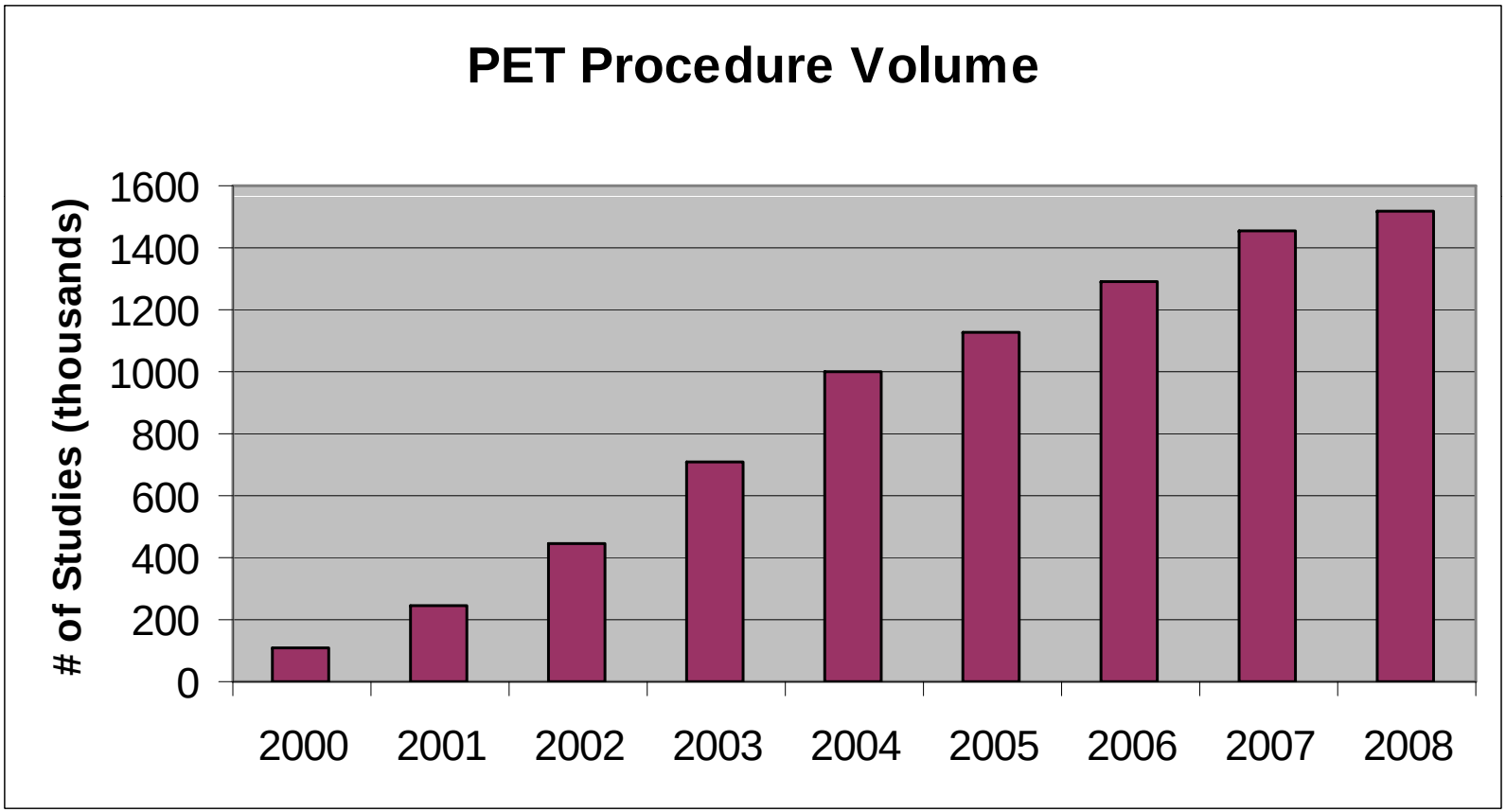
PET NUCLEAR PHARMACY

Growth in Number of PET Procedures (clinical only)



PET Nuclear Pharmacy Radionuclides

- More common Diagnostic Products
  - ^{18}F, ^{13}N
- Less common Diagnostic Products
  - ^{15}O, ^{11}C

- R&D Diagnostic
  - ^{64}Cu, ^{124}I, ^{74}As, ^{76}Br
- R&D Therapy
  - ^{67}Cu, ^{77}Br

