

Building and Operating a PET Radiopharmaceutical Centre

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Positron Emission Tomography (**PET**) Cameras require an efficient & effective source of **PET** radioisotopes.

What are the challenges?



Discussion Points

- Cost-effectiveness in radioisotope production?
- Physical location of radioisotope production centre
- General design considerations for centre
- Selection of major equipment; options & challenges
- The infrastructure construction phase
- Installing & commissioning equipment
- Operating the Production Centre

Cost-effectiveness PET isotope production?

Facts

- Product is unusable after 8 hrs (activity drops by half every two hours)
- It is highly radioactive and needs specialised & rapid transport
- Costs are relatively less dependent on labour
- **F-18** products (inc. FDG), are the only *effectively transportable PET* products

Costs strongly influenced by:

- Depreciation of capital equipment & support infrastructure
- Costs of consumables (“heavy” water, radiopharmaceutical synthesis kits)
- Operating in a regulated environment (radiation, GMP)

- **Cost-effectiveness** strongly influenced by
- Daily numbers of patient doses delivered to PET cameras (*economy of scale*)

Considerations

- Need to know number of PET cameras (patient doses) that can be supplied from FDG source - *all customers (cameras, patients & society) benefit from economies of scale*

Location of Production Centre

Facts

- Product must be delivered to customer within <5 hours; sooner is better!
- Production schedule is usually early morning - air transport regulations (?delays) are important, if moving product >300km

Considerations

- If supplying a city or region with several PET cameras, then close to a highway
- If supplying nationally or internationally, then close to airport
- In association with a major hospital with a PET/CT camera. Then non-F-18 PET (eg; C-11) possible

General design of Production Centre

Requirements

- **Heavily shielded bunker** with maze access, control room, plant rooms
- **Cyclotron** for production of radioisotopes, most particularly Fluorine-18.
- **Radiochemistry laboratory** with general lab, air lock, QA room & “sterile” room. Lab linked to bunker by shielded trench for product & services
- **Service Connections** to chilled water, multiple gas bottles, purified water, high pressure air, ~40kVA power, airlocked rooms, *significant* air conditioning
- **Radiation surveillance** of lab, bunker air emission, external bunker walls

Considerations

- Must satisfy local radiation safety regulations; in partnership with **Government Radiation Regulator**
- Should be physically enabled to operate when required by regulations, to produce product under **Good Manufacturing Practice** (if not *now*, then *soon*).
- Must plan for 20+ years operational life, and expected production increases; unlikely *cyclotron* or *hot-cell* technology will be significantly altered

Preliminary radiation measurements & calculations

Calculations:

- * PET suite shielding calculations (γ) *
- * bunker shielding calculations (n & γ)
- * air activation (eg; Ar-41)
- * long-term activation of bunker walls
- * activation of cyclotron components

Measurements:

- * radiation dose to areas adjoining PET suite from bolus of FDG
- * radiation dose outside bunker (including measurement of attenuation by earth) from neutron source inside bunker

The Perth site: Neutron attenuation measurements



Selection of major equipment; options & challenges

Note: “Perth project” is only one of many operational solutions

Key equipment

- Cyclotron
- Radiochemistry hot-cells (which? What type/ How many?)
- FDG radiopharmaceutical synthesis units (Which? How many?)
- FDG Product QC equipment
- Radiation surveillance technology & personal monitoring
- Equipment to “drive” GMP sterile, controlled laboratory environment (Hepa filters, differential room pressures...)
- Services (electricity, chilled water, high pressure air, specialised gases.
- General laboratory consumables

Equipment selection: cyclotron

- Four well known manufacturers; three with reasonable southern hemisphere technical support. Others exist.
- Choice of **manufacturer** depends on;
 - Available space in bunker
 - Manufacturer's reputation for post sales service
 - Your objectives; commercial production vs production + R&D
 - Which radioisotope(s) are important? (in addition to Fluorine-18).
Depends on where your customers are geographically located
 - Who will do your repair, maintenance, and at what cost?
- Choice of **model** depends on;
 - Planned volume of production
 - ?Plans for "innovative" (ie; non Fluorine based) production; 5-10 yr-time frame). *FDG the main current economically viable product*
 - Number of cameras to be supplied
 - Available targetry for F-18 production (*see later*)

