

Design, Operation and Management of GTP/GMP Cell Engineering Facilities

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HCT/P Manufacturing Facilities

- Roles of the GTP facility and the GTP/GMP facility
 - GTP facility
 - Lower risk, basic cell therapy products, minimal manipulation.
 - GTP/GMP facility
 - Higher risk, more complex cell therapy products, more-than-minimal manipulation. More control needed.

GTP Facility

- Lower-risk, minimally manipulated products, such as cryopreserved autologous peripheral blood progenitor cells
- No requirement for cleanroom, but GTP systems needed
 - Organization, personnel
 - Facilities, monitoring
 - Equipment, supplies and reagents
 - Quality program
 - Procedures
 - Process validation, controls, changes
 - Storage, receipt, distribution
 - Tracking
 - Labeling controls, records, complaint file

Cytotherapy 2003 5:289-298

Cell & Gene Therapy 2004 1:16-22

GTP Elements	Specifics
Quality Program	Formal quality program, all aspects of operations, assure GTP compliance
Organization and Personnel	Personnel qualification, training
Procedures	SOPs for all significant manufacturing steps, authorization of deviations
Facilities Environmental Control, Monitoring Equipment	Facility and equipment operations, cleaning, validation Equipment and environmental monitoring
Supplies and Reagents	Requirements, qualification, control of materials
Process Controls Process Changes Process Validation	Validation, control of manufacturing processes, process modifications. Corrective action plan.
Labeling Controls	Controlled product labeling, prevention of mix-ups
Storage	Provisions for raw material, product storage
Receipt and Distribution Records Tracking Complaint File	Record keeping, data management Tracking – from donor-recipient, recipient-donor Outcome analysis, deviation tracking, AE reporting

GTP Facility - Quality Program

- Required under GTPs
- Address communicable disease risks
- Specific for types of products manufactured
- Cover core GTPs
 - Establish and maintain procedures related to core GTPs
 - Receive, investigate, evaluate and document information relevant to core GTPs

GMP Facility

- Higher-risk, more complex cell therapy products (“351” HCT/Ps)
- Cleanroom facility, with GMP systems in place
 - Organization, personnel, training, evaluation
 - Buildings and facilities
 - Equipment, reagents and supplies
 - Procedures
 - Production and process controls
 - Finished product control
 - Laboratory controls
 - Records and reports

Quality Assurance (QA)

- Oversight responsibilities
 - “Process of monitoring a study to assure management that the facilities, equipment, personnel, methods, practices, records and controls are in accordance with applicable regulations.”
- Auditing methods, results, systems and processes. Separate from Quality Control.
- QA must maintain independence, and so should not report to Manufacturing.

Quality Control (QC)

- Responsible for accepting or rejecting:
 - Components, in-process material and product
 - Procedures and specifications
 - Review manufacturing records prior to release
- Laboratory facilities to perform testing
- Separate from Manufacturing staff

Documentation/Record-keeping

- Batch Production Records (BPRs)
 - Fundamental GMP process documents, include manufacturing process, cleaning, etc.
- Standard Operating Procedures (SOPs)
- Laboratory records
 - Notebooks, training logs, etc.
- Distribution records
- Documents should be approved by Quality unit
- GMP facility records should allow traceability
 - Who did what, and when?

Qualification, Validation Programs

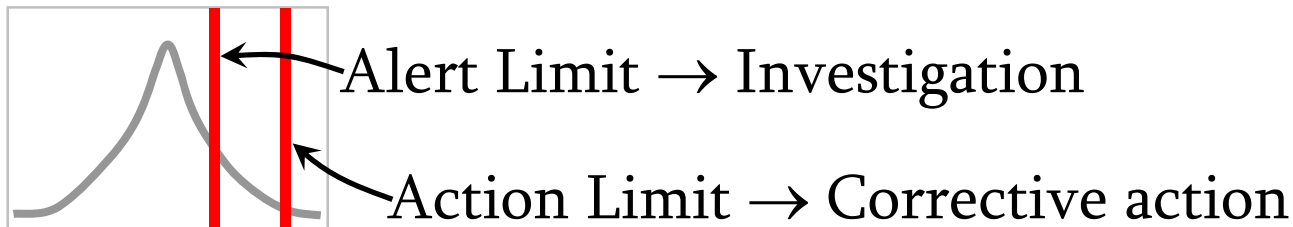
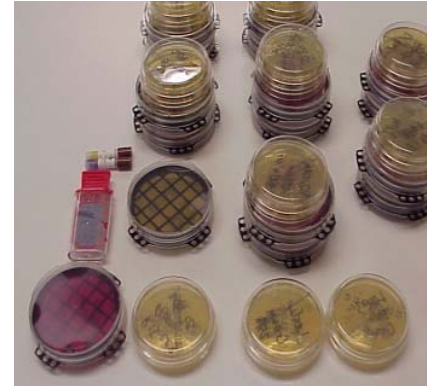
- Process
- Cleaning
- Quality Control Assays
- Equipment
- Facility