- General R&D
  - Some distribution of Radiochemicals to Universities or Hospitals for research

Typical PET Nuclear Pharmacy Radionuclides – Cyclotron activation products

- Fixed components
  - Sodium-22
  - Manganese-54
  - Cobalt-57
  - Cobalt-60
  - Zinc-65
  - Cadmium-109
  - Silver-110m
  - Cesium-134
  - Europium-152
  - Tungsten-181

- **Replaceable components**
  - **Vanadium-48**
  - **Manganese-54**
  - **Cobalt-56**
  - **Cobalt-57**
  - **Iron-59 (Fe-59)**
  - **Cobalt-60**
  - **Zinc-65**
  - **Cadmium-109**
  - **Silver-110m (Ag-110m)**
  - **Tungsten-181 (W-181)**
  - **Tantalum-182**

PET DIAGNOSTIC

Clinical Applications of PET

- Oncology
  - Staging, recurrence, therapy response
- Neurology
  - Alzheimer's, Parkinson's Disease
- Cardiac

Overview of Typical PET Nuclides – Diagnostic

Fluorine-18 (^{18}F)

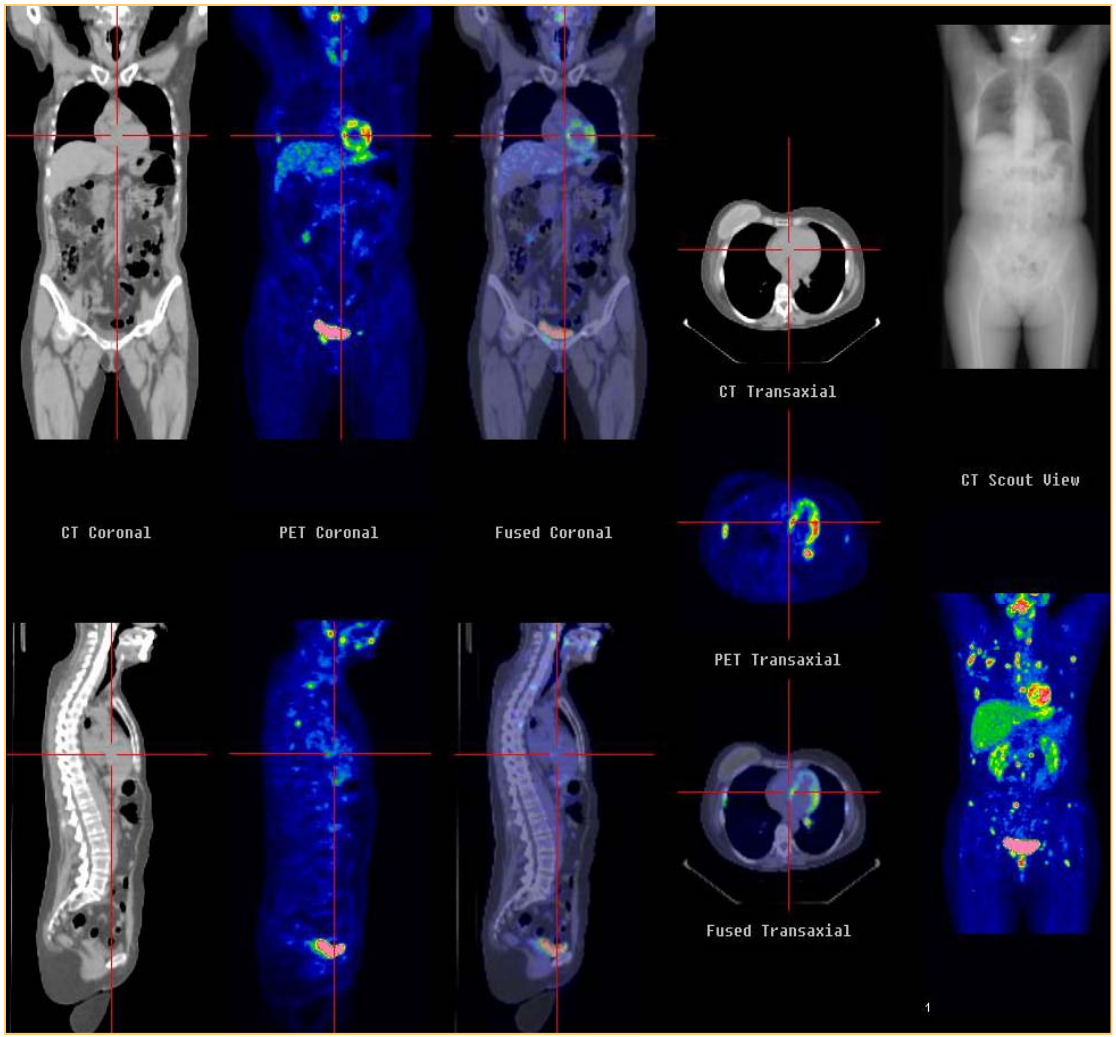
- 109.7 minute $t_{1/2}$
- β^+ decay 96.7% (E_{max} = 633 keV, E_{avg} = 211 keV)
- γ 511 keV (193%)*
- HVL = 4 mm Pb; 2.8 mm W
- Γ = 6 R/hr per mCi @ 1cm

