

# FDG Synthesis Modules

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## Pre-installation Information & Site Requirements

- ⌘ Radiation Safety - all automated chemistry modules must be housed in a ventilated, shielded **hot cell**
- ⌘ eg Comecer, Von Gahlen,
  - ☑ Amercare



Hot Cell for automated production of radiopharmaceuticals

## Comecer BBS6-75-6

### ⌘ Specifications

- ☒ Dimensions (L x D x H)
- ☒ outside 1650 x 900 x 2400 mm
- ☒ inside 600 x 500 x 600 mm
- ☒ Shielding , 75mm Pb, also between units
- ☒ Wt = 5100 Kg
- ☒ Recommend Pb glass window (~75mm Pb)
- ☒ Airtight, acrylic glass & pneumatic rubber seals
- ☒ Constant ventilation discharge (>30 Pa, >30 changes / hr) ie. Grade B
- ☒ Filtered air in, activated charcoal filtered air out
- ☒ Stainless steel finish
- ☒ Swag-loc gas fittings, 4 power outlets
- ☒ Swing-out tray
- ☒ Drawer for laptop computer
- ☒ 2 lights in each compartment

## Gas Requirements

### ⌘ Compressed Air

- ☒ Free of any particles, water & air (medical grade)
- ☒ 6 - 8 Bar (never <4 Bar)
- ☒ External tap on hotcell
- ☒ Internal pressure regulator (external for IBA)
- ☒ IBA -heater unit - 35 Liters/hour

### ⌘ Nitrogen

- ☒ Quality is critical
- ☒ UHP & Dry
- ☒ 2 - 10 Bar
- ☒ External tap on hotcell
- ☒ Internal pressure regulator (eternal for IBA)

