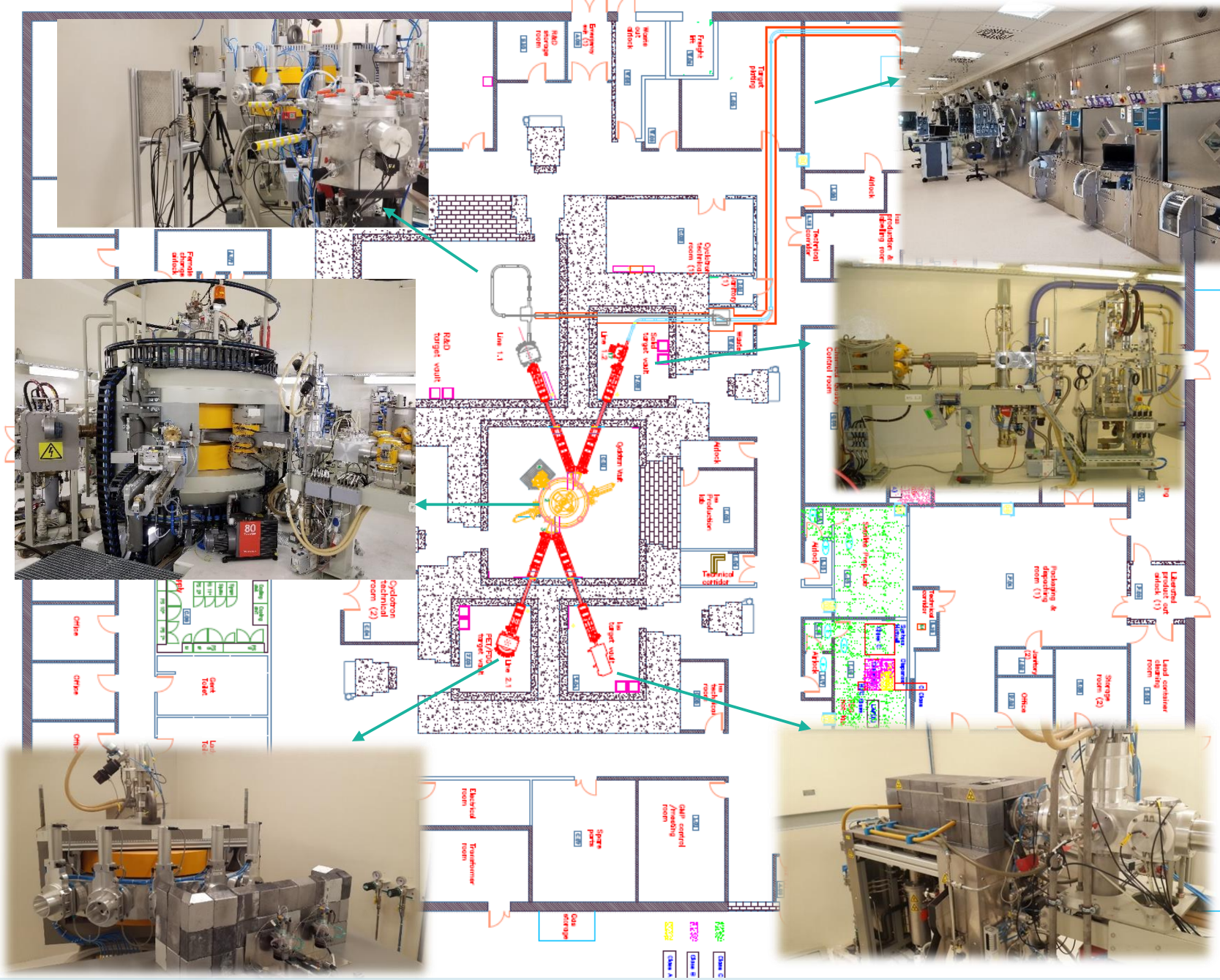
- *Type: CYCLONE-30 (IBA)*
- *Proton beam energy: 15-30 MeV*
- *Maximum proton current: 1.2 mA (variable)*
- *4 Beamlines*
- *Dual beam*

Maintenance

- *Vacuum Pumps*
- *Ion Source*
- *Stripper Foils*
- *Vacuum Guages*
- *Target Systems*

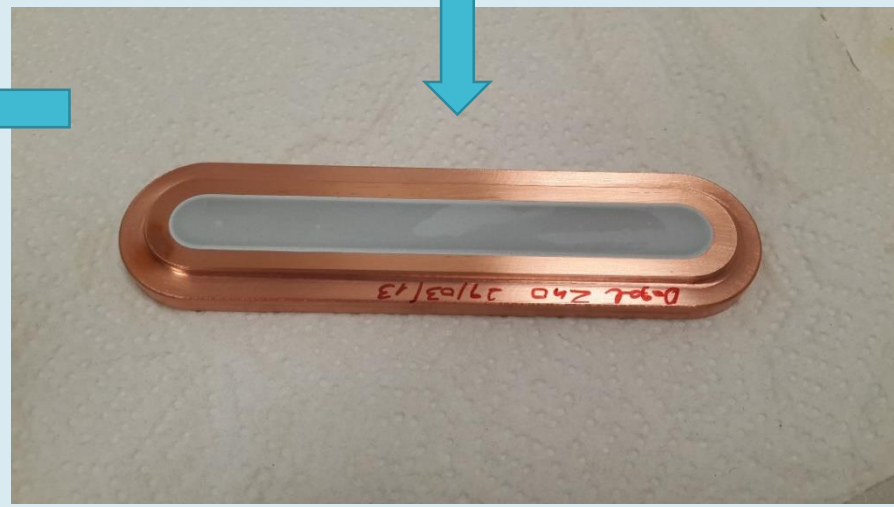
TENMAK PHT

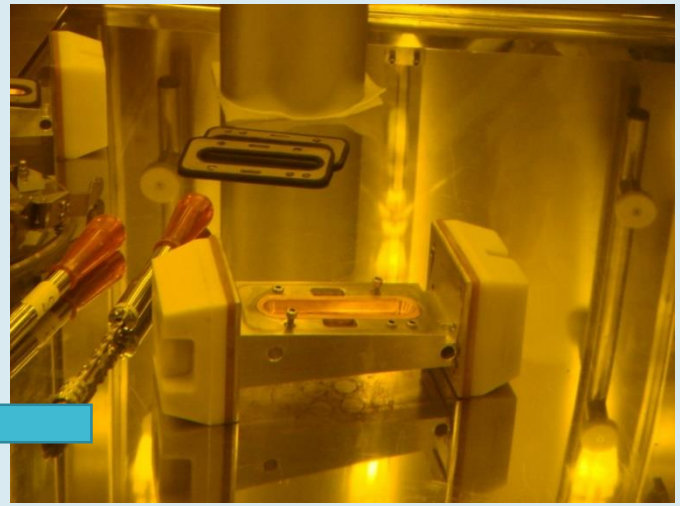
- ~7000 m² kapalı alan.
- 13 ofis
- 3 toplantı odası
- 12 laboratuvar
- 5 depo
- 2 kafeterya

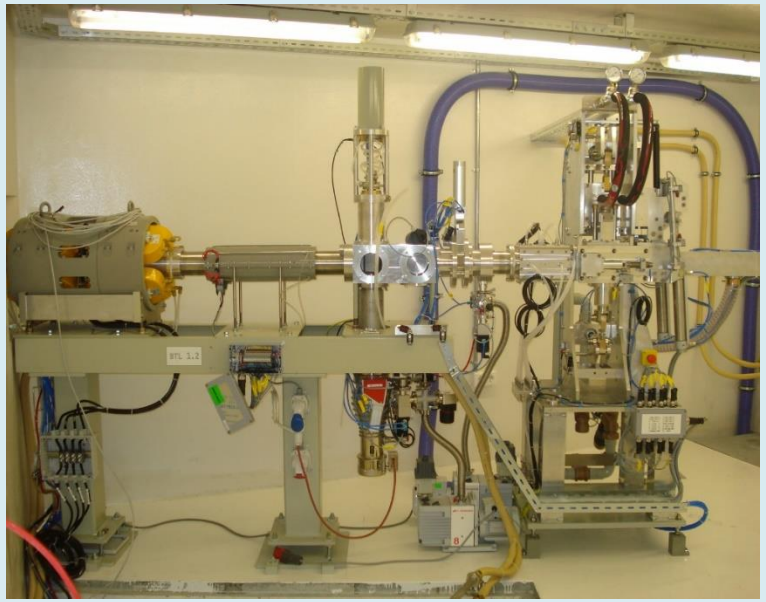


SOLID TARGET/ ^{201}TI-TICI

- Copper plate is electroplated (70-100 μm) by enriched matarials
- Target is transported by pneumatic transport system
- Beam energy: 28-29 MeV
- Beam current 200-250 μA
- Irradiation time: depend on activity, optimum 9-10 hours.





