

# Isolators for Cell and Gene Therapy: Closing the Process for ATMPs

PDA SoCal Chapter  
Aseptic Process and Sterilization  
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# Agenda

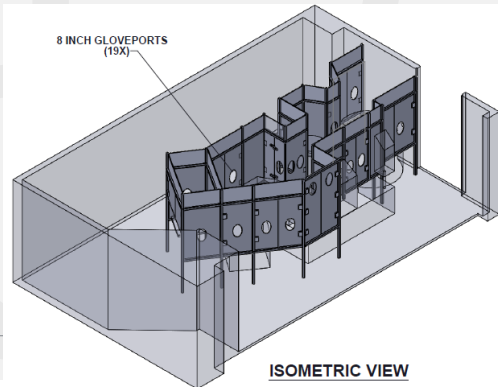
- 1 Isolator 101 – Biosafety cabinets, RABS, Glove Boxes and Isolators
- 2 Modular Isolator System Design
- 3 Example Application: Cell and Gene Therapy...CAR-T Process in Isolators

# Non-isolators...Biosafety Cabinets



- Lab or open production processes
- Open front, unidirectional flow
- Stainless steel interior, Powder coated exterior
- Operate typically under positive (or sometimes negative) pressure
- Unidirectional airflow to create Grade A (ISO 5) aseptic environment ONLY possible when used with FULL GOWNING in a Grade B (ISO 7) environment
- No H<sub>2</sub>O<sub>2</sub> decon system
- Transfers via open front
- Simple controls

# Non-isolators...RABS



## **RABS – Restricted Access Barrier System**

- Not just panels with glove ports – it is a ‘system’ which includes...
- Ergonomically designed access to the process
- Enhanced air flows
- Safety interlocks
- Door position sensors / notification of opening
- Transfer systems for sterile supply or component entry
- Sanitization (manual or new gassing methods)
- Needs to operate with doors CLOSED (to restrict access), otherwise it is just conventional processing with machine guarding.
- Any open door intervention requires line clearance and re-sanitization.

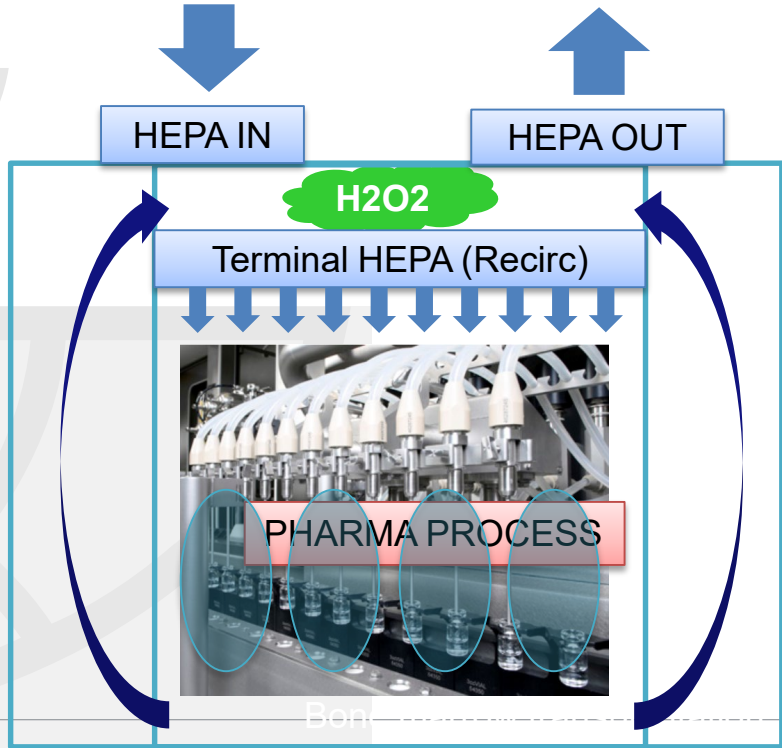
# Non-isolators...Glove Boxes



- Containment or API closed processes
- Glove ports
- Stainless steel interior (usually)
- Stainless or Powder coated exterior
- Operate typically under positive (or often negative) pressure
- Turbulent airflow (usually)
- No H<sub>2</sub>O<sub>2</sub> decon system (manual decon or non-sterile applications)
- Transfers via open front or closed valve or other transfer systems
- Simple controls (sometimes PLC)

# What makes an isolator an isolator?

- Basics
- Typical





# Official Definition of an Isolator

*From FDA Aseptic Processing Guidance Document – Sept 2004*

**Isolator-** A decontaminated unit, supplied with Class 100 (ISO 5) or higher air quality, that provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding cleanroom air and personnel). There are two major types of isolators:

**Closed isolator systems** exclude external contamination from the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.