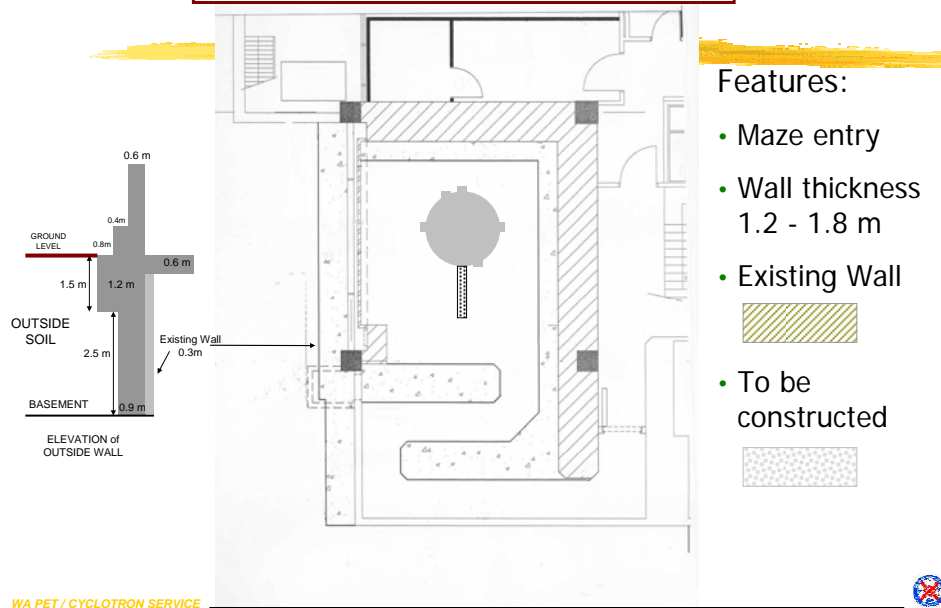


# Transfer Lines

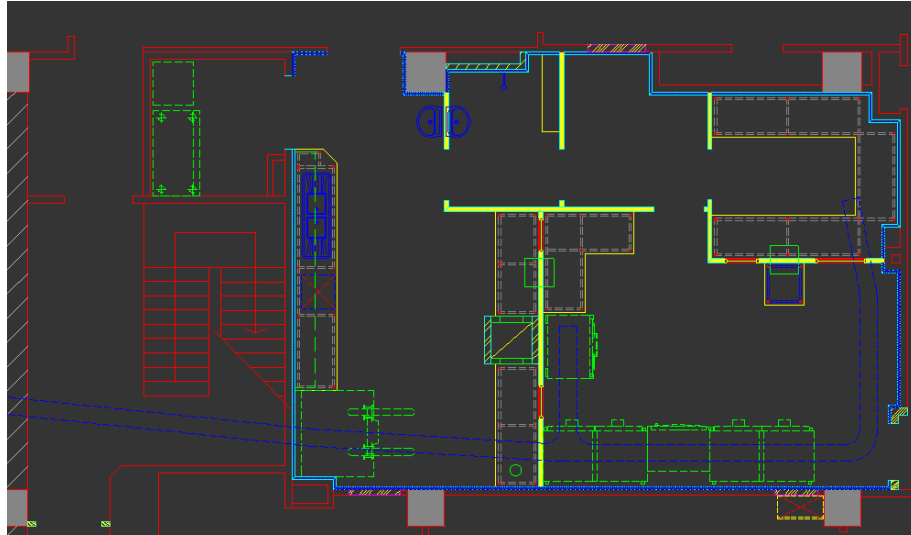
## ⌘ Cyclotron to hot cells

- ☒ Teflon v's Polyethylene (PE) v's PEEK
- ☒ F-18, radiation burden
  - ☒ change every 6 months
  - ☒ Spare lines
- ☒ Diameter 0.86mm
- ☒ Transfer gas - UHP Helium (2-4 Bar, usually 1.8-2)
- ☒ Outlet to LAF hot cell
- ☒ Waste collection

## Bunker Plan-View



## Radiopharmaceutical Laboratory



WA PET / CYCLOTRON SERVICE



## GE Module

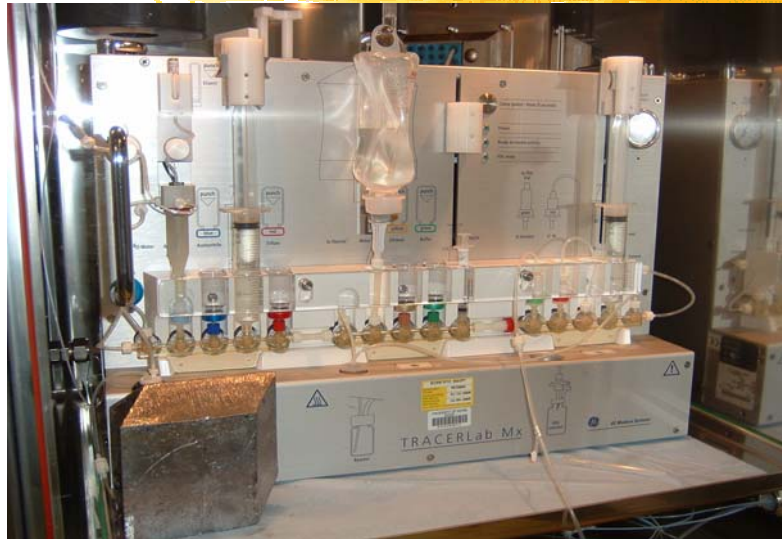
### ⌘ TRACERLab MX FDG

- ⊞ Module (L x D x H) 564 x 362 x 420mm
- ⊞ Weight 50kg
- ⊞ Free space, 2cm sides, 6cm top, 5-10 rear

### ⌘ Features

- ⊞ 4 gamma detectors (QMA, R/vial, C-18, final vial)
- ⊞ Laptop - user friendly interface
- ⊞ Remote control box
- ⊞ Efficiency  $50 \pm 5\%$