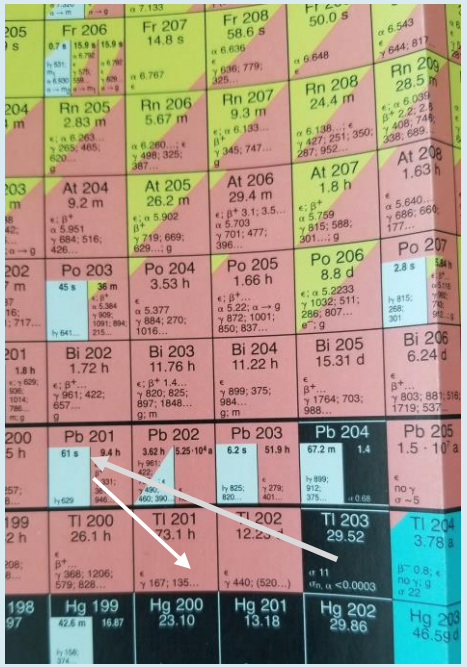


^{201}Tl-TlCl Üretimi

- Active material recovered from the target at the end of bombardment is Pb-201
- Pb-201 is then quickly purified to eliminate the Tl-203 target material
- Pb-201 is left to decay to Tl-201 for roughly 30-35 hours
- Tl-201 is then purified to remove the remaining Pb-201
- Pb-201 recovery efficiency is higher than 98%

Tl-203 (p,3n) Pb-201

Pb-201 ⟶ Tl-201(74 h)



$$A_{EOB} = \lambda \cdot N^{*}(t_{irr}) = \Phi \cdot N_T \cdot \sigma(E) \cdot \left(1 - e^{-\lambda \cdot t_{irr}}\right)$$

$$Y_{EOB}(t) = \lambda \cdot N^{*}(t) = \frac{N_A}{M_T} \cdot \frac{I}{q} \int_{E_E}^{E_I} \sigma(E) \cdot \frac{dE}{S(E)} \cdot \left(1 - e^{-\lambda \cdot t}\right)$$

GAS TARGET/ ^{123}I-NaI

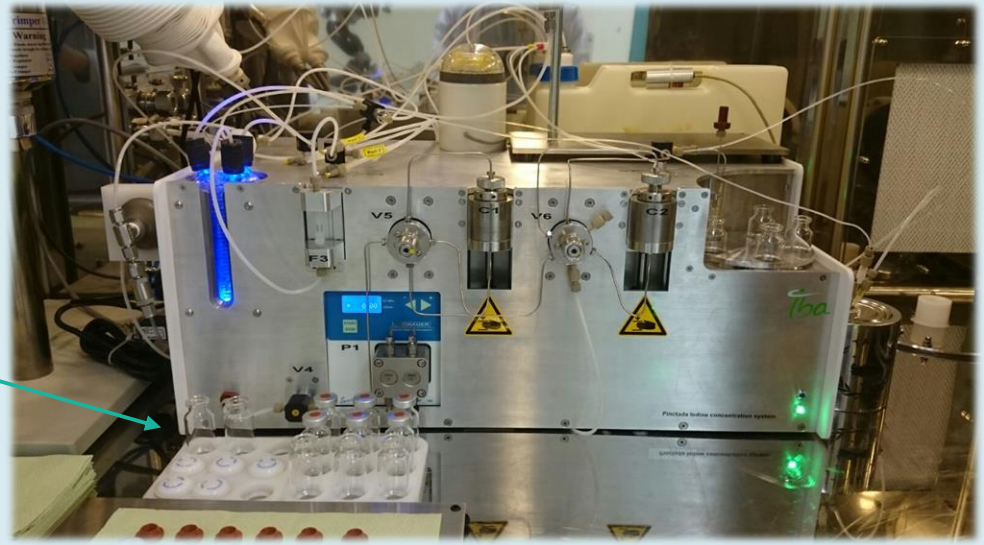
- High purity of the Xe-gas used as target material (99.8%)
- The Xe-124 transfer from the storage bottle to the target and the recovery of the gas after irradiation to the bottle is made cryogenically with liquid nitrogen, through stainless steel pipes.
- Beam energy: 29 MeV
- Beam current 50-70 μA
- Irradiation time: depend on activity, optimum 5-10 hours.

