FACILITIES

HARBANS DHILLON
UNIVERSITY MALAYA MEDICAL CENTRE
KUALA LUMPUR

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Singapore

UNIVERSITY OF MALAYA
KUALA LUMPUR
UM MEDICAL CENTRE

SAFE HANDLING OF CYTOTOXIC DRUGS

- Increased usage of cytotoxic drugs, therefore increased exposure
- No established safe level of exposure to these drugs
- Personnel may be subjected to low level of exposure
- Single event exposure to a single drug is considered less of a hazard than long term exposure to multiple drugs!

SIGNIFICANT REPORTS OF OCCUPATIONAL EXPOSURE TO CTX DRUGS: 1979 - 1999

Falck	1979	mutagens in urine of nurses preparing CTX
Neal	1983	CPM & FU aerosols in air of clinics
Hirst	1984	CPM detected in blood of nurses
Selevan	1985	foetal loss in exposed pregnant nurses
Hemminki	1985	defects in offspring of exposed nurses
Saurelle-Cubizolles	1993	factor in ectopic pregnancies
Sessink	1994	skin contamination a major cause
Valanis	1999	foetal loss, reduced fertility in males, females

OCCUPATIONAL EXPOSURE

- Inhalation of aerosols & drug particles
- Skin absorption
- Needlestick injuries

Resulting from:

- manufacture
- transport of drugs
- drug preparation
- drug administration
- handling, transportation & disposal
- maintenance
- spills

- Worksafe Victoria
- Handling cytotoxic drugs in the workplace

POTENTIAL EFFECTS OF EXPOSURE

- Contact dermatitis
- Cytogenetic abnormalities & mutagenic activity related to biological uptake by exposed personnel
- Alterations to normal blood cell counts
- Excretion of drug or metabolites in exposed personnel
- Abdominal pain, hair loss, nasal sores
- Foetal loss
- NOT appropriate to wait for indisputable evidence of harm

RISK CONTROL

ELIMINATE | REDUCE | ISOLATE

- Establish written policies & protocols
- Effective planning & design of workplace
- Use of "*best practice*" control measures & specialised equipment
- Training & education of employees
- Wearing PPE
- An integrated health monitoring system

RISK MANAGEMENT APPROACH

- Eliminate or reduce risk of illness or injury associated with work
- Generally involves
  - Hazard identification
  - Risk assessment
  - Risk control
  - Evaluation of control measures
  - Consultation
  - Personnel management
  - Training
  - Documentation of activities
  - Regular review of management system

SAFETY ISSUES

PRODUCT INTEGRITY - ASEPTIC MANIPULATION

OPERATOR'S SAFETY

ENVIRONMENTAL CONTROL

FACILITIES FOR CYTOTOXIC DRUG RECONSTITUTION

- Protection of product
  - Use of aseptic techniques
  - Prevent microbial contamination
  - Protect from chemical & particulate contamination
- Protection of operators
  - Negative pressure techniques
  - Use of closed system

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CENTRALISED PREPARATION

- ⬆ Quality of preparation
- Enhances safety of patient
- Economic benefits
- Location:
  - Commonly ~ pharmacy
  - Sometimes located in outpatient oncology department or close to inpatient ward
  - Ease of transport
- Enhanced communication between pharmacy, medical & nursing staff
- Must be under control of pharmacist

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FACILITIES FOR CYTOTOXIC DRUG RECONSTITUTION

- Walls must be lined with a smooth & durable surface
- Stainless doors
- Lighting recessed into the ceiling (top access ~ maintenance)
- Room should contain as few projecting ledges or shelves as possible
- Floors should be poured & seamless
- Vinyl tiles should not be used

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CLASS OF CLEANROOM

- ISO 14644-1 international standard
- Classification takes into account both particulate & microbiological contamination
- For sterile medicinal products, classification referred to as "grade" – EudraLex GMP Annex 1, Vol 4 (pharmaceutical industry)& by the draft PIC/S guidelines (pharmaceutical inspection services controlling hospital pharmacies)

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CLASS OF CLEANROOM

- Designed to provide containment of cytotoxic drugs in the event of
  - failure of biological safety cabinet/isolator
  - spillage
- BSC & compounding aseptic isolator shall be 100% vented to the outside air through HEPA filtration

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AIRBORNE PARTICULATE CLASSIFICATION

	AT REST	IN OPERATION		
GRADE	Maximum permitted number of particles/m3 equal to or above			
	0.5µm	5µm	0.5µm	5µm
A (ISO Class 5)	3500	1	3500	1
B	3500	1	3500 000	2000
C (ISO Class 7)	350 000	2000	3 500 000	20 000
D	3 500 000	20 000	Not defined	Not defined