Performance Qualification (PQ)

- Verifies system performance, tested under actual running conditions across anticipated working range
- Process (method) validation
 - Consistency of process, evidence of control
 - Evaluate performance effects
 - Ongoing monitoring

Monitoring – Environmental, Personnel

- Baseline monitoring, trend analysis
- Particle counts, CFUs, microbial identification
 - Airborne, surfaces
 - Test under dynamic and static conditions
- Action/alert limits based on process, products, consequences



Equipment

- Qualification, validation
 - IQ, OQ, PQ
- Equipment maintenance system
 - Tracking
 - Scheduled calibration, preventive maintenance
- Monitoring
 - Incubators, LN₂ tanks, freezers, refrigerators
 - Temperature, CO₂ concentration, humidity, other
 - Establish acceptable/alarm ranges
 - Monitoring data
 - Archive data -- WORM drive, other
 - Review data regularly, maintain review records



GMP Facility – Separate/Defined Areas

- Materials management, storage
 - Unqualified raw material
 - Rejected materials
 - Released raw materials storage
 - In-process materials storage
- Manufacturing and processing operations
- Aseptic processing
- Packaging and labeling
- Product storage
 - Quarantine, pre-release
 - Released product
- Control and laboratory operations
- Controlled, limited access overall

Aseptic Processing Area (21 CFR 211.42)

- HEPA-filtered air supply
- Temperature and humidity controls
- Environmental monitoring system
- Cleaning and sanitization system
- Equipment maintenance system

FDA Guidance for Industry: Sterile Drug Products
Produced by Aseptic Processing - Current Good
Manufacturing Practice

Aseptic Processing Space – Key Points

- Isolate individual products, prevent cross-contamination
- Unidirectional pathways – personnel, raw materials, waste
 - Entry → Staging → Process → Exit
- Process room dimensions, access locations
 - Gowning/degowning airlocks
 - Consider doorway effects on room air quality, BSC air quality
- Facilitate cleaning and sterilization
 - Smooth, non-porous, easily cleaned surfaces
 - Movable furnishings, fixtures, avoid Clean-In-Place
- Externally-supplied resources
 - LN₂, CO₂, other
 - Limit sinks, drains