*Primary photon for imaging

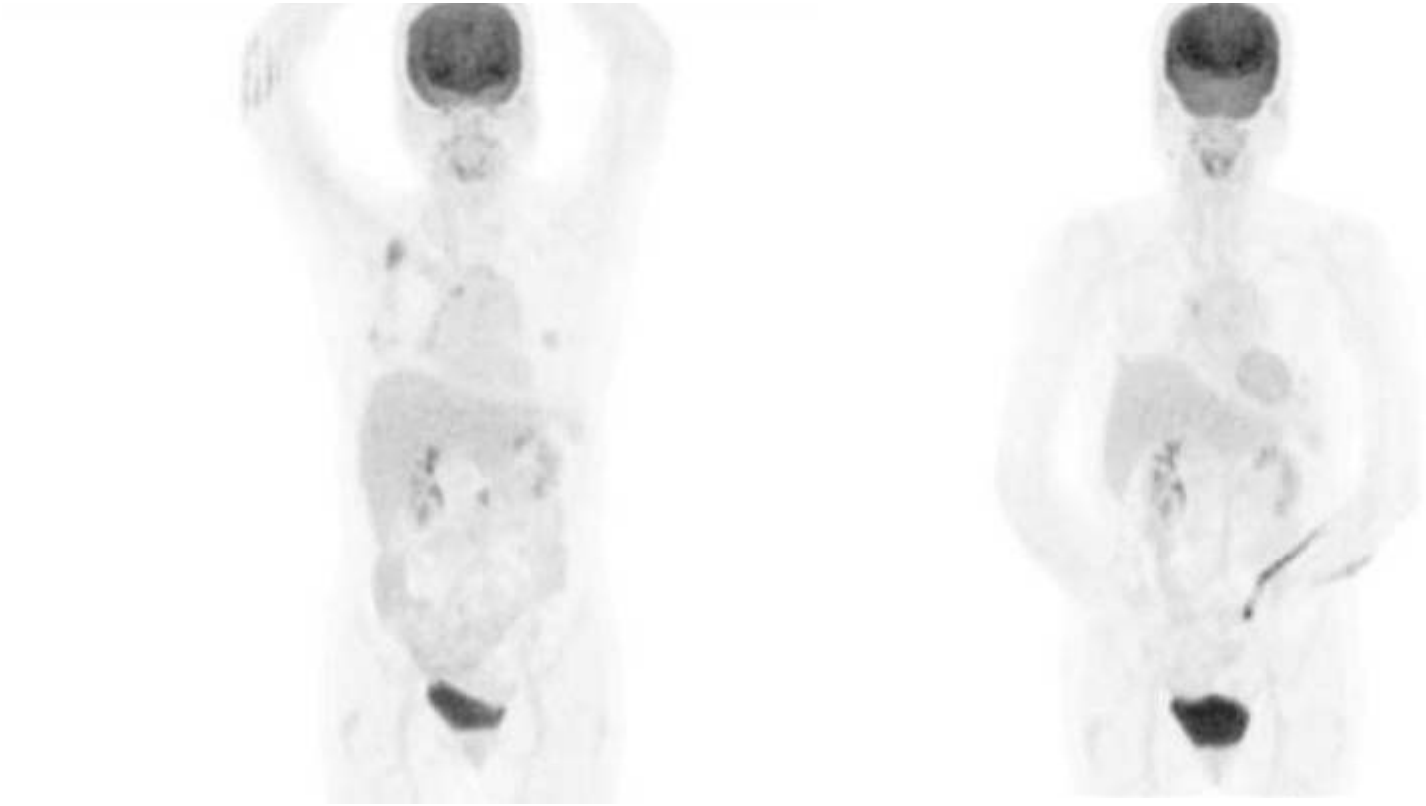
PET Oncological Imaging

- ^{18}FDG (10-20 mCi)
- Imaging begins approx. 45 min post-injection
- Patient must remain still to reduce uptake of FDG into muscle