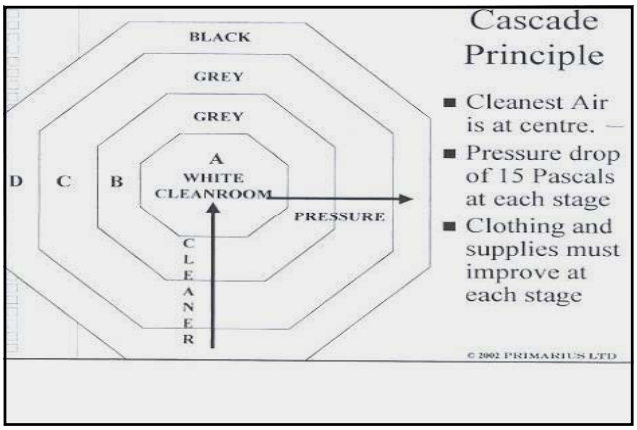
CLASSIFICATION OF AIR CLEANLINESS ISO 14644-1

ISO Class	0.1um	0.2um	0.3um	0.5um	1 um	5 um
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1,000	237	102	35	8	
ISO Class 4 (10)	10,000	2,370	1,020	352	83	
ISO Class 5 (100)	100,000	23,700	10,200	3,520	832	29
ISO Class 6 (1000)	1,000,000	237,000	102,000	35,200	8,320	293
ISO Class 7 (10000)				352,000	83,200	2,930
ISO Class 8 (100000)				3,520,000	832,000	29,300
ISO Class 9				35,200,000	8,320,000	293,000

FACILITY

GRADE D	GRADE C	GRADE B
• Changerooms •Common work area • Cleaner's room • Storage of raw materials	• Anterooms • Cyto change room	• Cyto Suites
60 kPa	45 kPa	30 kPa

- 15 kPa (DP) → - 15 kPa (DP) →



FACILITIES

- Pressure differentials of 10-15 Pascals between adjacent rooms though this does not apply in the case of a negative pressure room
- Air changes
  - minimum of 20 room volumes per hour
  - areas known to generate large numbers of particles need up to 60 volumes per hour
- Temperature control to ensure comfort of personnel of 18-20°C
- Controlled humidity to prevent corrosion & condensation of 30-70%

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FACILITIES

- LFC not suitable
- Class II biological safety cabinets
  - Vertical down flow exhausting vertically from the cabinet & not towards the operator
  - Protects operator, product & work environment
  - Class II (B2) is preferred as it has total exhaust, maintains minimum inflow velocity of 0.34m/s & has HEPA-filtered downflow air
- Isolators types are covered in ISOPP Standards of Practice Section 8 – Ventilation Tools

PASS THROUGH HATCH

- Used to pass items in & out of cleanroom
- MUST have interlocking doors
- Should allow separation of work prepared & work waiting to be prepared

FACILITIES FOR CYTOTOXIC DRUG RECONSTITUTION

- Separate access for personnel & material/equipment flow
- Designed
  - According to workflow
  - Cleaning
  - Room grading & differential pressures
  - Emergency shower & eye washing station
  - Lighting (lux)
  - Room surfaces designed to minimise particle shedding & prevent build-up of particulate matter

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EMERGENCY SHOWER & EYE WASH STATION

MONITORING

- Manometers must be installed to give continuous indication of pressure differential within cytotoxic suite
- Log kept to record daily pressure differential readings, RH & temperature of rooms & refrigerators
- Log kept of cabinets & servicing

MICROBIOLOGICAL MONITORING

- Passive air sampling using settle plates exposed for 4 hours
  - Grade A environment <1cfu/plate
  - Grade B environment 5cfu/plate
  - Grade C environment 50cfu/plate
  - Grade D environment 100cfu/plate
- Active air sampling using biocollectors
  - Grade A environment <1cfu/plate
  - Grade B environment 10cfu/plate
  - Grade C environment 100cfu/plate
  - Grade D environment 200cfu/plate
- Microbiological monitoring of surfaces using contact plates or swabs
  - Grade A environment <1cfu/plate
  - Grade B environment 5cfu/plate
  - Grade C environment 25cfu/plate
  - Grade D environment 50cfu/plate

AIR PARTICLE SAMPLING

- Performed to verify environment reaches specification
- Airborne particle counter is used to measure concentration of particles at designated sizes equal or greater than threshold stated
- Maximum levels depend on the environment grade measured at rest & under normal working conditions

EQUIPMENT IN CYTOTOXIC CLEANROOMS

- Chairs or stools should be ergonomic & must not shed particles
- Must use dedicated equipment & not moved around
- Spill switch to reverse airflow
- Possess good communication system

REQUIREMENTS OF PPE

Class D	Hair/beard covering Normal protective clothing
Class C	Hair/beard covering Clothes gripped at wrist with raised collar Clothing must not shed fibres or particles
Class A/B	Hood or other head covering Mask Sterile, non-powdered gloves Sterile clothing, must not shed fibres or particles Sterile clothing must be capable of retaining particles shed by operator

PERSONNEL PROTECTIVE EQUIPMENT

- Coverall or gown
  - Disposable gown made of non-linting & non absorbent polyethylene-coated polypropylene material
- Head covering
- Closed footwear – cleanroom booties
- Gloves
  - double gloving (nitrile, neoprene latex)
  - long enough to cover cuffs of gowns or coveralls
  - changed every 30 minutes
- Protective eyewear/goggles
- Respirator masks

REFERENCES

- ISOPP Standards of Practice J Oncol Pharm Practice (2007) Supplement to 13: 1-81
- Guidelines for handling cytotoxic drugs and related waste in health care establishments WorkCover New South Wales

THANK YOU