Product range determined by radioisotopes that can be produced

Radioisotope	Reaction	T _{1/2} (min)
¹⁸ F	¹⁸ O (p, n) ¹⁸ F	110
¹⁵ O	¹⁴ N (p, n) ¹⁵ O	2
¹³ N	¹⁶ O (p, α) ¹³ N	20
¹¹ C	¹⁴ N (p, α) ¹¹ C	10

- ◆ The bombarding proton or deuteron is absorbed in the target nucleus forming a compound nucleus which subsequently decays by positron emission.
- ◆ Different targets are required in order to produce different radioisotopes. They *all* have short half lives.
- ◆ Time does not permit *other* interesting and potentially commercial possibilities (I-123, I-124, Cu-64, Y-86)

The WA choice, (“medium-energy”) based on production *plus* R&D needs

- Supply to 2.5M population
- Potentially to >5 PET cameras, within 30 km radius
- Development of new products, including solid-targetry based radioisotopes



Cyclotrons; comments (A)

- Cyclotrons more difficult to maintain a high delivery response (>96%) than other medical systems, because the technology requires high-precision, high-energy acceleration of charged particles
- However, it *is* possible to produce a 98% delivery response, with skilled staff (eg; Perth)
- 3/4 major manufacturers have generally good customer records
- 1/4 does not produce “true” medium energy cyclotron
- There are *other* vendors (eg Japan, France); ? increased risk because fewer operational units worldwide
- **Manufacturer advice** on building infrastructure, assistance with shielding calculations, regulatory etc. focusses on “fixed” solutions. *Better suited for “greenfield” sites.*

Cyclotrons; comments (B)

- **Choice of targetry for cyclotron** depends on planned volume of F-18 production, and desired reliability of supply. *Need two F-18 targets (large & small)*
- **Detailed site planning** can basically be done “in-house”, by the medical & radiation physicist professional community.
- **Repair & maintenance of cyclotron:** expensive - around 10% of capital cost - significant efficiencies possible with majority “in-house” maintenance.

Example; Cyclotron - IBA Cyclone 18/9

- ▶ Negative Ion Source Injection System
- ▶ Vacuum System
- ▶ RF Assembly
- ▶ Extraction
- ▶ Target Systems

Beam Energy	Protons	18.0 MeV
	Deuterons	9.0 MeV
Beam Current (on target)	Protons	80 μ A
	Deuterons	35 μ A
Beam Dimension (on target)	Gaussian profile	10 x 10 mm
Simultaneous Beam Extraction		Standard
External Beam Line		Licence to Develop Based on commercial design
Targets		F-18, F ₂ -18, C-11, N-13, O-15
Radiofrequency		42 MHz
Magnet		4 sector, 1.3 T

Equipment selection: hot-cells

- Two reputable manufacturers.
- Choice of **manufacturer** depends on;
 - cost and timeframe for delivery
 - how readily the modules satisfy GMP requirements (see later)
- Choice of **units & numbers of units** depends on;
 - your planned volume of production
 - your ?plans for “innovative” (ie; non Fluorine based production; 5-10 yr-time frame). *FDG is the main current commercially viable product*

Equipment selection: FDG synthesis units

- Four reputable manufacturers.
- Choice of **manufacturer** depends on;
 - cost and timeframe for delivery
 - how readily the modules satisfy GMP requirements (see later)
 - reputed efficiency & reliability
 - cost of disposable synthesis kits
- Choice of **numbers of units** depends on;
 - your planned volume of production. Need at least two FDG synthesis units