## GE TRACERLab MX FDG Module

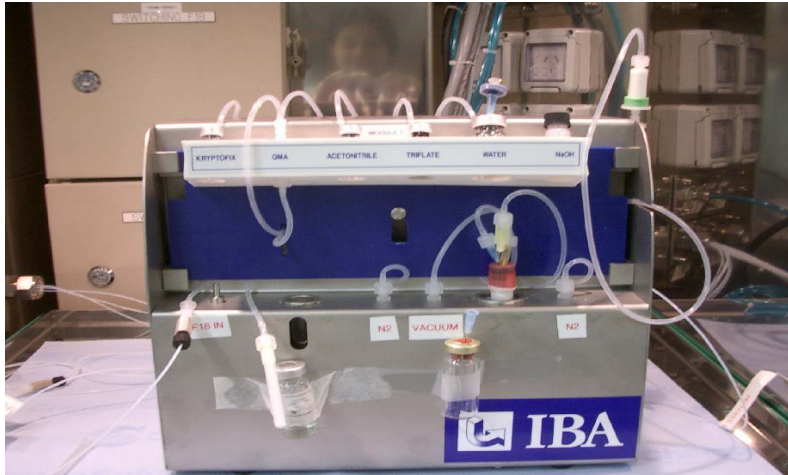


## IBA FDG Processing Module

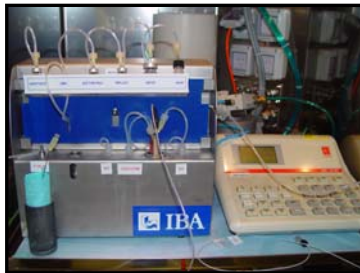
### ⌘ Components

- ☒ Module (H X D x W)    270 x 180 x 300mm
- ☒ Weight    5.8Kg
- ☒ Control system - Siemens Programmable Logic Control (PLC), outside of hot cell
- ☒ Gamma detector (1, on reaction vial)
- ☒ Laptop
- ☒ Efficiency  $45 \pm 5\%$

## IBA FDG Processing Module

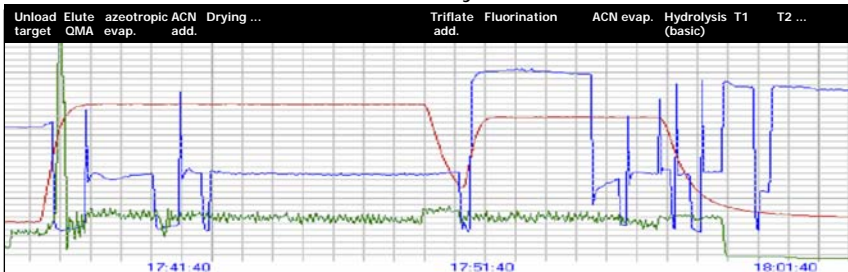


## FDG Module



### Operational Principle

- Pneumatic Pinch Valves
- Single Use Kit (IBA-ABX)
- Transfers by Aspiration
- Temperature Regulation with TWO Set Points
- Basic (NaOH) Hydrolysis
- Total Synthesis Time < 30 minutes



**FDG module synthesis yields typically vary between  $45 \pm 5\%$  E.O.S.**

Production Data from Aug 2004

## IBA's New Module



## Consumables

⌘ O-18 Water, >95% purity (0.20% in nature)

### ⌘ Manufacturers

- ☒ Rotem
- ☒ Cambridge Isotope Laboratories (CIL)
- ☒ Nippon Sanso
- ☒ Marshall
  
- ☒ Other suppliers eg Medical Isotopes (? Source)
- ☒ GMP O-18

⌘ Price US\$85-90 / gram



## Consumables

### ⌘ Reagents

### ⌘ Suppliers

☒ Advanced Biochemical Compounds (ABX)

☒ IBA (ABX)

☒ Rotem

⌘ Chemical v's pharmaceutical grade

⌘ List ; Mannose triflate\* (25, 40, 75mg), kryptofix  
K2.2.2/acetonitrile/ethanol/sodium hydroxide  
(syringe)/citrate buffer/water for injection

⌘ \* refrigerate

## Consumables

⌘ Reagent kit price - ABX €55 [Product No. K-150TM]

⌘ IBA €200\* [Product No. K-250IBA]

⌘ Rotem US\$51 [Product No. KT50]

### ⌘ Cassettes (sterile)

☒ GE A\$153 [Product No. P5150ME]

☒ Tri-Star A\$147

☒ Rotem A\$ ?