Aseptic Processing

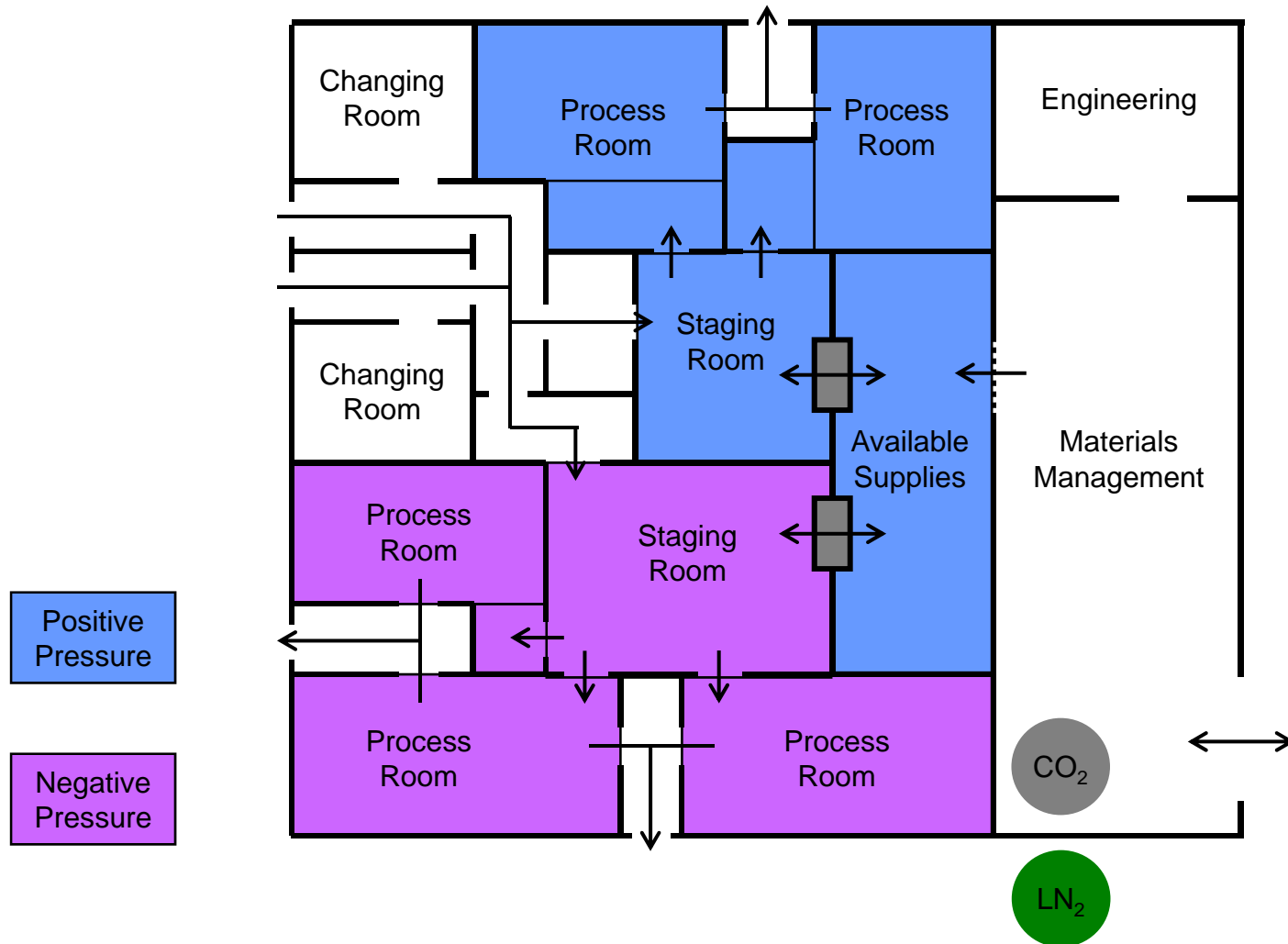
- Personnel attire - full gowning, gloves, masks
- Air quality
 - ISO 7/Class 10,000 or ISO 8/Class 100,000
 - Single-pass air for vector production
- Differential air pressure
 - Positive pressure (purity) for transduction/expansion
 - Negative pressure (containment) for vector production
- Processing in functionally-closed systems whenever possible
- Open process steps in ISO 5/Class 100 biological safety cabinet



Example Specifications - BL-2 Aseptic Processing

Temperature	72 ± 2.5°F
Humidity	45 ± 5%
Air velocity	60 ft/min ± 2%
Air flow	20-30 room air changes per hour
Air pressure	Positive pressure, 0.05 inches water between aseptic processing and other areas
Airborne particulates	<100,000 measurable particles ≥0.5 μm diameter/ft ³
Airborne microbial contamination	<1 CFU per 9-cm settling plate, 0.1 hr exposure
Surface microbial contamination	<2 CFU/contact plate
Personnel – Gowns	<40 CFU/contact plate
Personnel – Gloves	<10 CFU/contact plate