$^{124}Xe(p,2n)^{123}Cs$

^{123}Cs ^{123}Xe ^{123}I

Target System

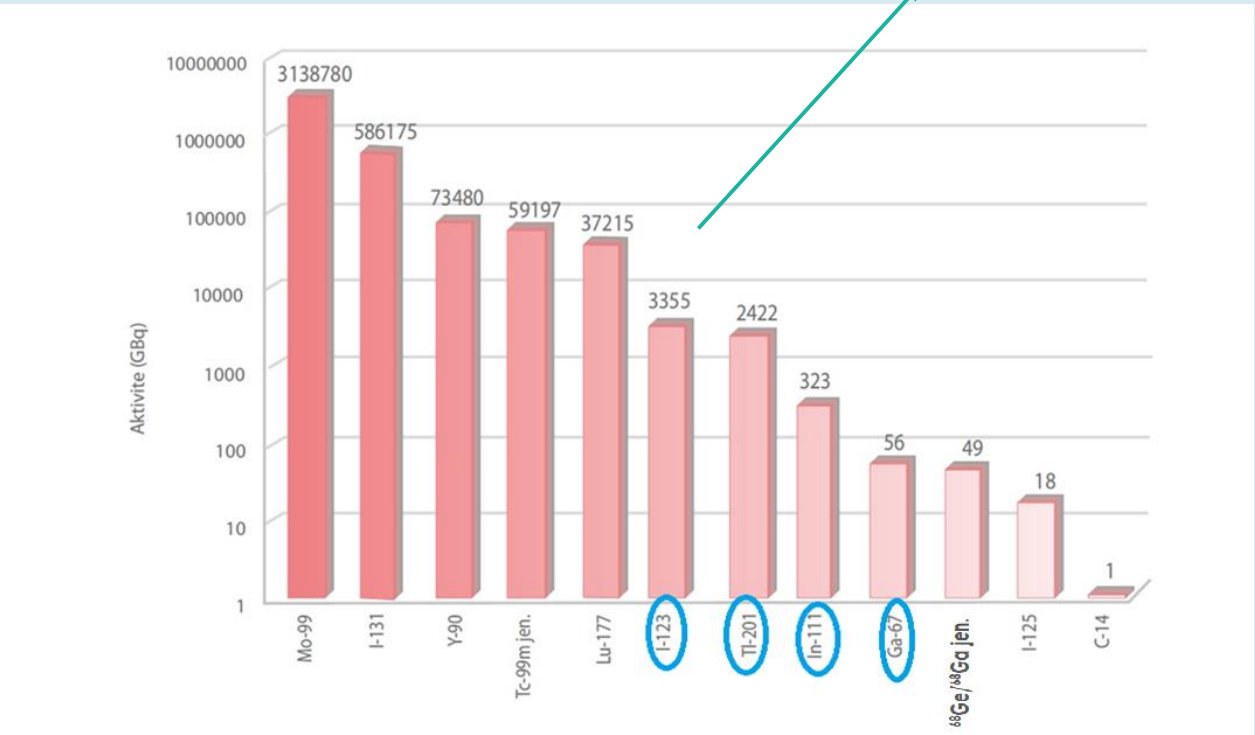
Synthesis Module



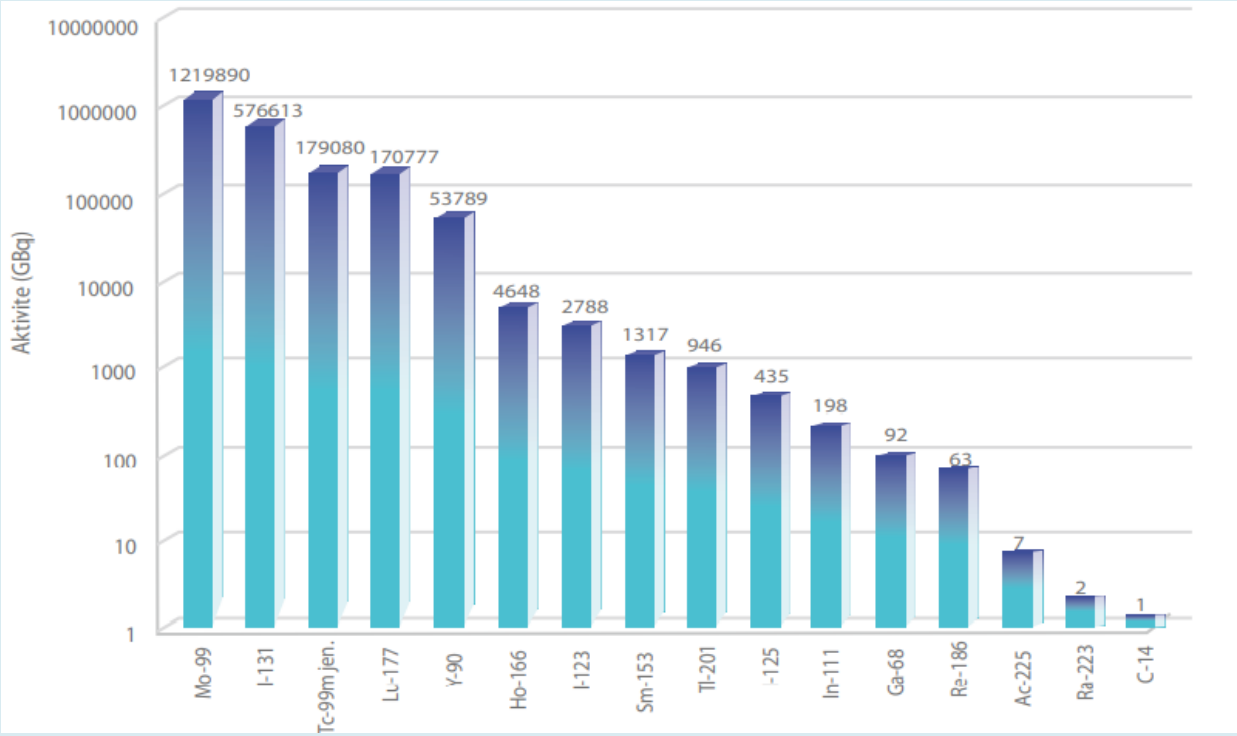
Despensing Module

IMPORTED RADIOISOTOPES

- Two days a week
- 1 batch /day
- ~37 GBq/batch
- ~3375 GBq/year(45 weeks)



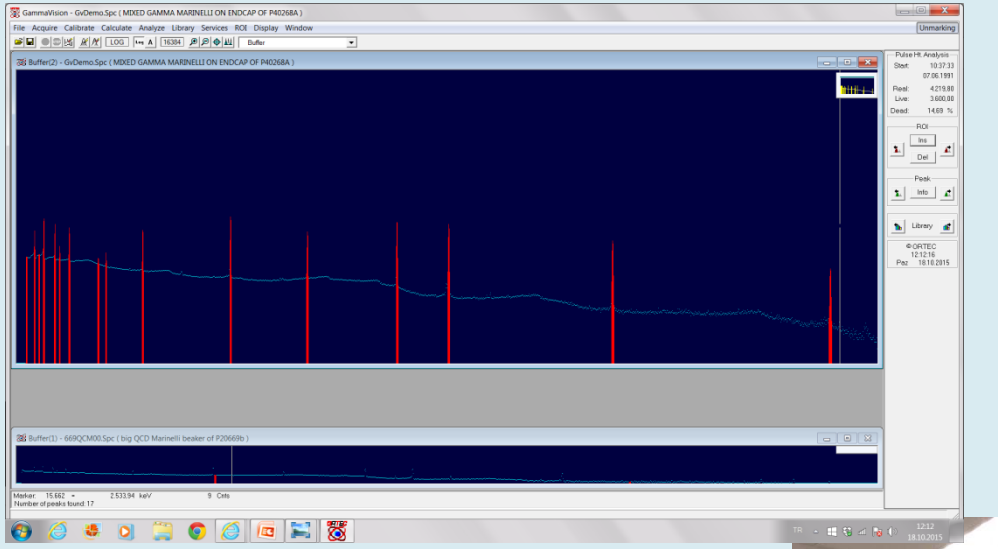
2017/TAEK Radyasyon Kaynakları

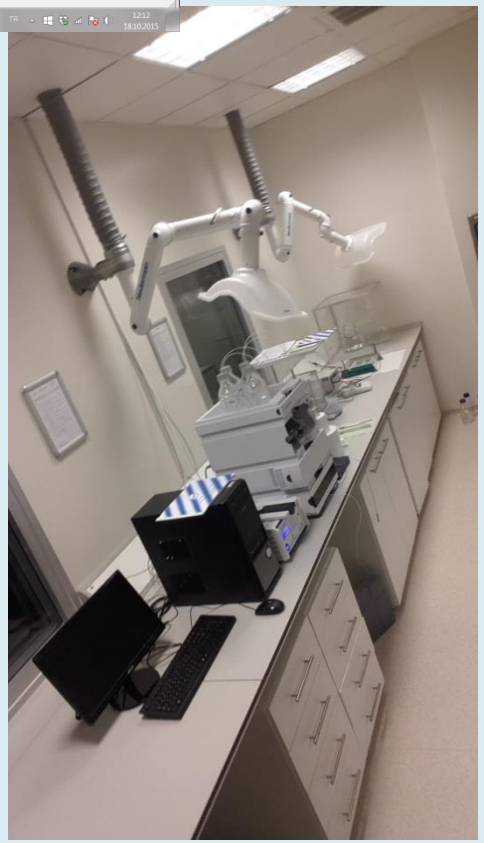


2019/NDK Radyasyon Kaynakları

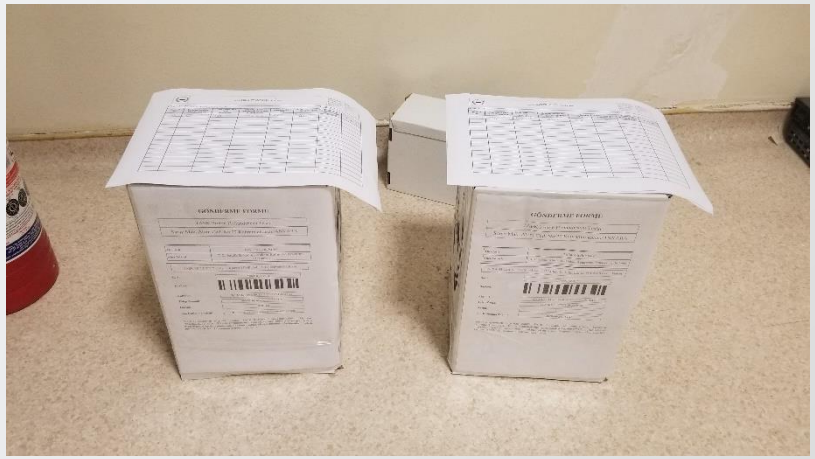
Quality Control Laboratories

- Radionuclidic,
  - Gamma Spectrometry
  - Dose Calibrator
- Radiochemical
  - HPLCs
  - TLC
  - Electophoresis
- Chemical
  - GC
  - Polarograph
- Micrbiological quality control tests
  - BET
  - Steritest pump
  - LAF and Biosafety cabinets
  - Incubators
  - Auoclave etc.