☒ \*Total cost

# Consumables

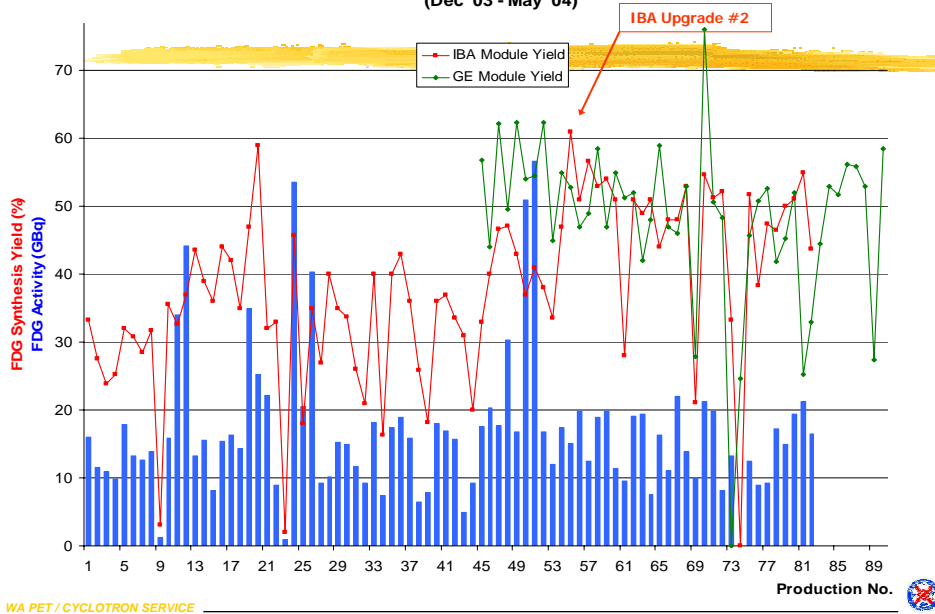
## ⌘ Accessories (GE)

☒ Conical reservoir, 25mL sterile vial, 30mL syringes (2), 19G needle, Sep Pak light Acell Plus OMA cartridge, GS Cathivex sterile filter, FG Millex sterile filter, Millex-25 sterile vent filter

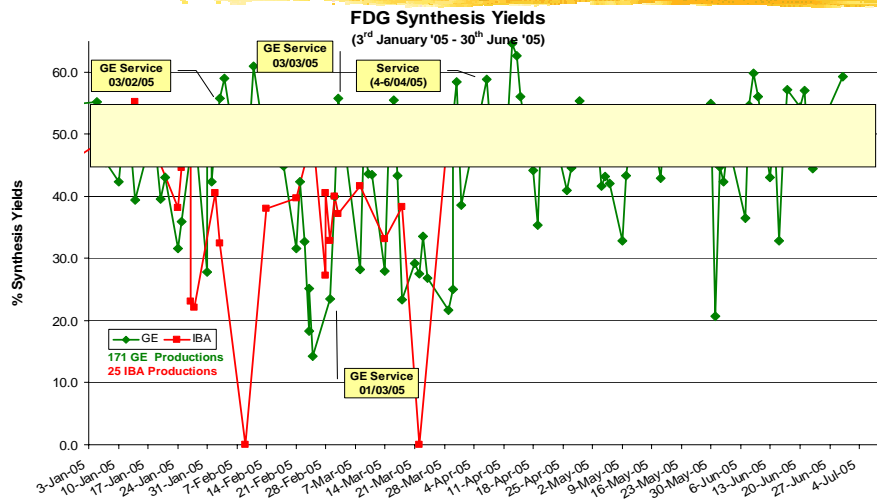
☒ Product No. P5150MF                      A\$47

# FDG Production Performance

FDG Module Production Data  
(Dec '03 - May '04)

