

A GMP/ISO PET Radiopharmaceutical Facility: From Concept to Commissioning

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History

- ⌘ Commonwealth Review Steering Committee, established to oversee PET in Aust.
- ⌘ August 2000 - Report
- ⌘ Recommendations,
 - ☑ funding, distribution of services, clinical applications, camera type

History

⌘ “manufacturers of therapeutic goods must hold a licence obtained through demonstrated compliance with Good Manufacturing Practice (**GMP**) guidelines and codes”

⌘ **TGA** - Therapeutic Goods Administration

GMP Codes

⌘ Aust Code of GMP for Therapeutic Goods, Medicinal Products, August 1990

⌘ EU's **PIC's** - Pharmaceutical Inspection Convention

⌘ 28 countries

⌘ Guide to GMP for Medicinal Products, Jan 2002

⌘ TGA adopts this code, Aug 2002

Therapeutic Goods Administration

Department of Health and Ageing
GPO Box 100
AU - WODEN ACT 2606
Australia



National Pharmaceutical Control Bureau

Ministry of Health Malaysia
PO Box 319
46730 Petaling Jaya
MY - SELANGOR
Malaysia



Definition of GMP

- ⌘ **GMP** - that part of QA which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorisation or product specifications
- ⌘ **Basic requirements**
 - ⊗ All manufacturing clearly defined
 - ⊗ Critical steps validated
 - ⊗ Necessary facilities for GMP are provided
 - ⊗ Clearly written instructions
 - ⊗ Trained operators
 - ⊗ Record keeping, traceable & accessible
 - ⊗ No risk to the product on distribution
 - ⊗ A system available to recall any batch of product from sale or supply
 - ⊗ A system to deal with complaints, quality defects, to prevent re-occurrence

GMP Code

⌘ Code includes,

- ☒ Quality management
- ☒ Personnel
- ☒ Premises & Equipment
- ☒ Documentation
- ☒ Production
- ☒ Quality Control
- ☒ Complaints & Product Recall
- ☒ Self Inspection

⌘ Annexes

- ☒ Manufacture of Sterile Medicinal Products
- ☒ Manufacture of Radiopharmaceuticals
- ☒ Qualification & Validation

Personnel

- ⌘ An adequate number of personnel with necessary qualifications
- ⌘ Specific duties recorded in a written job description
- ⌘ Production manager & quality manager
- ⌘ Training
- ⌘ Personal hygiene

Premises & Equipment

- ⌘ Premises & equipment must be located, designed, constructed & maintained to suit operations carried out
- ⌘ The layout & design aim to minimise risk of errors, permit effective cleaning & maintenance
- ⌘ QC area separate from production area

Documentation

- ⌘ Essential part of QA system
- ⌘ Batch record for every batch produced
- ⌘ Validation
- ⌘ Equipment assembly & calibration
- ⌘ Maintenance, cleaning & sanitation
- ⌘ Personnel matters, including training
- ⌘ Environmental monitoring
- ⌘ Pest control
- ⌘ Complaints
- ⌘ Recalls & returns
- ⌘ Operating procedures for all major items
- ⌘ Log books

Production, QC & Complaints

⌘ Production

- ☒ Production operations must follow clearly defined procedures

⌘ Quality Control

- ☒ QC is concerned with sampling, specifications & testing, as well as the organisation, documentation & release procedures

⌘ Complaints & Product recall

- ☒ Written procedures

Self Inspection

⌘ Self Inspection

- ☒ Audits of all facets at intervals following a pre-arranged programme
- ☒ recorded

Manufacture of Sterile Products

⌘ Grade A (Class 3.5, 100)

- ☒ Laminar flow work station, for aseptic work

⌘ Grade B

- ☒ In Case of sterile preparation, the background environment to Grade A zone

⌘ Grade C & D (Class 350, 10,000) & (Class 3500, 100,000)

- ☒ Clean areas for carrying out less critical stages of the manufacture

Airborne Particulate Classification

Recommended (Acceptance) Limits for Airborne Particulate.

Grade	At Rest		In Operation	
	0.5µm	5µm	0.5µm	5µm
A	3,500	0	3,500	0
B	3,500	0	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	not defined	not defined

Microbial Contamination Limits

Recommended (Acceptance) limits for Microbial Contamination:

Grade	Air Sample cfu/m ³	Settle Plates (diam 90mm) cfu/4 hours
A	< 1	< 1
B	10	5
C	100	50
D	200	100