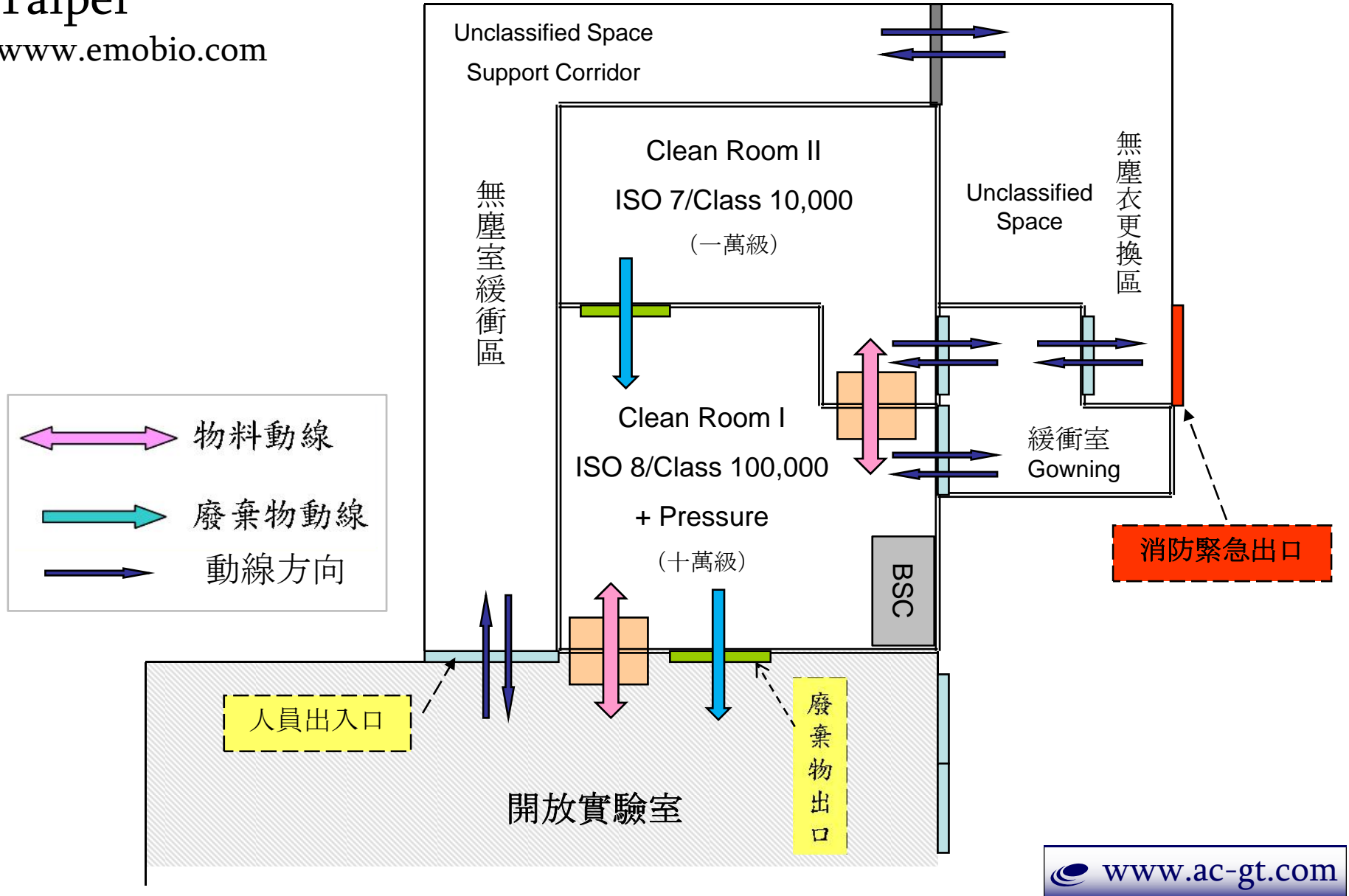
GMP Facility Layout - Example



EMO Biomedicine Facility

Taipei

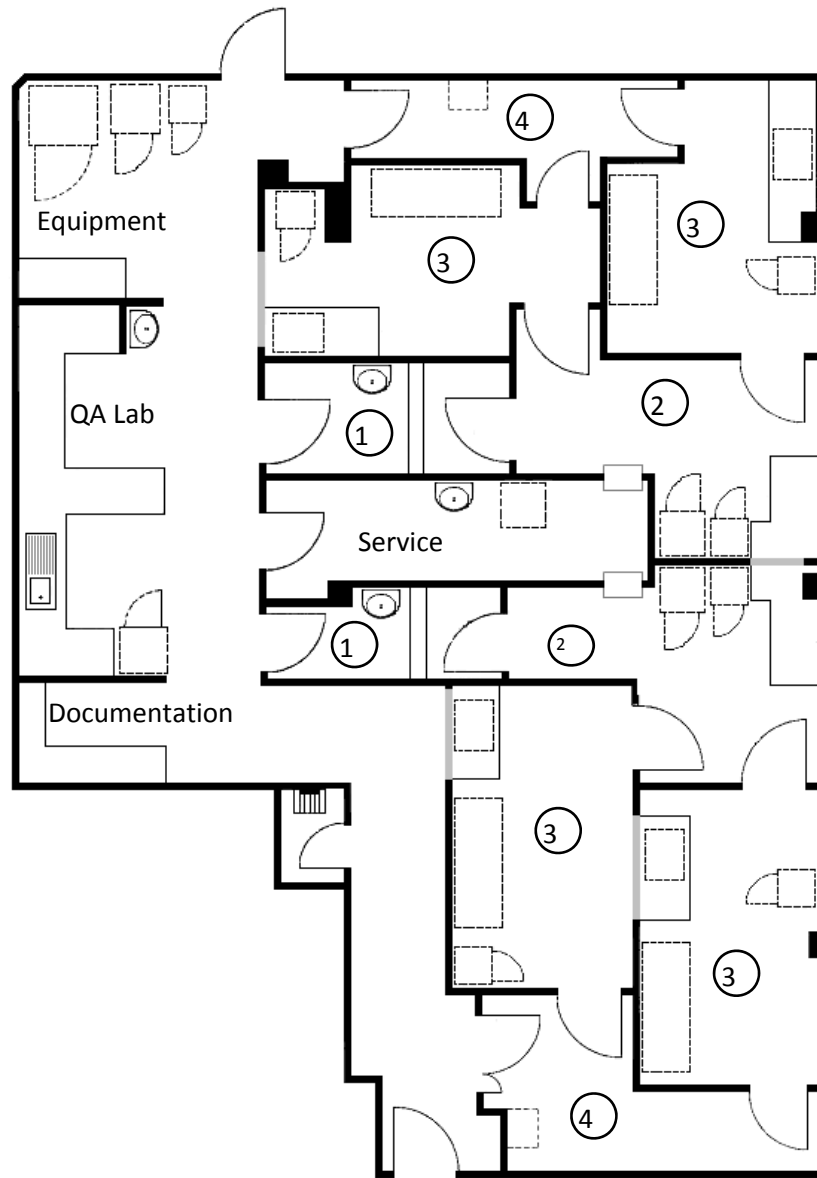
www.emobio.com



Cell Therapies Pty

Melbourne, Australia

www.celltherapies.com.au



Legend

1. Gowning
2. Materials
 - General storage
 - Blood refrigerator, incubators
 - Pass-through hatch
3. Cleanroom
 - Biological safety cabinet
 - Centrifuge, incubators
 - Processing
4. Degowning