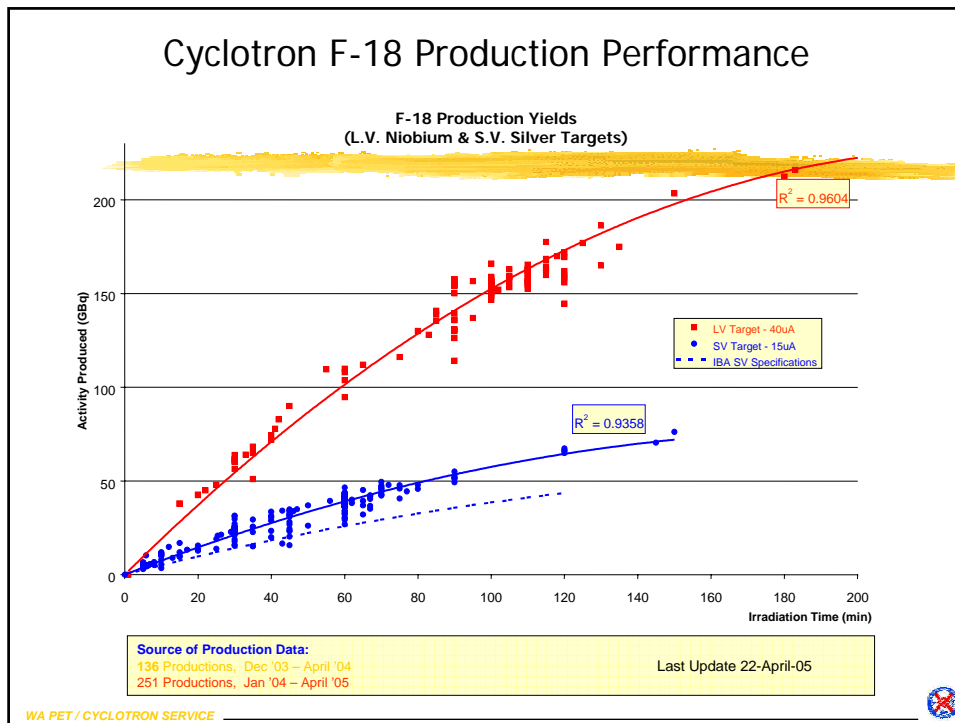


## FDG Production Performance



## Principles of Production

Radioisotope	Reaction	T <sub>1/2</sub> (min)
<sup>18</sup> F	<sup>18</sup> O (p, n) <sup>18</sup> F	110
<sup>15</sup> O	<sup>14</sup> N (p, n) <sup>15</sup> O	2
<sup>13</sup> N	<sup>16</sup> O (p, α) <sup>13</sup> N	20
<sup>11</sup> C	<sup>14</sup> N (p, α) <sup>11</sup> C	10



## Principles of FDG Production

⌘ Irradiate O-18 (0.5mL SV, 2mL LV target)

- ⊞ irradiate up to 2 hours
- ⊞ transfer  $^{18}\text{F}$  bolus via transfer line to hot cell
- ⊞ load onto automated chemistry module
- ⊞ start module, duration ~26 minutes

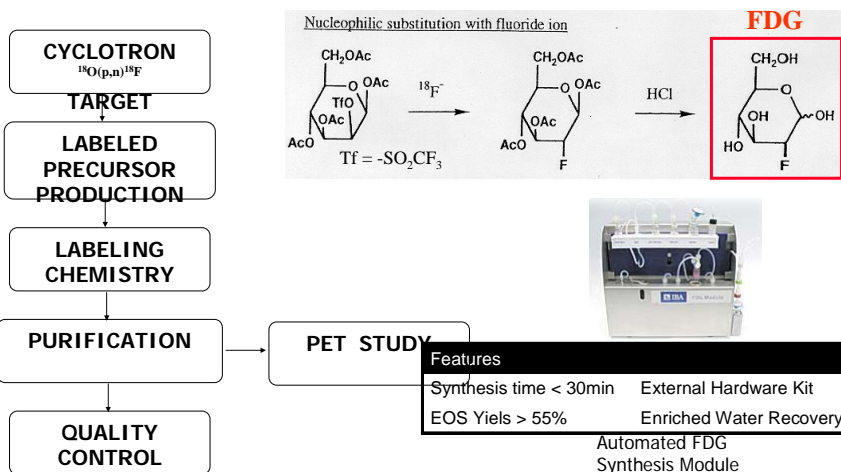
⌘ 1st synthesis 1976 of 2-deoxy-2[ $^{18}\text{F}$ ]fluoro-D-glucose, BNL.