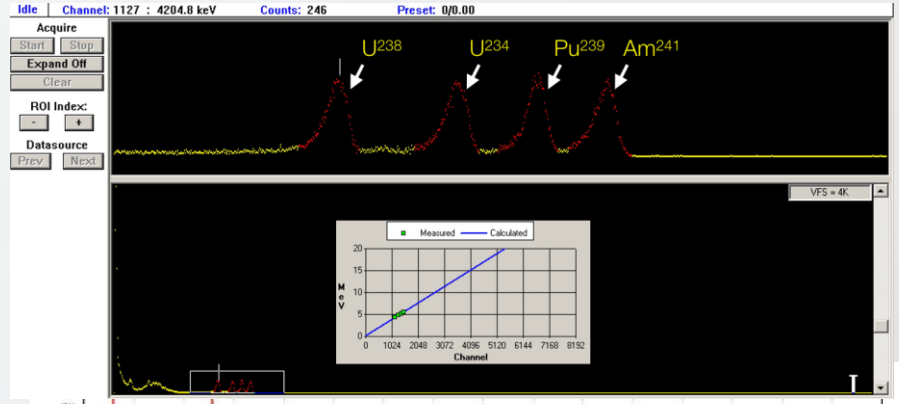
Paketleme ve Sevkiyat

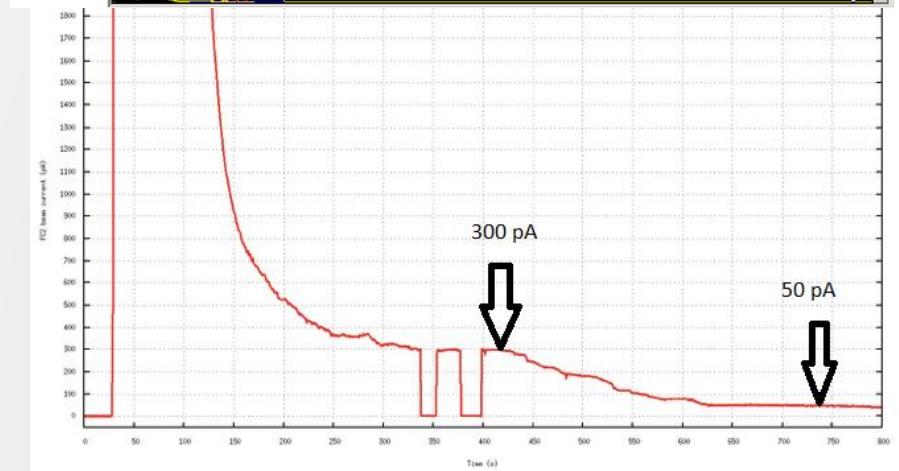


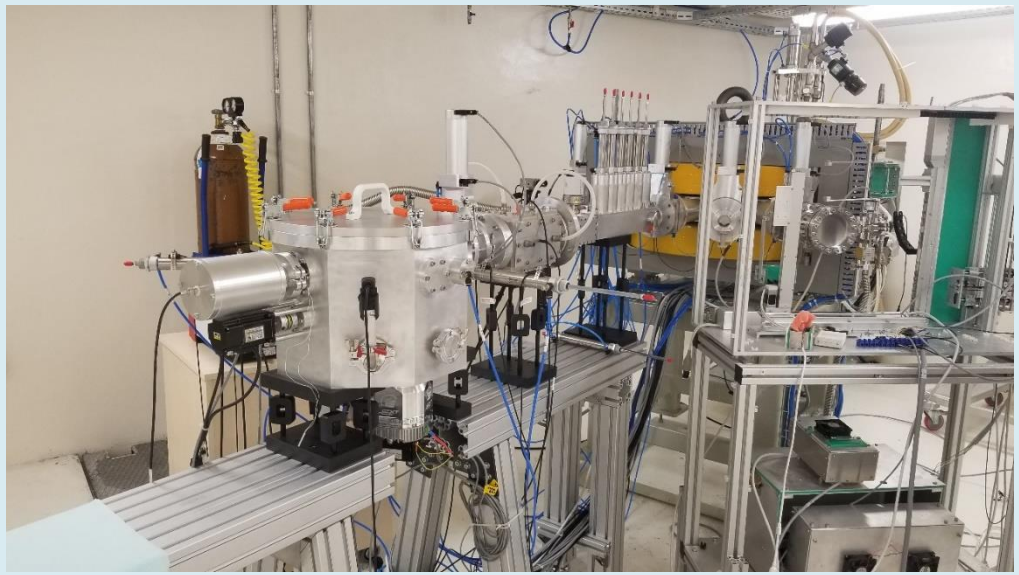
YEFAM/2020

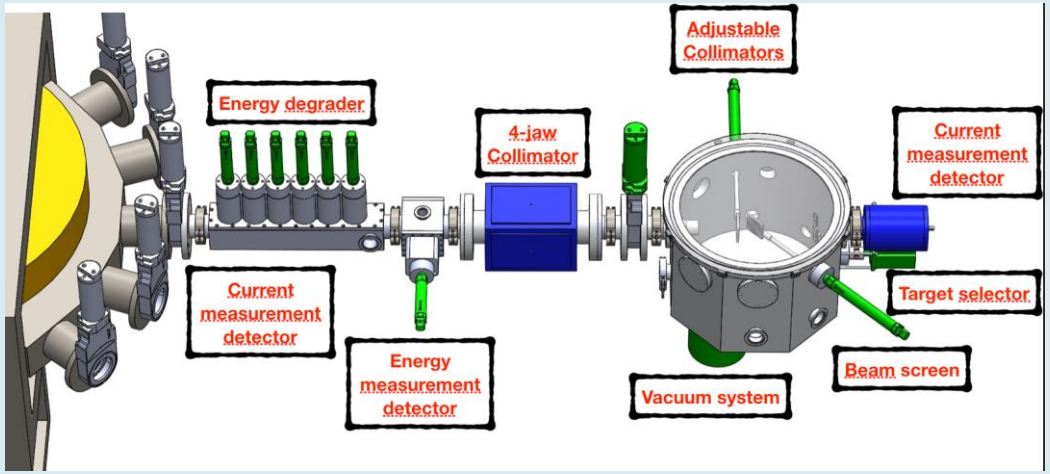
R&D VAULT

- TAEK Project: *«Installation Of The Low Current Irradiation System at TAEK PAF » (Complated in 2019)*
- *Design and Production of 68Ge\68Ga Radionuclide Generator/started in April 2019*
- *Irradiation Systems for Ion Beam Analysis Techniques (PIGE,PIXE,RBS,..)/ started in May 2020*
- METU Project









DESIGN AND PRODUCTION OF $^{68}Ge\backslash^{68}Ga$ RADIONUCLIDE GENERATOR

- PET tipi bir radyoizotop
- Yarı ömür: T1/2=67.7 dakika,
- Bozunum: $^{+}\beta$ bozunumu 89.1%,
- Doğrudan ya da jeneratör yolu ile üretilebilmektedir,
- ^{68}Ga-ETDA, ^{68}Ga-PSMA, ^{8}Ga-DOTA gibi radyofarmasötik formları kullanılmaktadır.