Equipment selection: Radiopharmaceutical Laboratory: *Perth*

For production

- Two hot-cells
- One IBA ^{18}F -FDG synthesis module
- One GE ^{18}F -FDG synthesis module
- One robot dose dispenser (*not obligatory*)

These located within GMP environment

For R&D

- *Four hot-cells*
- *One development ^{18}F -FCh synthesis module*
- *One development ^{18}F -FMISO/FLT synthesis module*



Hot-Cells in Clean Room: *Perth*



Automatic dispensing inside hot-cell



Equipment selection: Product QC validation

- Numerous reputable manufacturers. QA equipment industry is very mature; most apparatus are required in other types of laboratories (eg; general analytic etc)
- Choice of **manufacturer** depends on;
 - cost and timeframe for delivery
 - local availability of backup support (maintenance, spares etc)
 - reputed efficiency & reliability
 - actual cost of maintenance

QC equipment; FDG product validation

- Gamma Spectrometer
- Thin Layer Chromatography
- High Pressure Liquid Chromatography
- Double distilled water plant for HPLC
- Dose Calibrators
- Gas chromatograph *(not needed for FDG)*

- *All QC equipment is contained in a QC Room situated within the GMP Clean Room environment. (This is **not** mandatory, since sample product entering QA room is not exported to the customer)*



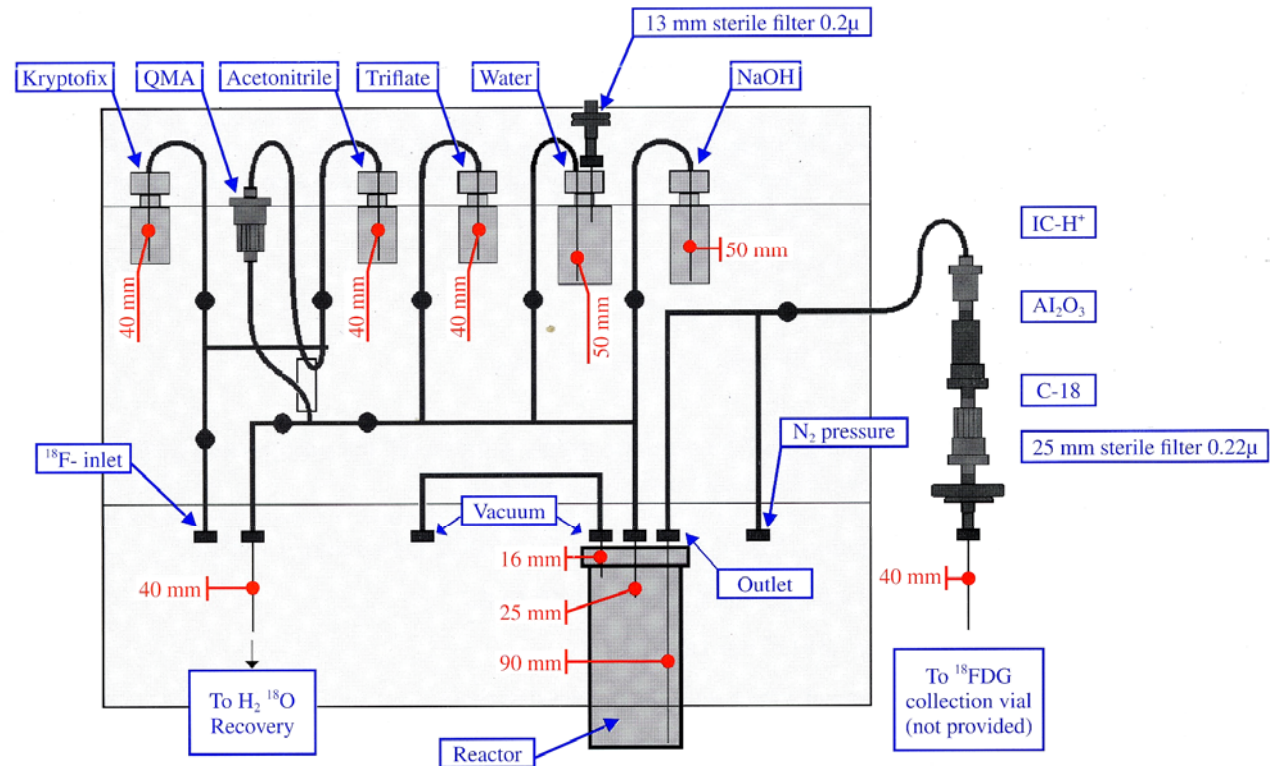
Laboratory Production & QA equipment: comments