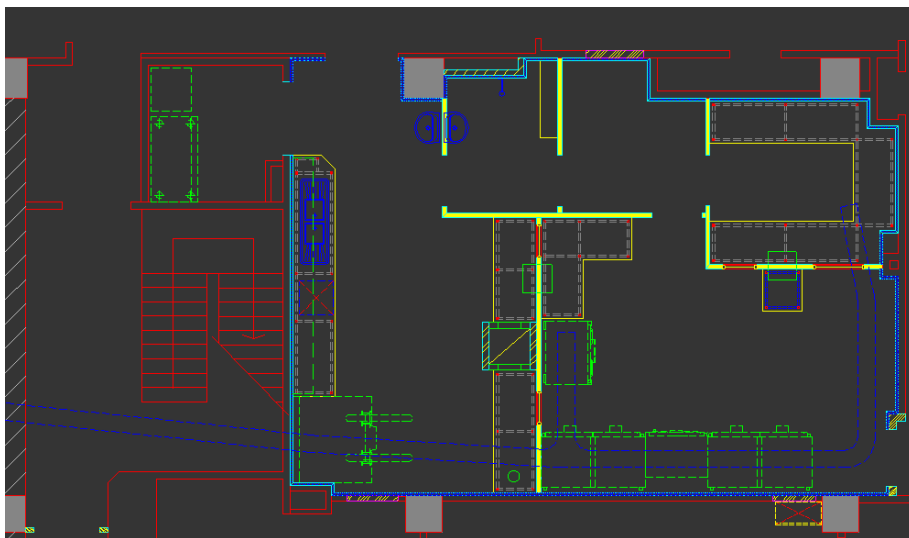
Clean Room Personnel

- ⌘ Minimum number, trained
- ⌘ Personnel hygiene
- ⌘ Clothing (minimum shedding garments)
Gloves, overshoes, hair-nets etc

Clean Room Premises

- ⌘ Clean areas - all exposed surfaces should be smooth, impervious & unbroken
- ⌘ Sinks & drains prohibited in Grade A/B
- ⌘ Airlocks - physical separation
 - ☒ Doors should not be opened simultaneously
- ⌘ Filtered (HEPA) air - positive pressure (10-15 Bar)
- ⌘ Radioactive waste air, no recirculation
- ⌘ Warning system

Radiopharmaceutical Laboratory Design



Hot Cells in Clean Room



WA PET / CYCLOTRON SERVICE



Commissioning

⌘ IQ OQ

☒ Installation Qualification (IQ) & Operational Qualification (OQ)

☒ Manufacturer / supplier IQ

☒ Air change rate, pressure, light intensity, sound level

☒ Owner / operator OQ

☒ eg Particle counts, environmental monitoring etc

Equipment Performance Testing

⌘ Frequency - annual certification

- ☒ HEPA filters 12 months
- ☒ LAF's, hot cells, fume hoods 12 months
- ☒ QC Equipment 12 months
- ☒ Dose Calibrators 12 months
- ☒ Survey / radiation meters 12 months

- ☒ Environmental Monitoring (micro) 1 month
- ☒ Particle counting 3 months

GMP Code & PET Products

⌘ Radiopharmaceuticals - **unique**

- ☒ Testing & release of product by a separate individual from the person who manufactured the batch
- ☒ Radioactive starting materials need not be tested
- ☒ Laminar flow Grade A hot cells located on a Grade D room
- ☒ Filter integrity test should be performed immediately & before batch release
- ☒ Sterility testing should be performed ASAP, ie ~24Hr
- ☒ Endotoxin testing should be performed immediately & before batch release for injection

Radiation Licensing

⌘ Radiation Health Dept of WA

- ☒ Site licence
- ☒ Production & Quality Manager licence
- ☒ Maintenance staff
- ☒ Equipment (cyclotron) licence
- ☒ RSO

Site Licence Submission, July 2003

⌘ Shielding

- ☒ Shielding barrier calculations, definition of constructed walls, bunker maze & floor

⌘ Handling of PET radiopharmaceuticals

- ☒ Production, transport & delivery

⌘ Generation, release &/or disposal of radioactive wastes

- ☒ Air, bunker walls & cyclotron activation
- ☒ Release of radioactive waste

⌘ Radiation monitoring

- ☒ Area & air monitoring
- ☒ Portage monitoring, personnel monitoring
- ☒ Staff training

⌘ Safety Features

Links

- ⌘ PIC's - www.picscheme.org
- ⌘ TGA - www.tga.gov.au
- ⌘ Malaysia - www.bpfk.gov.my

- ⌘ European Pharmacopoeia - www.phEur.org

Quality Management System (QMS)

- ⌘ Medical Technology & Physics, SCGH
 - ☑ ISO accredited 1998 (ISO 9001:2000)

- ⌘ ISO - International Organisation of Standardisation



History

- ⌘ 1950's - aviation industry, standards introduced to deal with inspection, the control & disposal of products not matching requirements
- ⌘ Military standards Inspection System Requirements & Quality Program Requirements
 - ☒ NATA, BS, AS etc
- ⌘ 1980's - ISO formed
 - ☒ Member countries' National Standard bodies
- ⌘ 1987 - ISO 9000 family of standards

QMS Criteria


- ⌘ Basics of good business practice
 - ☒ Set quality goals
 - ☒ ensure customer requirements are understood & meet
 - ☒ Train employees
 - ☒ Control your production process
 - ☒ Purchase from suppliers that can provide quality products
 - ☒ Correct problems & make sure they don't happen again

ISO 9001



⌘ The requirements cover everything from how you plan your processes, to how you carry them out, measure them and improve on them.

⌘ GMP merges into ISO



Thank you
Terima kasih