**Open isolator systems** are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g., using continuous overpressure) to exclude the entry of external contamination into the isolator.



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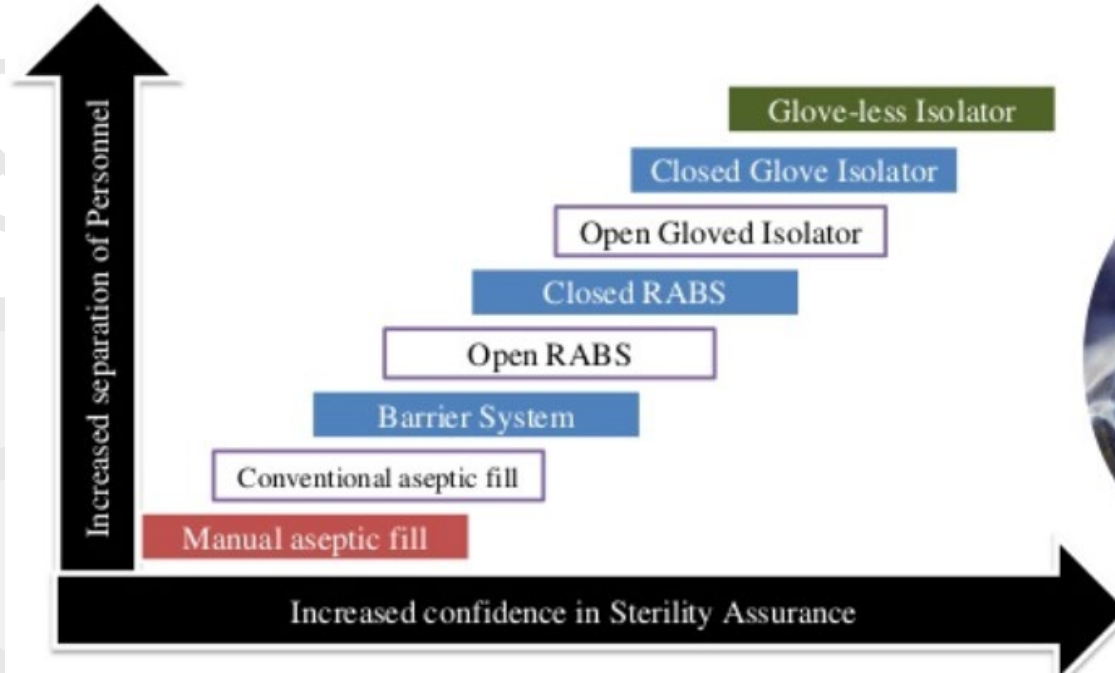
# Today's key isolator features

- Usually rigid wall, glass and stainless steel construction
- Glove ports
- Operate typically under positive (or rarely negative) pressure
- Unidirectional airflow to create Grade A (ISO 5) aseptic environment
- Integrated H<sub>2</sub>O<sub>2</sub> decon system and safety monitoring
- Transfers with alpha/beta ports or closed sterile transfer methods. Active transfers with validatable decon process (e.g. rapid H<sub>2</sub>O<sub>2</sub> airlocks, e-beam, depyrogenation tunnel).
- PLC-based controls for
  - Pressure control and monitoring
  - Air flow control and leak testing
  - Interfaces with interior process equipment
  - H<sub>2</sub>O<sub>2</sub> decon system control, monitoring, and operation
  - Safety and access control





# Increasing sterility assurance – closed systems



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# Benefits of isolators

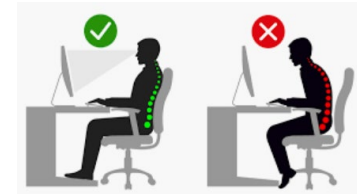
- Reduced chance of contamination / better sterility assurance
- Increased safety (for BSL-2 and potent compounds like ADCs, etc...)
- Allows aseptic processing with a Grade C (ISO 8) cleanroom background
  - Reduced gowning
  - Fewer airlocks
  - Less environmental monitoring
- Lower facility costs
  - Less square footage – lower capital costs
  - Lower operating costs – utilities