IBA selected to Equip IRE's new Radioisotope Production Unit Dedicated to Cancer Diagnosis

The Institute of Radioelements (IRE) has commissioned the Louvain-la-Neuve-based company IBA to install a particle accelerator for the production of radioisotopes for the diagnosis of numerous cancer types such as neuroendocrine tumors and prostate cancer

Louvain-la-Neuve, Belgium, September 15th 2020 - IBA (Ion Beam Applications S.A., EURONEXT), the world's leading provider of solutions for the diagnosis and treatment of cancer, and IRE, the world leader in the production of radioisotopes for diagnostic and therapeutic applications in the field of nuclear medicine, announce today that they have signed a contract for the installation of a cyclotron with an energy of 30 MeV (mega electron volt) on an IRE site. Commissioning is scheduled for 2023.

Belgium is internationally recognized for its significant role in the advancement of nuclear medicine. These two Belgian companies, world leaders in their field, are joining forces to install this new cyclotron, the Cyclone® IKON, that will enable IRE to produce Germanium-68 (Ge-68), the raw material for the Germanium-68/ Gallium-68 (Galli Ad® and Galli Eo®) generators, for which demand is growing rapidly. These generators are manufactured on the Fleurus site by its pharmaceutical subsidiary IRE ELiT to serve hospitals around the world.

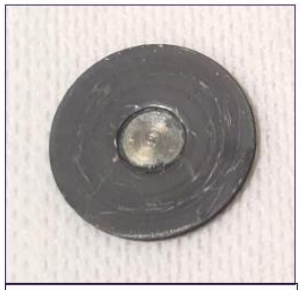
HEDEF MALZEME

- Doğrudan Üretim

Hedef malzeme zenginleştirilmiş ^{68}Zn

Katı ya da Nitrik asitte çözünmüş ^{68}Zn(3 ml)

Niobium disk with 8mm Ø cavity for metal powder



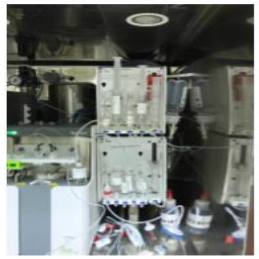
Niobium disk with 56mg of ^{68}Zn pressed into cavity

- Reaksiyon

$^{68}Zn(p,n)^{68}Ga$

IAEA TECDOC -1863/2019

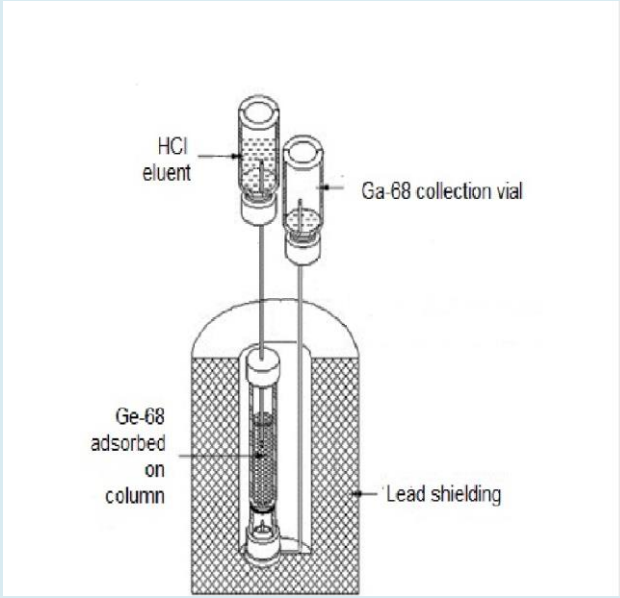
IBA Niobium target



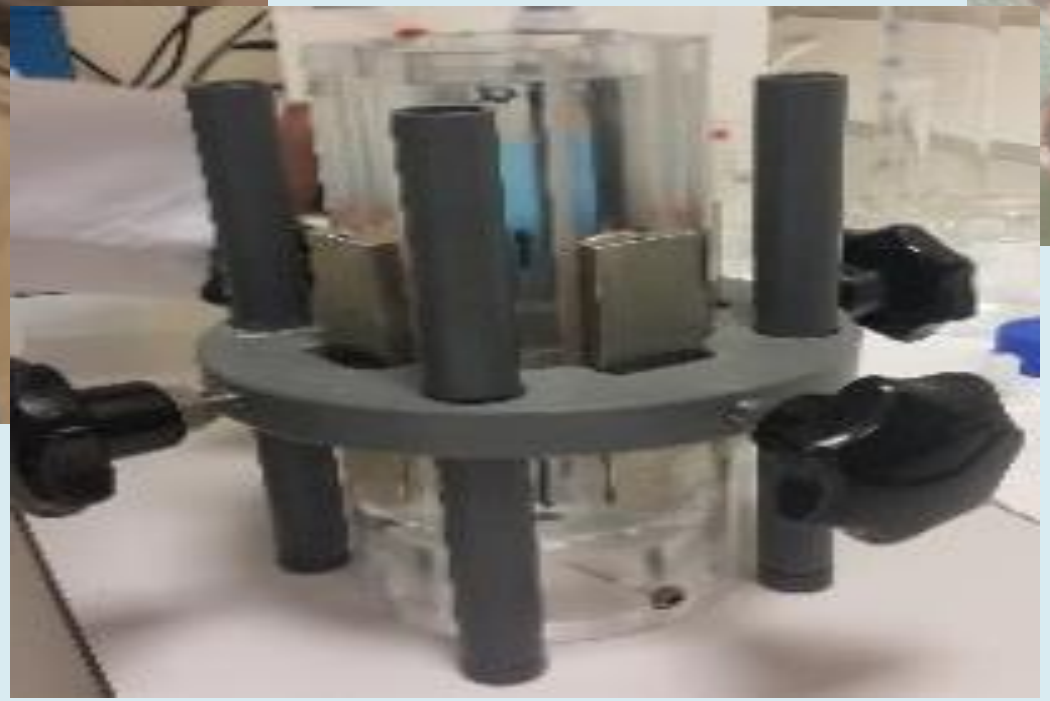
Synthera Extension

JENERATÖR

- ^{69}Ge zenginleştirilmiş malzeme ya da ^{nat}Ga+ Nikel çözeltisi ile kaplama.