^{18}F-FDG PET/CT



Response to Treatment



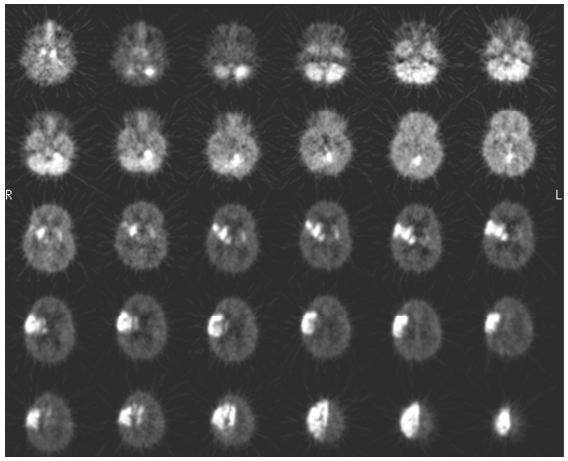
Pre chemotherapy

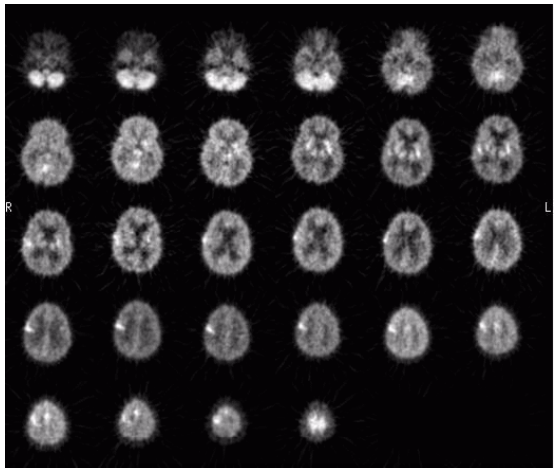
Post chemotherapy

PET Neuro Imaging

- ^{18}FDG (10-20 mCi) injected slowly
- Patient lies in a dimly lit room for 30-40min
- Imaging begins approx. 45 min post-injection

PET Neuro Imaging





8.6 mCi of ^{18}FDG administered with the patient in a pentobarbital-induced coma

PET imaging was repeated after a 2-week interval (with better pharmacologic control of the seizure activity) to assess for change (10.5 mCi FDG)