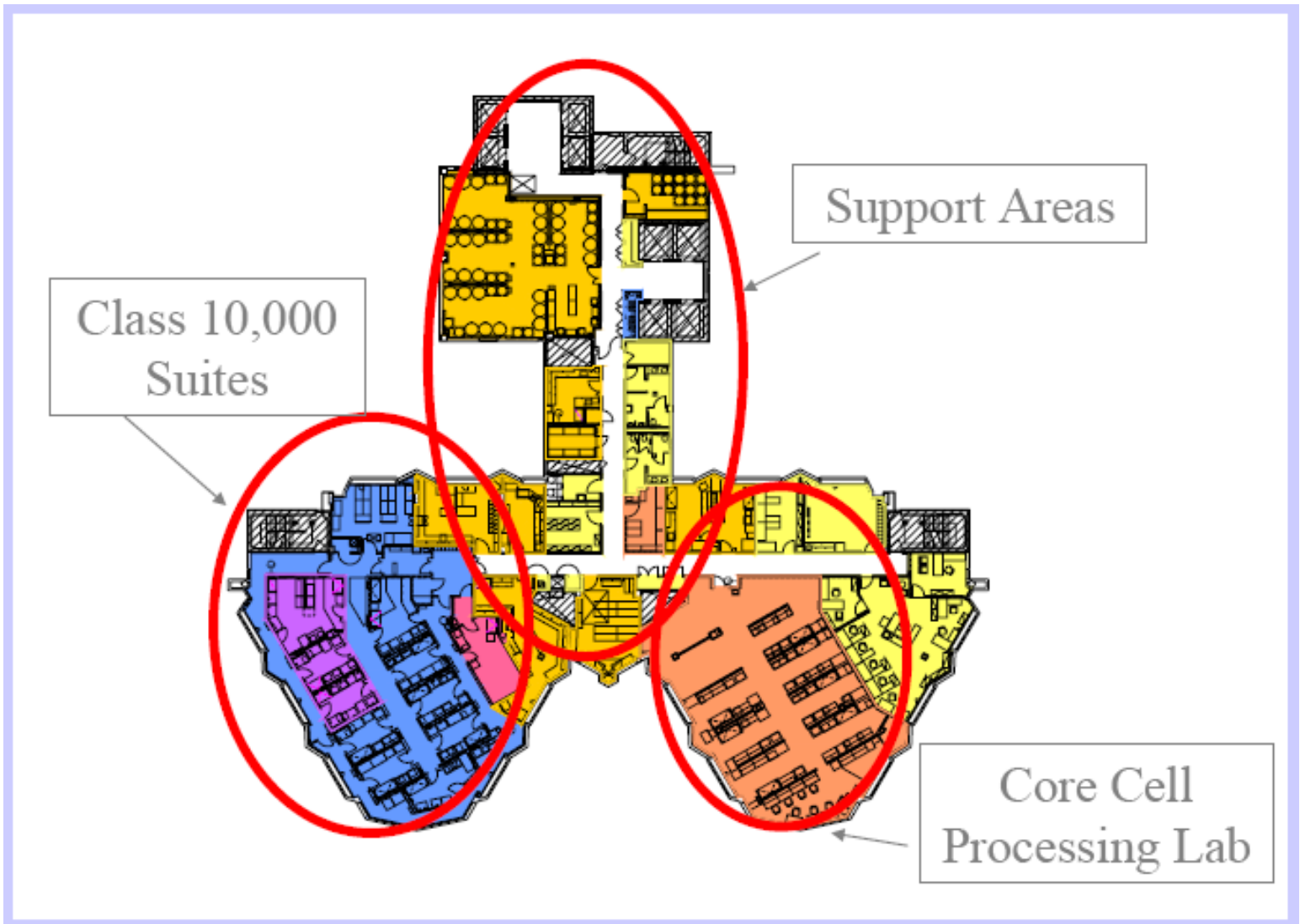
Direction of Travel

⇒ 1 ⇒ 2 ⇔ 3 ⇒ 4 ⇒

Scale: 1 metre

MD Anderson Cancer Center

Houston, Texas, USA



MD Anderson Cancer Center

Houston, Texas, USA



- Minimal manipulation area
 - One product per lab bay
 - Shared equipment with appropriate segregation
 - Quarantine areas for supplies, reagents, products
 - Validated supply area, separate from GMP supplies



MD Anderson Cancer Center

Houston, Texas, USA



- 11 ISO 7/Class 10,000 suites
 - 7 Positive pressure
 - 3 negative pressure
 - 1 cell sorter
 - Airlock/Gowning
- Unidirectional flow
 - Entrance corridor
 - Exit corridor
- Single-pass air



MD Anderson Cancer Center

Houston, Texas, USA

- ISO 7/Class 10,000 cleanroom area
 - Unidirectional flow of products, personnel, waste
 - One protocol per suite
 - Multiple patients per suite if appropriate segregation
 - Quarantine areas for all supplies, reagents, products
 - Validated supply area
 - Each suite must be self-sufficient
 - Pass-through boxes
 - Manifold gas supply to all rooms

MD Anderson Cancer Center

Houston, Texas, USA



- ISO 7/Class 10,000 cleanrooms
 - Hard surfaces for ease of cleaning
 - Seamless vinyl floors with integral coved base
 - Hard ceiling in production suites, gasket ceilings elsewhere
 - Stainless steel work surfaces
 - No sinks/hands-free



Summary

- GTP and GMP/GTP cell therapy manufacturing facilities serve different roles in supporting clinical cell therapy.
- Multiuse cell therapy manufacturing facilities are most common, and must have robust segregation policies and procedures.
- Large GTP/GMP cleanroom facilities are impressive and glamorous, but very costly to build, and even more expensive to operate. Explore alternatives thoroughly before establishing a new facility!

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14th

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Program Format:

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Preliminary Program Topics:

- Gene Therapy
- Cell Therapy Commercialization
- Lab Practices
- Hematopoietic Stem Cells
- Immunotherapy
- Dendritic Cells
- Mesenchymal & Tissue Stem Cells
- Legal & Regulatory Affairs

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