## Radiopharmaceutical Production of FDG

Method

<sup>18</sup>F Labelling Chemistry



## Radiopharmaceutical Production of FDG

- ⌘ <sup>18</sup>F ions are trapped on the anion exchange cartridge (QMA)
- ⌘ O-18 water passes through and retained (re-use)
- ⌘ <sup>18</sup>F washed off the QMA into the reaction vial by K222/acetone nitrile mix
- ⌘ Solvents dried (@95° C) in the reaction vial (under nitrogen flow & vacuum)
- ⌘ Reconstituted mannose triflate added to dry residue in the reaction vial
- ⌘ Nucleophilic reaction occurs (@85° C). Critical step
- ⌘ Water flushed through reaction vial
- ⌘ [<sup>18</sup>F]fluoro-tetra-O-acetyl-D-glucose trapped on C-18 cartridge, <sup>18</sup>F ions to waste
- ⌘ Alkaline hydrolysis [NaOH] (to remove protective acetyl groups) occurs on C-18 cartridge to form <sup>18</sup>F FDG
- ⌘ Alkaline FDG neutralised by citrate buffer and not retained on C-18
- ⌘ FDG solution purified by 2nd C-18 cartridge, trapping hydrolysed compounds
- ⌘ FDG solution then passes through a Alumina N cartridge to remove remaining free <sup>18</sup>F ions
- ⌘ Finally, FDG solution passes through a sterile 0.22µm filter into a sterile collection vial

## GE TRACERLab MX FDG Module



## FDG QC



## FDG QC

### ⌘ European Pharmacopoeia, 3rd Ed, Supplement 2001

- ⌘ 1) Label inspection - correct batch #, product, date
- ⌘ 2) Visual inspection - clear, colourless, particulate free
- ⌘ 3) Radiochemical purity - (TLC) - >95% <sup>18</sup>F FDG
- ⌘ 4) Isomeric purity - (HPLC) - >90% <sup>18</sup>F FDG
- ⌘ 5) pH - 4.5 - 8.5
- ⌘ 6) Chemical purity - Kryptofix - <100ppm
- ⌘ 7) Residual solvent analysis - (GC)
  - ⊠ Acetonitrile <0.04%

⌘ Pass - before product release for injection

## FDG QC

### ⌘ Retrospective Tests

- ⌘ 1) Radionuclide half-life -  $T_{1/2} = 105-115$  minutes
  - ⌘ 2) Radionuclide purity - (gamma spect) - 0.511 MeV
  - ⌘ 3) Specific activity - concentration
  - ⌘ 4) Bubble point test - passes test
  - ⌘ 5) Sterility test\* - passes test
    - ⊠ Sterility<sup>^</sup>
    - ⊠ Bacterial endotoxins - LAL - <175/VI.U
- ⊠ \* out sourced                      ^ 14 day test

## FDG QC

- ⌘ **HPLC** - Dionex CarboPac PA10 Analytical (4 x 250mm) column (product No. 46110)
- Dionex CarboPac PA10 Guard (4 x 50mm) column (product No. 46115)
  - 10 $\mu$ L sample loop
  - 0.1M NaOH HPLC grade eluate
  - Rate 1mL/min



## FDG QC

- ⌘ **GC** - column HP INNOWAX (30M x 0.53mm)
- ⊗ Agilent part No. AG119095N-123
  - ⊗ 0.5 $\mu$ l sample



⌘ **Thin Layer Chromatography (TLC)**

- ⊗ Merck 25 TLC aluminium sheets, 20 x 20 cm, Silica gel, part No. 1.05553
- ⊗ Solvent; acetonitrile:water (95:5)
- ⊗  $R_f$  ~0.4



## Links

- ⌘ ABX - [www.abx.de](http://www.abx.de)
- ⌘ GE - [www.gemedical.com.au](http://www.gemedical.com.au)
- ⌘ IBA - [www.iba-worldwide.com](http://www.iba-worldwide.com)
- ⌘ Comecer - [www.comecer.com](http://www.comecer.com)
- ⌘ Agilent - [www.agilent.com](http://www.agilent.com)
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- ⌘ CIL - [www.isotope.com](http://www.isotope.com)
- ⌘ Rotem - [www.hyoX18.com](http://www.hyoX18.com)
- ⌘ European Pharmacopoeia - [www.pheur.org](http://www.pheur.org)

Thank you  
Terima kasih