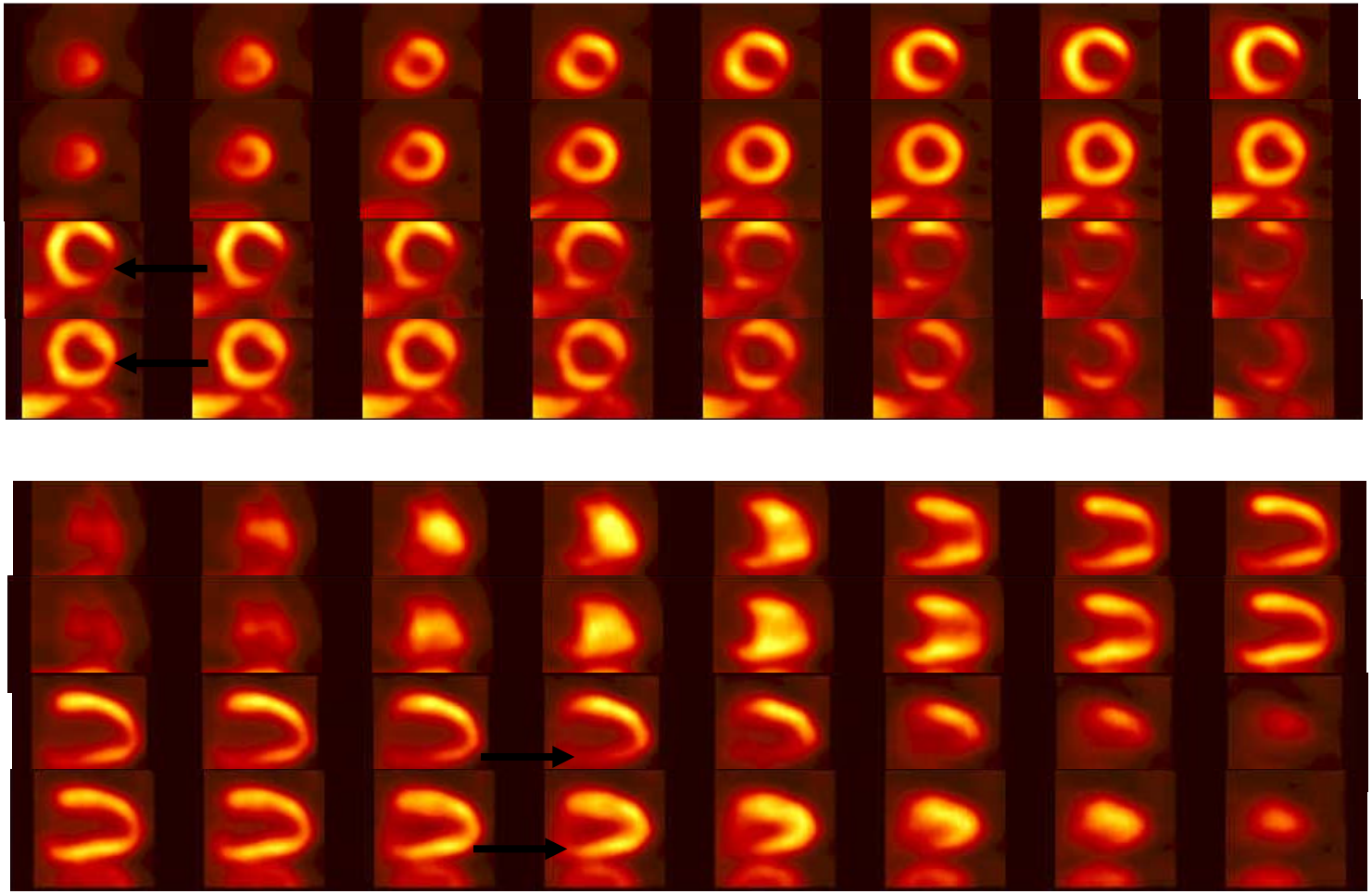
Overview of Typical PET Nuclides – Diagnostic

Nitrogen-13 (^{13}N)

- 10 minute $t_{1/2}$
- β^+ decay 100% (E_{max} = 1200 keV, E_{avg} = 400 keV)
- γ 511 keV (200%)*
- HVL = 4 mm Pb; 2.8 mm W
- Γ = 6 R/hr per mCi @ 1cm

*Primary photon for imaging

Abnormal ^{13}N perfusion study



Overview of Typical PET Nuclides – Diagnostic

Carbon-11 (^{11}C)

- 20 minute $t_{1/2}$
- β^+ decay 100% (E_{max} = 960 keV, E_{avg} = 320 keV)
- γ 511 keV (200%)*
- HVL = 4 mm Pb; 2.8 mm W
- Γ = 6 R/hr per mCi @ 1cm

*Primary photon for imaging

Overview of Typical PET Nuclides – Diagnostic

Oxygen-15 (^{15}O)

- 122 second $t_{1/2}$
- β^+ decay 100% (E_{max} = 1732 keV, E_{avg} = 735 keV)
- γ 511 keV (200%)*
- HVL = 4 mm Pb; 2.8 mm W
- Γ = 6 R/hr per mCi @ 1cm

*Primary photon for imaging

R&D Positron Emitting Isotopes

Isotope	Half-life	fraction	Max. Energy
^{11}C	20.4 m	0.99	0.96 MeV
^{13}N	9.96 m	1.00	1.20 MeV
^{15}O	123 s	1.00	1.74 MeV
^{18}F	110 m	0.97	0.63 MeV
^{22}Na	2.6 y	0.90	0.55 MeV
^{64}Cu	12.7 h	0.19	0.65 MeV
^{68}Ga	68.3 m	0.88	1.90 MeV
^{74}As	17.8 d	multiple	0.95 MeV
^{76}Br	16.2 h	multiple	3.90 MeV
^{82}Rb	78 s	0.96	3.15 MeV
^{124}I	4.18 d	0.22	3.16 MeV

Non-Clinical Applications of PET

- Drug discovery
- Pharmacokinetics
- Basic research
- A PET nuclear pharmacy will often ship non-human doses to universities for R&D purposes – ensure license authorizes distribution of radiochemicals

PHARMACY STAFFING

Pharmacy Staffing – SPECT

- Number of staff is strongly dependent on the site's workload
  - –Two to three Authorized Nuclear Pharmacists (ANP)
    - ANPs listed on the RAM license
    - Typically the RSO will be an ANP
    - Board of Pharmacy (BoP) requires a Pharmacist in Charge (PiC) to be named
  - –One to three technicians
  - –Drivers if a courier service is not used
  - –Often "floater pharmacists" are used to supplement ANPs for vacations etc.