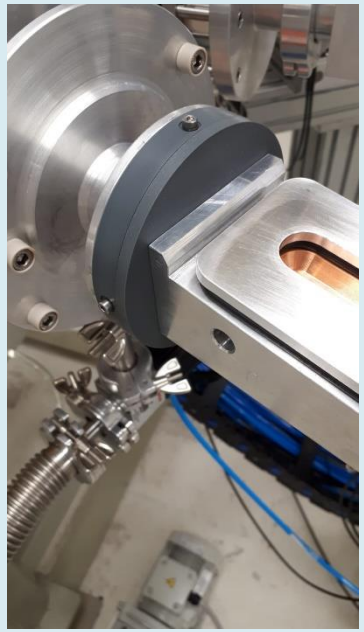


IŞINLANACAK HEDEFİN HAZIRLANMASI

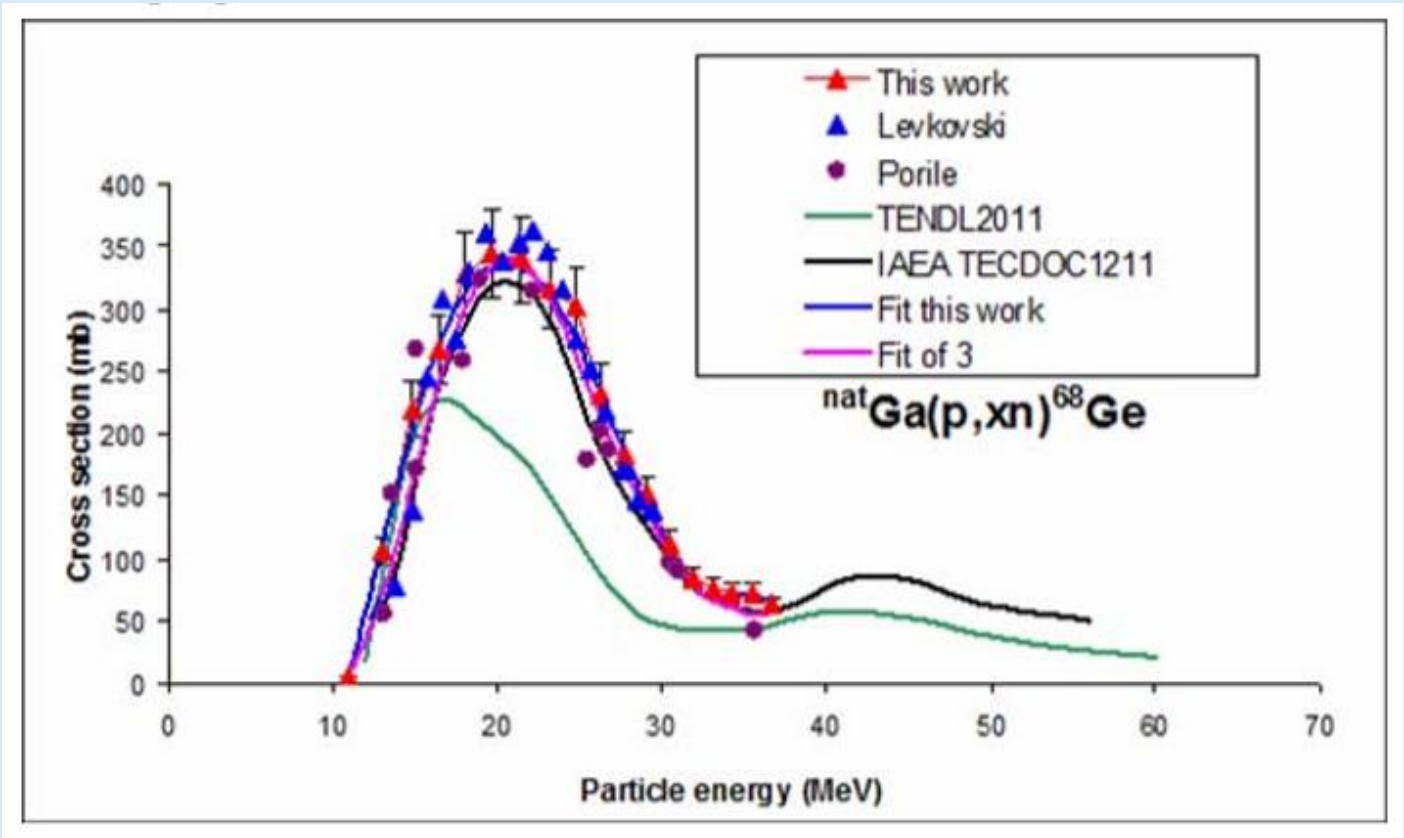


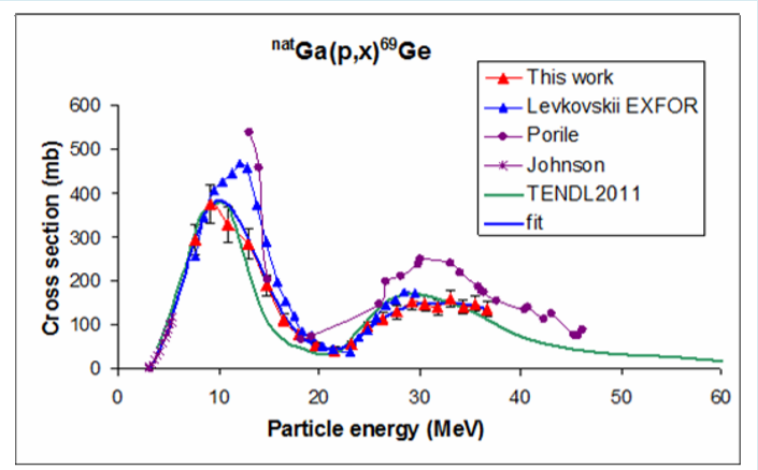
$^{68}Ge/^{68}Ga$ RADYOİZOTOP JENERATÖRÜ

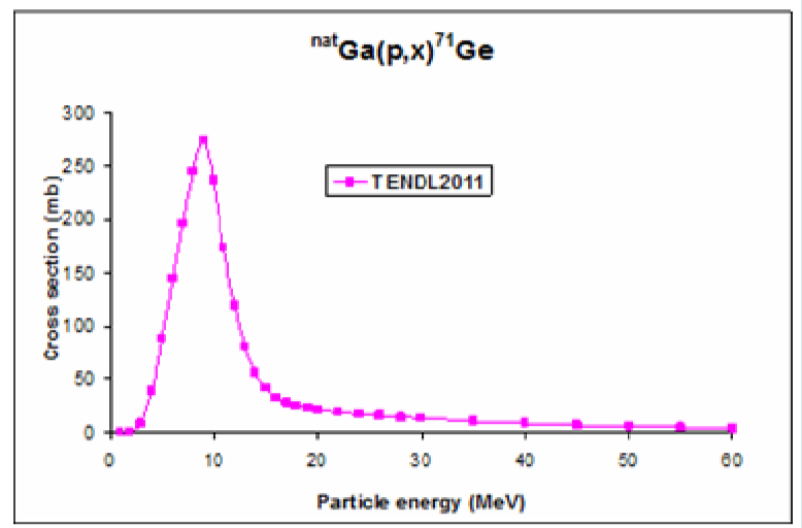
- Katı Hedef Sistemine uygun geometri,
- Vakum altında ışınlama,
- Akım ve Sıcaklık ölçümü,
- Enerji Ölçümü