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# Challenges of isolators

- Transfers
  - Every movement/transfer IN (and sometimes OUT) requires “process”
- Ergonomics
  - Reach / access for moving items in and out of equipment (like incubators)
  - Tactile / feel for fine motor operations
- Decon processes require understanding of residue effects
  - H2O2 penetration through plastic bags
  - Alternative ‘wipe and pass’ methods may be required
  - NOTE: Some of these same issues EXIST in non-isolator processing, but not studied



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# Agenda

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# How Isolator Production has Changed



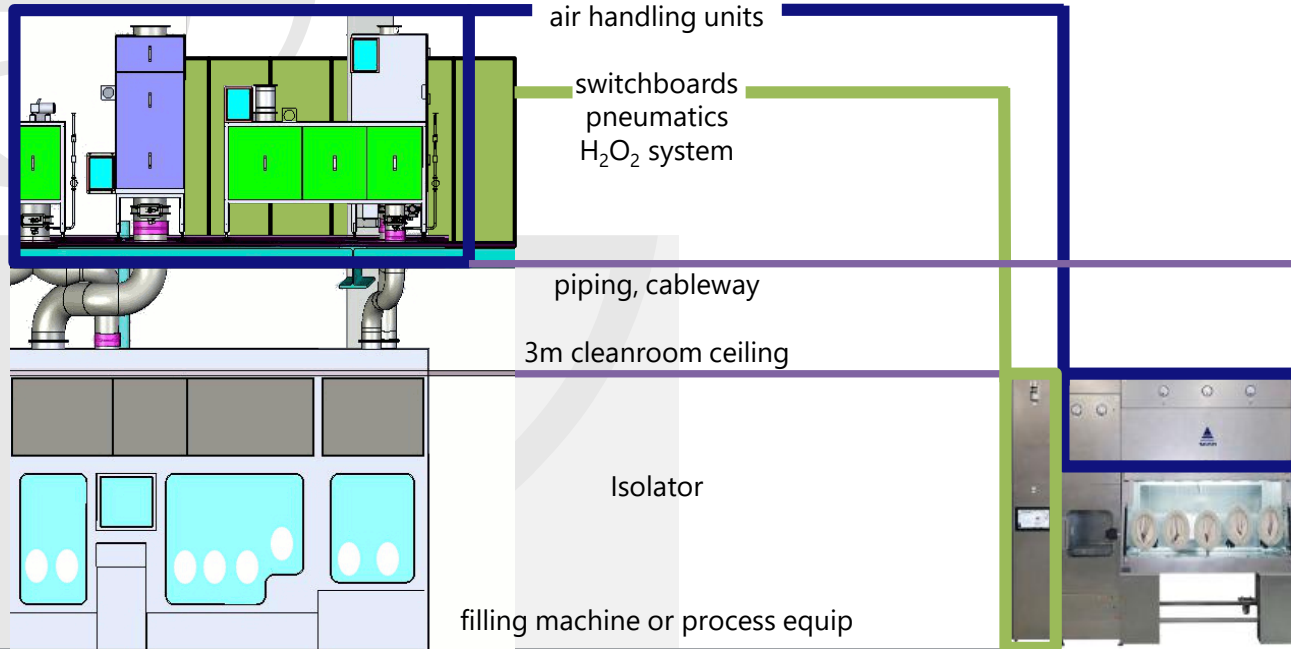
- More and new processes in
  - Aseptic Handling
  - Containment
  - Equipment/Process Integration
  - Cell and Tissue Culture, Master Seed, Gene and Cell Therapy
  - Biologics and ADCs
  
- New HEPA filter options for potent compounds or hazardous materials.
  