Pharmacy Staffing – PET

- Number of staff is strongly dependent on the site's workload
  - –Similar to SPECT staffing if operated as a pharmacy (compounding) plus
  - –Cyclotron Engineer if cyclotron is on-site
  - –Field Service Engineers (factory or corporate)
- If operating as a drug manufacturer
  - –Chemists for producing radiopharmaceuticals under an FDA manufacturing license

Authorized Nuclear Pharmacist

- The Authorized Nuclear Pharmacist (ANP) is the primary type of Authorized User (AU) on Nuclear Pharmacy licenses
  - All radiopharmaceuticals must be prepared by an ANP or a person working under the supervision of an ANP [10 CFR 32.72(b)(1)]
  - Holds a current active pharmacist license

Authorized Nuclear Pharmacist

- ANP is defined in 10 CFR 35.2 as:
  - Meets the requirements in Sec. 35.55(a) and 35.59; or
  - Is identified as an authorized nuclear pharmacist on another NRC or Agreement State license; or
  - Is designated as an authorized nuclear pharmacist by virtue of the PET grandfathering requirements in 32.72(b)(4)

Authorized Nuclear Pharmacist

- What are the requirements in Sec. 35.55(a)?
  - certified by a specialty board recognized by the Commission or an Agreement State
  - Specialty board must require candidates to:
    - Have graduated from a pharmacy program accredited by the American Council on Pharmaceutical Education (ACPE) or have passed the Foreign Pharmacy Graduate Examination Committee (FPGEC) examination;
    - Hold a current, active license to practice pharmacy;
    - Provide evidence of having acquired at least 4000 hours of training/experience in nuclear pharmacy practice. Academic training may be substituted for no more than 2000 hours of the required training and experience; and
    - Pass an examination in nuclear pharmacy administered by diplomates of the specialty board

Authorized Nuclear Pharmacist

- PET grandfathering requirements in 32.72(b)(4)
  - –May designate a pharmacist (as defined in Sec. 35.2 of this chapter) as an authorized nuclear pharmacist if:
    - The individual was a nuclear pharmacist preparing only radioactive drugs containing accelerator-produced radioactive material, and
    - The individual practiced at a pharmacy at a Government agency or Federally recognized Indian Tribe before November 30, 2007 or at all other pharmacies before August 8, 2009, or an earlier date as noticed by the NRC.

Authorized Nuclear Pharmacist

- What about everyone else?
  - Has completed 700 hours in a structured educational program consisting of both:
    - 200 hours of classroom and laboratory training in the following areas
      - Radiation physics and instrumentation;
      - Radiation protection;
      - Mathematics pertaining to the use and measurement of radioactivity;
      - Chemistry of byproduct material for medical use; and
      - Radiation biology; and

Authorized Nuclear Pharmacist

- Supervised practical experience in a nuclear pharmacy involving
  - Shipping, receiving, and performing related radiation surveys;
  - Using and performing checks for proper operation of instruments used to determine the activity of dosages, survey meters, and, if appropriate, instruments used to measure alpha- or beta-emitting radionuclides;
  - Calculating, assaying, and safely preparing dosages for patients or human research subjects;
  - Using administrative controls to avoid medical events in the administration of byproduct material; and
  - Using procedures to prevent or minimize radioactive contamination and using proper decontamination procedures; and
  - Has obtained written attestation, signed by a preceptor authorized nuclear pharmacist, that the individual has satisfactorily completed the requirements [above] of this section and has achieved a level of competency sufficient to function independently as an authorized nuclear pharmacist
- NRC Form 313A (ANP) or State equivalent is used to document training & experience

Cyclotron Engineer

- Critical team member for a cyclotron equipped PET Pharmacy
  - Typically does not have a 4-year degree
  - Extensive experience in electronics often from military
  - RF skills very desirable
- Usually maintains chemistry modules
- Performs Preventative Maintenance (PM)
- Factory service personnel are also utilized