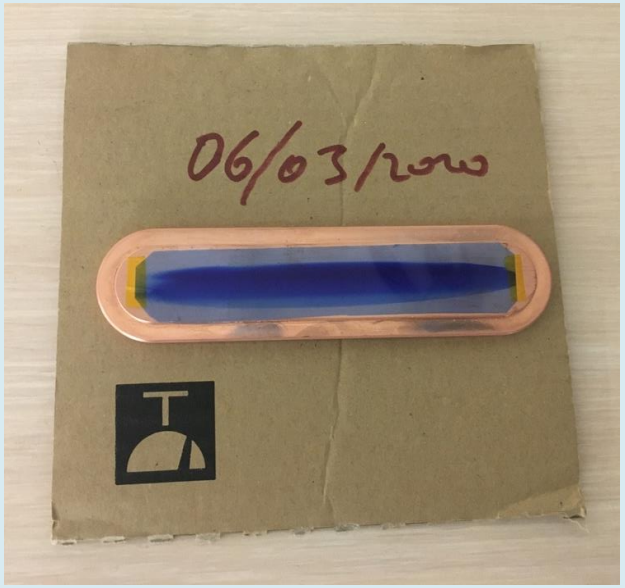
PROTON DEMETİ ENERJİSİ



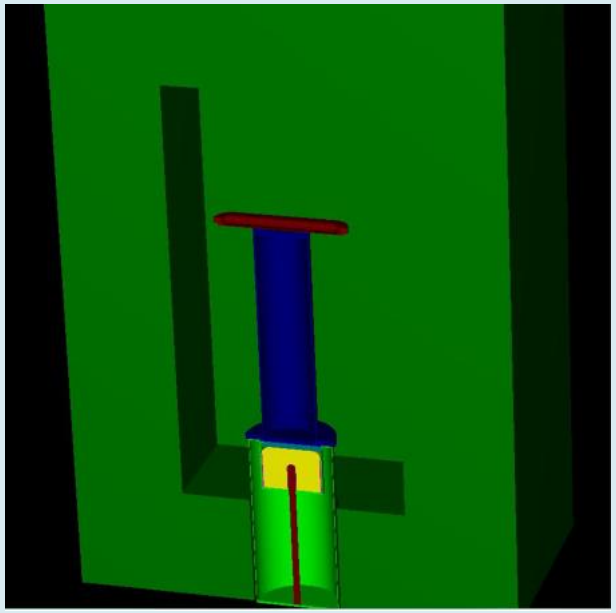




Hedef Işınlama ve Sayım



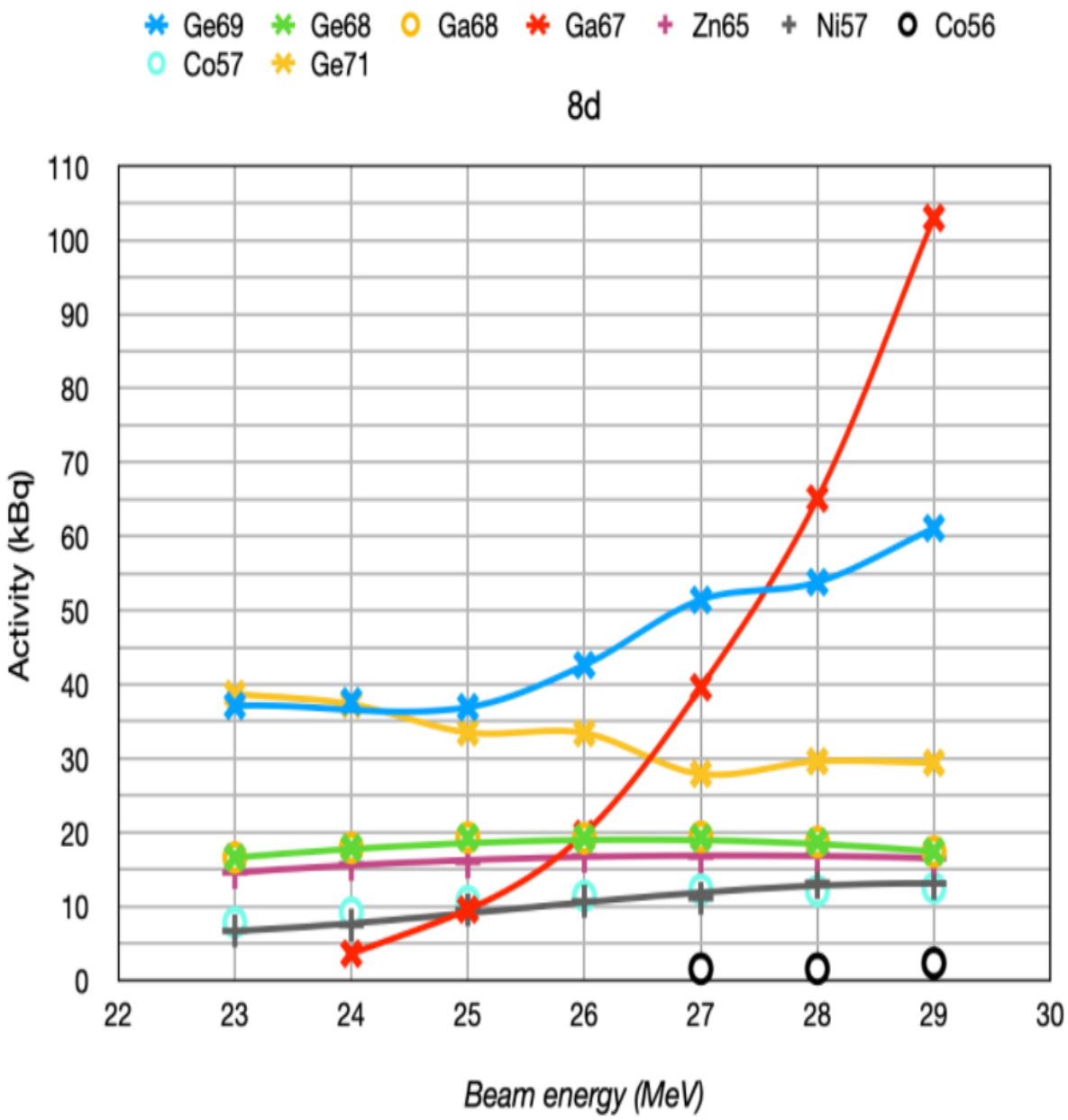
FWT-60 dozimetrik film üzerindeki proton demeti dağılımı.

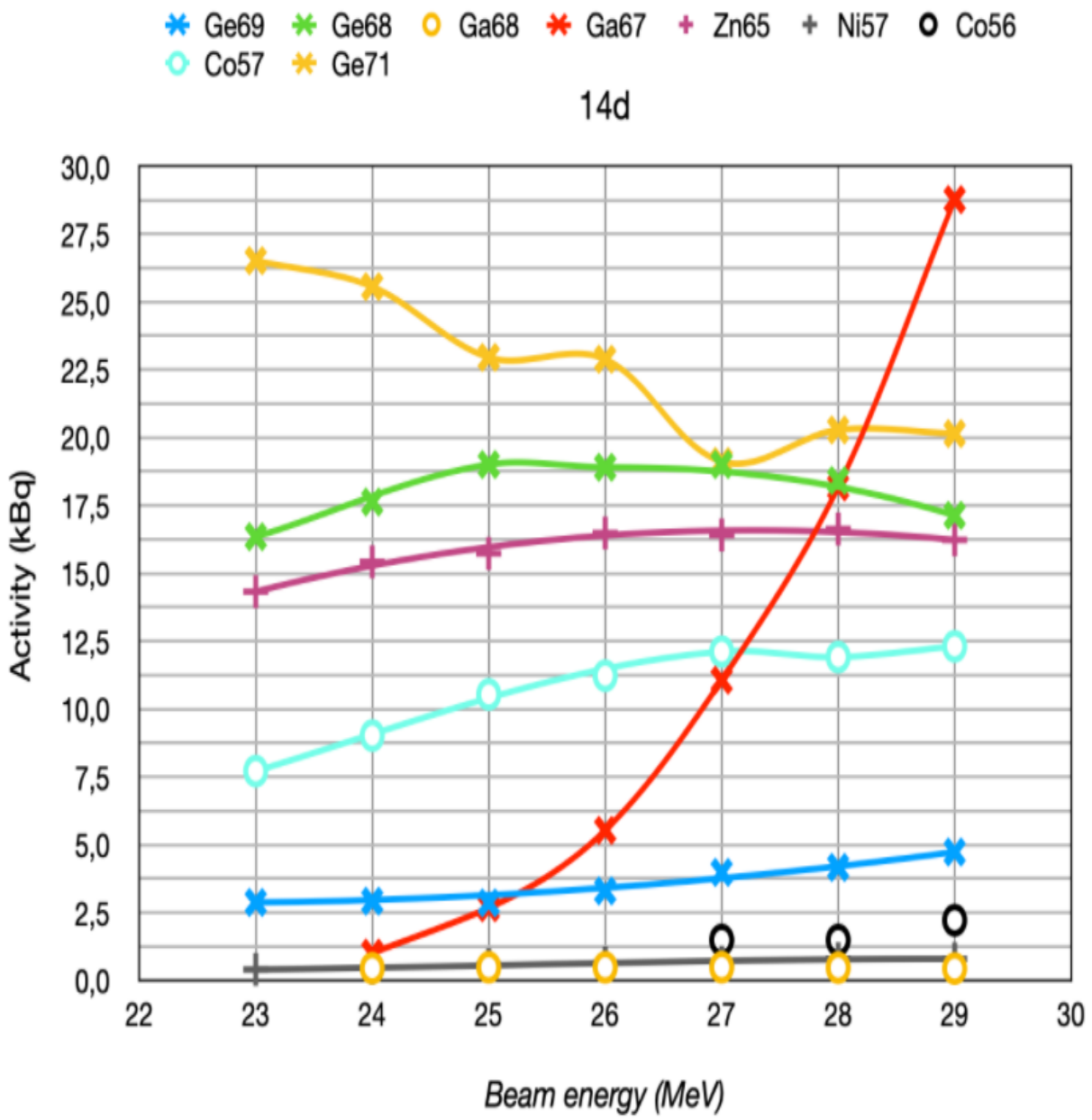


Kaplanmamış ve kaplanmış bakır plakaların EGSNRC Monte Carlo kodu ile benzetimi.