- Hot-cells *could* be produced by local manufacturers, but the GMP requirement creates challenges
- Supply of hot-cells from overseas can be a “bottle-neck” to project completion
- We found 1/2 of suppliers much more responsive; good post-sales service
- Getting the product trenches correctly placed in lab floor, wrt to hot-cell placement is *critical*
- The *reliability* of FDG module is critical, followed by EOS *efficiency*. Manufacturers over-emphasise the latter. Demand that they show you *actual production figures from more than one customer*.



FDG synthesis process

- moderately complex
- automated (*very limited real-time intervention possible*)
- expensive, disposable technology



The building infrastructure (A)

- **Contact your Government Regulator** *early*, and obtain their radiation emission (including “stack”) limits. The air in a bunker becomes radioactive (eg; Argon-41), and must be emitted in a prescribed manner
- **Concrete** is a major cost (\$AUD300k+) in our case, even with substantial existing shielding. Boronated concrete with high water content is best, but you can always solve the shielding problem with *more* concrete. The biggest challenge is in an existing building
- **Shielding** is all about stopping *neutrons*, hence the advantage of high water content concrete.
- **The GMP environment** requires particular expertise (see next slide), but you will find this in food and pharmaceutical & ?microchip fabrication industries - *Hepa air filtering, differential pressure between rooms, airlock, sterile surfaces, temperature control, microbial and particle monitoring, laminar flow environment between operator and product*

The building infrastructure (B)

- **Constant vigilance** is required in monitoring the construction of a GMP lab
- **The control room** must be *adequately air conditioned*, with “computer” floor). Large heat loads are generated by the RF generator that accelerates the beam, and thermal cut-outs can shut down Cyclotron.
- **Other services** such a chilled water, air pressure, purified circulating water, electric power are standard.
- **A “green field” site** significantly simplifies the design and construction
 - Bunker can be underground, constructed of prefab concrete
 - GMP lab can be within steel shed - attention only to internal surfaces

Sterile manufacture; laboratory requirements

Surface Finishes

Smooth/Prevent Particle Shedding/
Cleanable Recesses/Service Ducts

Airborne Classification

- ◆ 0.5 μ m/5 μ m particle /m³
 - ◆ Room Air Change Rates
-

Microbial Contamination

Air Sample/Settle Plates/
Contact Plates/Glove Print

Clothing/ Personal Grooming

Body Suit/Head Gear/
Gloves/Footwear

Insertion of bunker ceiling & cyclotron

Shows potential use of *prefab concrete blocks* to create an *inexpensive underground bunker*



Perth site: outside completion



Installing & commissioning equipment

- **Cyclotron should be installed as soon as possible** following delivery. Requires accurate project critical path
- **Be vigilant** about “signing off” on various stages of testing.
- **Negotiate exact terms of reference** for training of all personnel, and demand (before the contract is signed) that manufacturer honours this in writing. *Manufacturer will tend to reduce the training time if any other delays occur.*
- **Before sending staff overseas**, require that they read up extensively on the equipment, and formulate questions before they go.
- ***Familiarity with equipment is absolutely “mission-critical”. Do not believe any manufacturer who says that the technology is “turnkey”.***

Operating a PET isotope production centre (A)