BOARD OF PHARMACY & FDA

Board of Pharmacy

- The State Boards of Pharmacy are responsible for regulating the practice of Pharmacy and the manufacture and distribution of drugs within the State
- Importation of drugs into one State from another usually requires an out-of-state pharmacy permit
- National Boards of Pharmacy (similar to CRCPD)
  - http://www.nabp.net/

Board of Pharmacy

- Each Nuclear Pharmacy will hold a registration with the State in which it is located, as well as other States in which it does business
- In some instances the R.Ph. dispensing would also need to be licensed in the other State
- PET Manufacturing sites not operating under the practice of Pharmacy will hold a State or Federal drug manufacturing license

Compounding vs. Manufacturing

- FDA regards Traditional pharmacy compounding as the combining or altering of ingredients by a pharmacist in response to a licensed practitioner's prescription, which produces a medication tailored to an individual patient's special medical needs.
  - http://www.fda.gov/NewsEvents/Testimony/ucm154031.htm

PET Drug Regulation

- Due to their short half-lives, PET drugs cannot be subjected to the “normal” drug manufacturing rules

- In FDA regulation, such rules are referred to as cGMPs (current Good Manufacturing Procedures)

- Therefore, the manufacturing of PET drugs has been undertaken by Nuclear Pharmacies via compounding, with FDA regulating them by requiring adherence to USP procedures

PET Drug Regulation

This situation is about to change

- On 12/09/2009 FDA issued final current good manufacturing practices (CGMP) regulation for the production of Positron Emission Tomography (PET) drugs.
- Manufacturers will have two years to submit an NDA and register the facility

Pharmacy vs. Manufacturing

- A traditional Nuclear Pharmacy uses manufactured drugs produced under FDA GMPs and "compounds" these drugs under an FDA approved protocol to label them with radioactive materials
- Under the "Practice of Pharmacy," pharmacists are allowed to compound drugs that are not FDA approved under the USP (United States Pharmacopoeia)

Pharmacy vs. Manufacturing

- This is how PET drugs, such as FDG, have been produced up to this point.
- Due to the fact that Nuclear Pharmacies were compounding these drugs, the production of PET drugs has been licensed by the Agreement States as Nuclear Pharmacies
- Note: some PET drug manufacturing operations have already been separated from pharmacy operations

Pharmacy vs. Manufacturing

- From the standpoint of RAM Licensing, there has evolved a set of standard conditions and authorized individuals that are listed on a Nuclear Pharmacy License
  - Authorized Nuclear Pharmacists (ANP)
  - Requirement for BOP License/Permit
- In some cases, cyclotron operators or engineers have been added.

Pharmacy vs. Manufacturing

- In addition to RAM Licensing, the State Board of Pharmacy has regulated the "compounding" of PET drugs
- This has lead to requirements that a Pharmacist be present in the designated Pharmacy space
- With the pending regulation by the FDA, the Pharmacy Rules will not apply to the "manufacturing" of PET drugs (in some cases the state agency having oversight of a State manufacturing permit is also the BOP)

Pharmacy vs. Manufacturing

This will have implications for RAM Licensing and Boards of Pharmacy

- Under Manufacturing, Pharmacists will no longer be required since it will not be a Pharmacy
- However, in order to dispense a prescription and distribute doses, a separate Pharmacy will have to be present.
- The current physical space will have to be segregated

Pharmacy vs. Manufacturing

The New Regime

Manufacturing	Rx and Distribution
FDA/State regulation	BOP regulation
Cyclotron and Chemistry	Dose dispensing
Drug Vial	Individual syringe or vial