IŞINLAMA SONRASINDA OLUŞAN RADYONÜKLİDLER

110 sn 1 uA 73 um 8d	half life	unit	FLUKA (kBq)	errors are hidden						Meas (cps)	Efficiency (#)	Activity (kBq)	Gamma	Cross error (%)
Beam Energy			23	24	25	26	27	28	29					
Ge71	11	d	38,7	37,3	33,5	33,4	27,9	29,6	29,4				–	
Ge69	39	h	37,1	37,7	36,9	42,6	51,4	53,8	61,1				1106	
Ge68	271	d	16,6	17,9	19,3	19,2	19,3	18,7	17,4				–	
Ga68	67,7	min	16,6	17,9	19,3	19,2	19,4	18,7	17,4				1077	
Ga67	3,26	d	-	3,6	9,57	19,8	39,6	65,1	103				-	
Zn65	244	d	14,57	15,69	16	16,77	16,69	16,92	16,51		0,0002	0,000	1115	-100,0
Cu67	61,8	h	-	-	-	-	-	-	-				-	
Ni57	35,6	h	6,69	7,46	9,55	10,7	11,1	13,2	13,1				1377	
Co58			-	-	-	-	-	-	-				810	
Co57	271,7	d	7,83	9,16	10,7	11,4	12,3	12,1	12,5		0,00214	0,000	122	-100,0
Co56	77,2	d	-	-	-	-	1,57	1,57	2,34				846	
activities after	14	d	23	24	25	26	27	28	29					
Ge71			26,5	25,6	23,0	22,9	19,1	20,3	20,1		0,000002183	gr		
Ge69			2,9	2,9	2,9	3,3	4,0	4,2	4,7		0,000001566	gr		
Ge68			16,3	17,6	19,0	18,9	19,0	18,4	17,1		0,000051219	gr		
Ga68			-	0,4	0,5	0,5	0,5	0,5	0,4					
Ga67			-	1,0	2,7	5,5	11,1	18,2	28,8					
Zn65			14,3	15,4	15,7	16,5	16,4	16,6	16,2					
Cu67			-	-	-	-	-	-	-					
Ni57			0,4	0,5	0,6	0,6	0,7	0,8	0,8					
Co58			-	-	-	-	-	-	-					
Co57			7,7	9,0	10,5	11,2	12,1	11,9	12,3					
Co56			-	-	-	-	1,5	1,5	2,2					


Ge69
Ge68
Ga68
Ga67
Zn65
Ni57
Co56
Co57
Ge71
8d
Activity (kBq)
Beam energy (MeV)


Ge69
Ge68
Ga68
Ga67
Zn65
Ni57
Co56
Co57
Ge71
14d
Activity (kBq)
Beam energy (MeV)

IŞINLAMA ETKİSİ

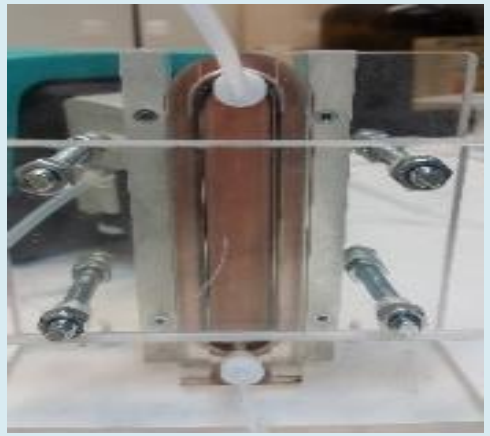
Işınlanmamış

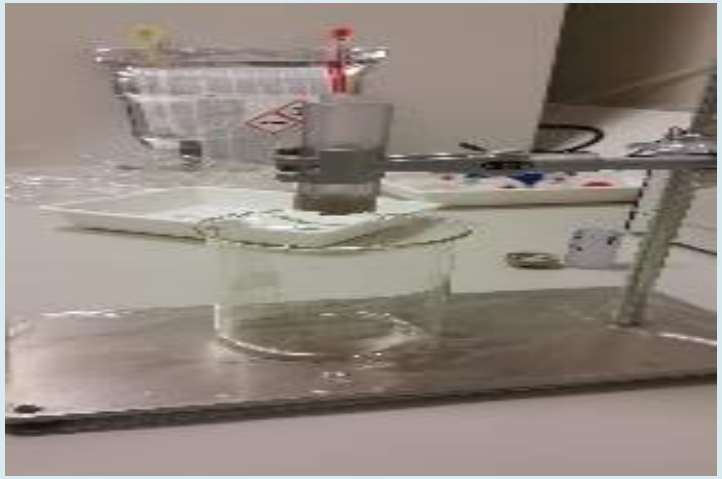
6 μA, 10 dk.

15 μA, 10 dk.

30 μA, 10 dk.

Soğuk deneyler: Işınlama işleminden önce hedefin çözünmesi ile ilgili herhangi bir problem olmadığını test etmek amacıyla soğuk hedef üzerinde çözme deneyleri gerçekleştirilmiştir. Hedefin başarıyla çözünmesi için gerekli parametreler optimize edilmiştir. Ayrıca ışınlama sonrasında hedef üzerinde ve çözme işleminin ardından çözelti içerisindeki metal içeriği, laboratuvarda hazırlanan aynı bileşimdeki çözelti ile simüle edilmiştir. Hazırlanan bu soğuk çözeltiden germanyum ekstraksiyonu için gerekli olan optimum şartların belirlenmesi için çalışmalar yapılmış ve ortalama %95 üzerinde bir verim elde edilmiştir.





Sıcak deneyler: Soğuk deneylerden belirlenen optimum şartlar, ışınlanmış hedefe uygulanarak ^{68}Ge eldesi, jeneratör kolonuna yüklenmesi ve jeneratör performansının tayini; projenin devamında planlanan çalışmalardır. Bu çalışmalar PHT'de bulunan sıcak hücre (hot-cell) içerisinde soğuk örnekler ile devam etmekte olup, optimum şartların belirlenmesinden sonra tüm işlemler bu hücrelerde gerçekleştirilecektir.

SONUÇ VE DEĞERLENDİRMELER

- Tesis altyapısı kullanılarak radyoizotop/radyofamasötik üretimi yapılmakta ve Ar-Ge faaliyetlerine devam edilmektedir.
- Mevcut altyapının kullanımını teşvik etmek gerekiyor.
- Üniversitelerin, özellikle bu alanda yetkili kamu kurumlarının stratejik planları doğrultusunda, nitelikli projelere katılması ve altyapıdan faydalanması önemlidir.
- Nükleer Tıp alanında daha etkili araştırma ve teşhis/tedavi uygulamaları için tesise entegre bir Görüntüleme Merkezi altyapısı düşünülmelidir.
- Kurumlar, üniversiteler ve diğer araştırma merkezlerinde öğrenci destek mekanizmalarının güçlendirilmesi gereklidir.
- Ülkemiz kaynakları ile kritik ürünlerin üretilmesini sağlamak hedeflenmelidir.

Teşekkürler