- **Training**, including in a “real” production environment
- **Documentation of standard operating procedures**
 - Equipment safe operation
 - Equipment maintenance (manufacturer and “in-house” manuals)
 - Radiation safety (personal & environmental)
 - GMP (or GLP) sterile environment - monitoring & maintenance
- **Accumulating & recording “in-house” knowledge.** Expect to accumulate “in-house” information, and document this, particularly for cyclotron.
- **Record keeping.** Keep records of production and personal radiation dosimetry for legal and warranty reasons
- **Logistics.** If maintaining equipment “in-house”, beware that spare parts can take significant time (~3 months) to be delivered

Operating a PET isotope production centre (B)

- **FDG synthesis boxes.** Production problems have essentially been of a *mechanical* nature:
 - transfer failures to dispensing area, due to blockages
 - valve failures
 - filter blockages
- **Radiation safety.** The highest radiation doses to staff will occur in first year ($>5\text{mSv/yr}$ for *production & maintenance staff*). With vigilance and good analysis of work practices (?using electronic monitors), it is possible to lower this by 50% or more
- **Multi-skilling.** Production staff should have significant knowledge of maintenance problems, in order to take immediate action during a run. (Production & maintenance duties overlap significantly)

Operating a PET isotope production centre (C)

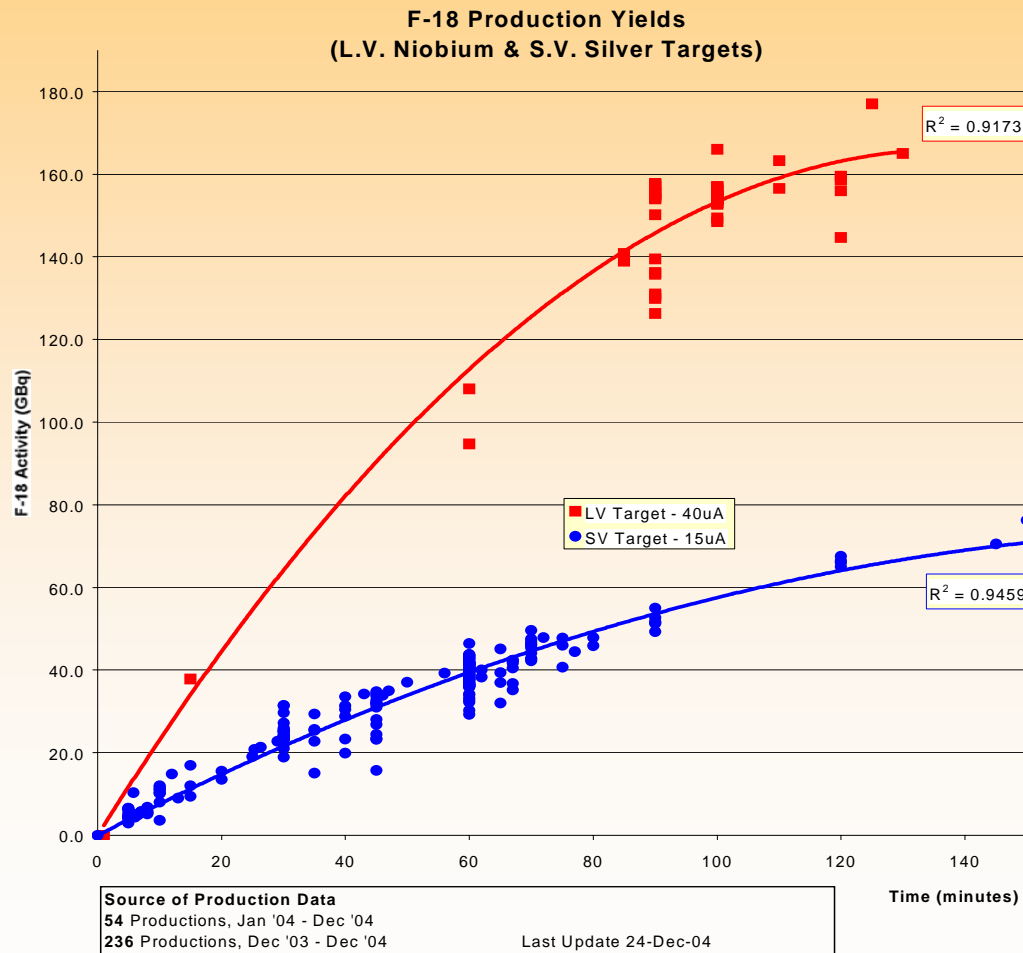
- **Maintenance strategy.** Maybe a good approach is to negotiate a limited maintenance contract with the manufacturer, allowing your own “in-house” staff to perform (say) 60-80% of the work.
- **Steep learning curve!** In Perth, many equipment failures (line blockages, failure of valves, stripper and window breakages, loss of vacuum, inadequate operation at high current, optimisation of FDG synthesis modules, routine maintenance and adjustments) have been overcome, and strategies developed. Manufacturer has been of some but not major importance in solving these
- **Briefing of general public.**
 - Cyclotron is *not* a nuclear reactor
 - Medical radioisotopes save lives
 - The environment is not affected