The New Regime

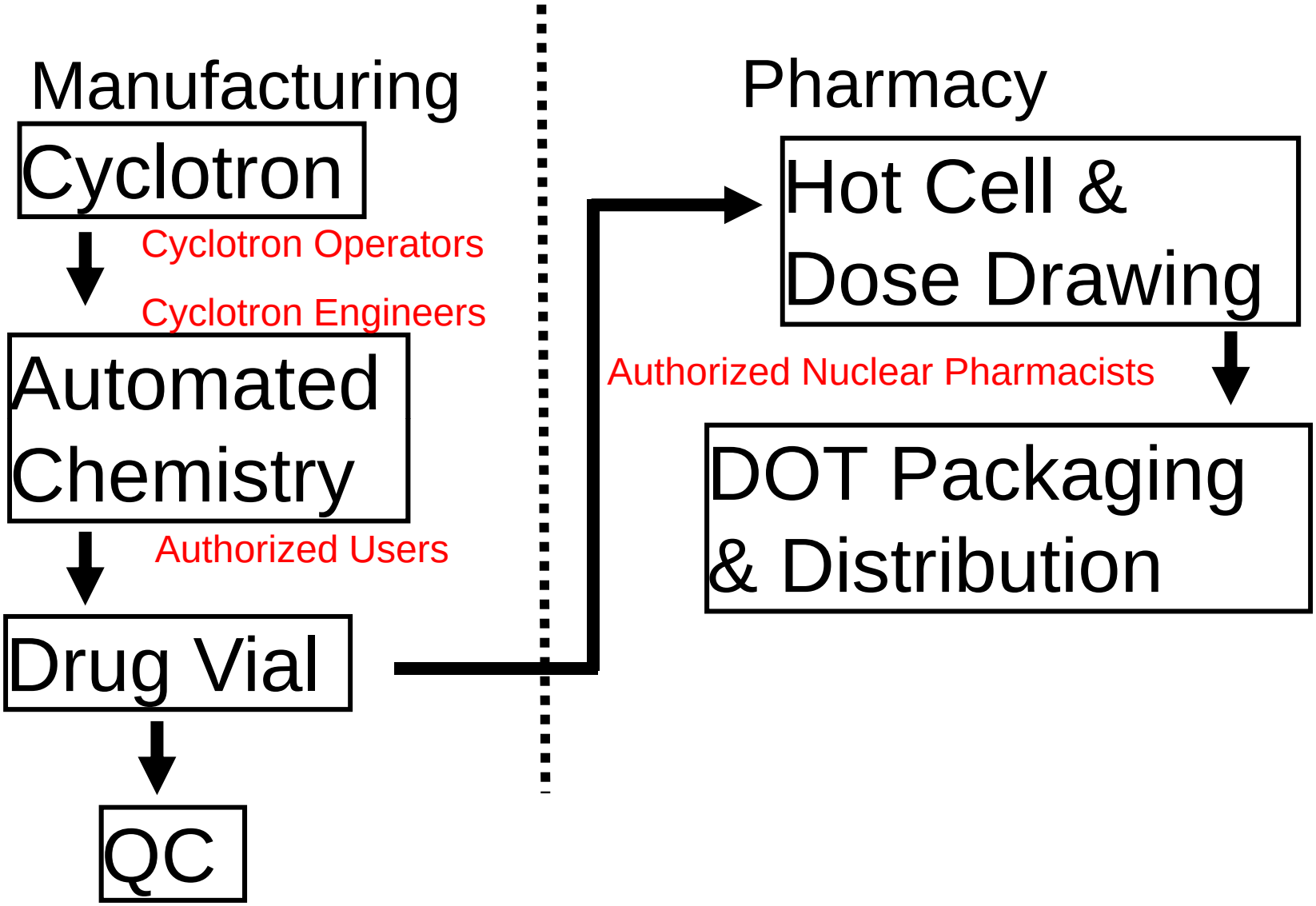
- Manufacturing
  - Pharmacists not required
  - ANPs not required
  - Authorized User status
  - Cyclotron Operator status (State)
  - Cyclotron Engineer status (State & NRC/Agreement State)
  - Separated from Pharmacy Operations

The New Regime

- Pharmacy and Distribution
  - Pharmacists are required
  - ANPs required
  - Cyclotron and chemistry not covered
  - Separated from Manufacturing Operations

The New Regime

- RAM Licensing
  - Two separate Operations where there is currently only one
  - How will this affect RAM Licenses?
    - Authorized User status (without ANP requirements) will be needed
    - Clear rules on Cyclotron Operators and Engineers will be needed


Manufacturing
Cyclotron
Cyclotron Operators
Cyclotron Engineers
Automated Chemistry
Authorized Users
Drug Vial
QC
Pharmacy
Hot Cell & Dose Drawing
Authorized Nuclear Pharmacists
DOT Packaging & Distribution

A Well Designed Manufacturing Space

A Well Separated Pharmacy Space

Authorized Individuals

- Authorized Nuclear Pharmacists
  - Existing Rules
  - NUREG-1556, Volume 13
  - Can be RSO
- Authorized Users
  - Operate Cyclotron
  - Work on Cyclotron and Chemistry Modules
  - Produce Radioactive Material
  - Manufacture Radiopharmaceuticals and Radiochemicals
  - Perform QC testing
  - Other work with Radioactive Material