Operating a PET isotope production centre (D): costs minimisation

- **Consumables are expensive.** Need to maximise number of patient doses of FDG per run.
 - “Heavy water” (MYR**750** per run).
 - Disposable FDG synthesis kit (MYR **1000** per run)
- **Reduce delivery time** of radiopharmaceutical to absolute minimum
- **Good SOPs**, because radioactive accidents or equipment malfunction cause delays, and this industry is time-critical.
- **Multi-skilling** of production & maintenance staff. Staff should be prepared to work irregular hours
- **Organising customers** to maximise number of patient doses per cyclotron run

F-18 production depends on target choice & time

Perth "F-18" targets



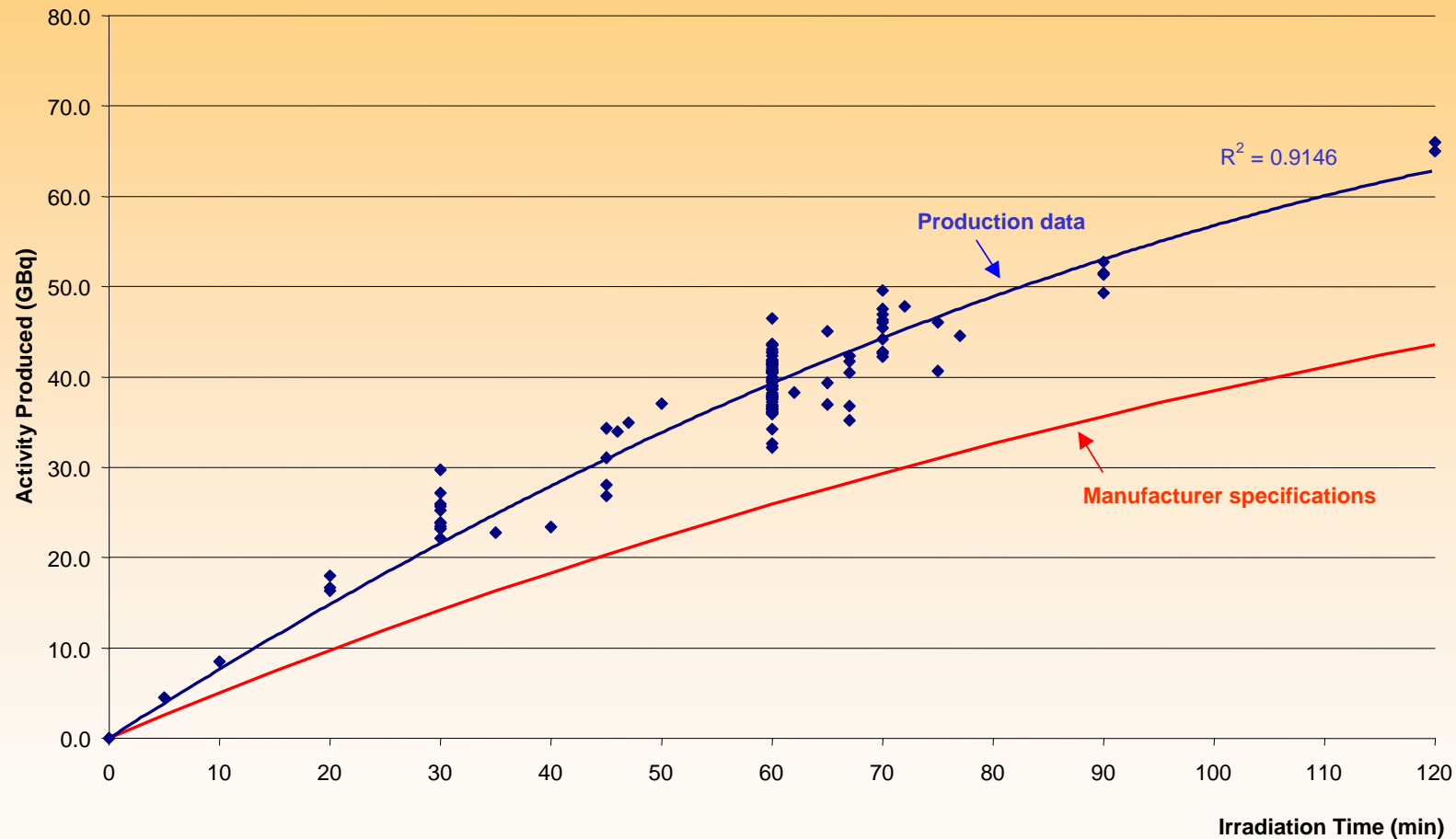
← 2 ml niobium target
(200GBq EOB)

← 0.5 ml silver target
(80 GBq EOB)

10³ GBq targets are coming!

Cyclotron F-18 production performance: Perth experience

F-18 Production Yields
(0.5ml silver target @ 15 μ A, E.O.B.)



Source of Production Data:
168 productions, Jan '04 – Aug '04

Last Update 09-Sept-04



Radiation protection in a PET Centre

Standard radiation protection dosimeter, detects gamma and neutron radiation

- Measurement Range: 10 μ Sv - 10Sv
- Energies 5keV - 40Mev



Radiation dosimetry: isotope production staff 2004

category of worker	Total Year Dose (mSv)
Maintenance	1.15
Production	0.79
Production & Maintenance	3.42
Maintenance	2.24
Maintenance	1.71
Production & Maintenance	1.44
Prod. Chief Radiochemist	1.49
Research	2.74
Production & Maintenance	1.69
Production	1.84
Principal Medical Physicist	0.18
Head of Department	0.10

- Less than 5 mSv/yr is acceptable maximum in Perth Centre.
- 20 mSv/yr is regulatory limit (ICRP 60)

Real-time electronic dosimeters can provide insight into relatively high dose work practices

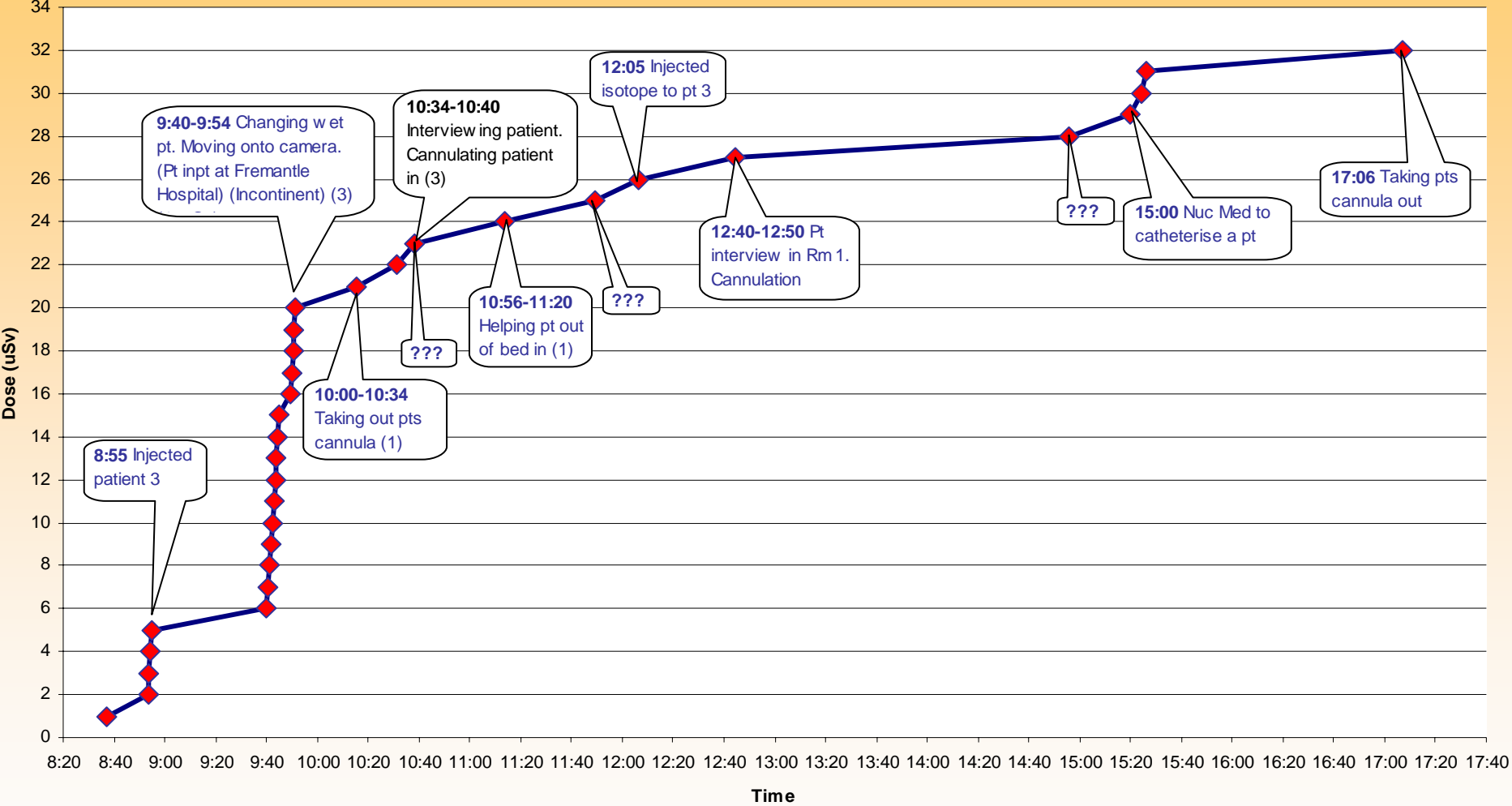


Log of time and task

Logs time and dose

LOG OF TASK AND DOSE

Radiation dose to Nurse B



Summary: PET radiopharmaceutical production

FDG production is

- a complex manufacturing process;
 - in a highly specialised & environmentally regulated facility;
 - creating a highly radioactive liquid product
 - that requires rapid and accurate QC &
 - specialised handling, packaging & transport;
 - has a commercial lifetime of only a few hours;
 - requiring rapid & on-time delivery to customers
- *However, next day there are no residual radioactive or toxic products. Completely safe environmental outcome!*

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The RAPID Team

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Thank you for your attention.
We welcome your comments & questions



Some of the RAPID staff (most have non-PET duties as well)
Mr Yves Jongen, Cyclotron Designer (IBA), is at centre