- Advanced controls and HMIs – data handling and control / reporting options

# Custom vs Modular Isolators

## Custom Isolator line



## Modular System





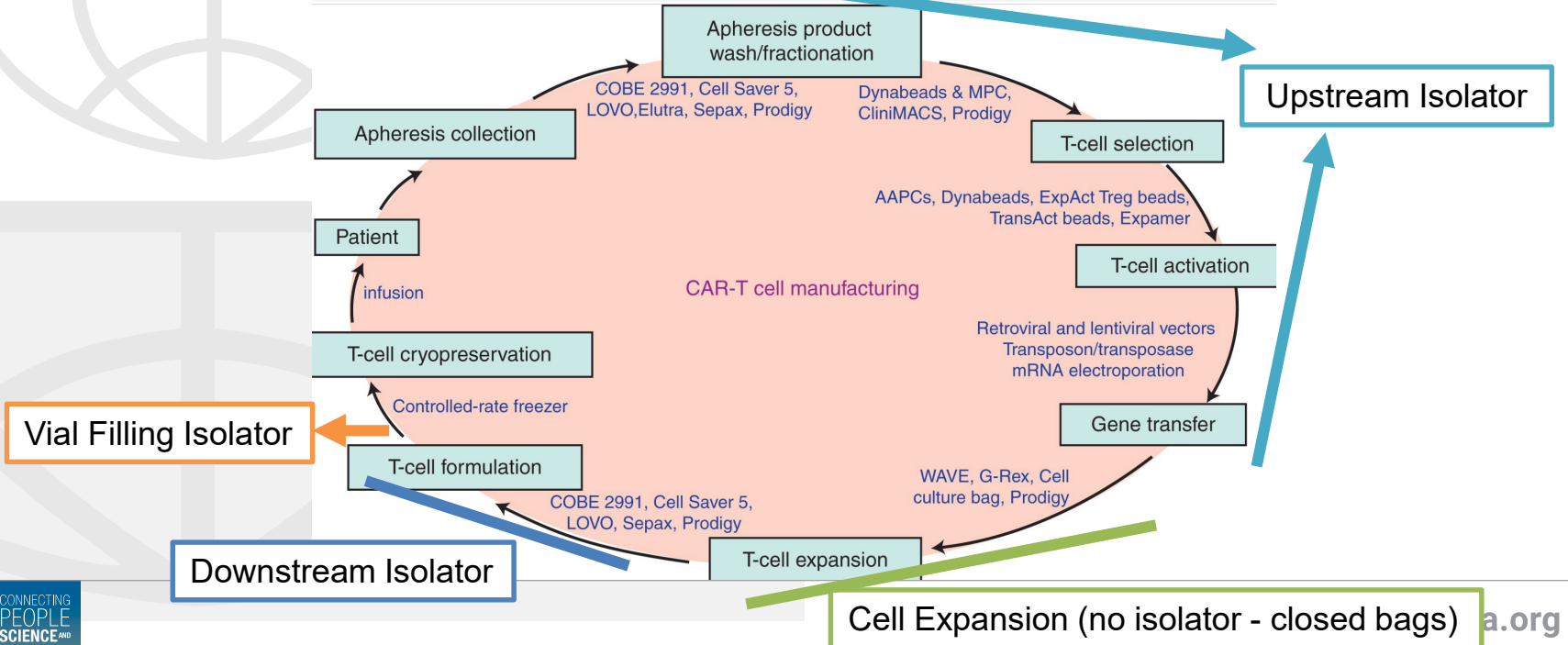
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# CAR-T Processes in Isolators

## What's going on in each isolator







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# CAR-T Processes

## Overall Process

- Upstream Isolator
- Cell Expansion Isolator (or closed systems outside isolators)
- Downstream Isolator
- Vial Filling Isolator

System	Vendor Supplied	Collectis/CRB Purchase
<b>Upstream Isolator ISO-001 &amp; 002</b>		
CO2 incubator	Yes	No
Centrifuge	Yes	No
Manual Plasma Extractor	No	Yes
Scale (5 kg)	No	Yes
Tubing Sealer	No	Yes
Tubing Welder	No	Yes
Electroporator	No	Yes
Microscope	No	Yes
<b>Cell Expansion Isolator ISO-003 &amp; 004</b>		
Xuri W25 rocking bioreactor (quantity - 4)	No	Yes
Tubing Sealer	No	Yes
Tubing Welder	No	Yes
<b>Downstream Isolator ISO-005 &amp; 006</b>		
CO2 incubator	Yes	No
Centrifuge	Yes	No
Manual Plasma Extractor	No	Yes
Scale (5 kg)	No	Yes
Tubing Sealer	No	Yes
Tubing Welder	No	Yes
Xuri W25 rocking bioreactor	No	Yes
Microscope	No	Yes
Miltenyi CliniMACS (or Prodigy)	No	Yes
Benchtop cooler (2 - 8C)	No	Yes
<b>Filling Isolator ISO-007</b>		
Aseptic Technologies Crystal L1 Automated Vial Filler	No	Yes
Orbital oscillator	No	Yes
Scale (top loading, 100gm)	No	Yes



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# Important Compressed Gas, Equip and Electrical Interfaces

- Many client supplied items shipped to vendor for integration
- Must demonstrate function and fit during FAT

System	Vendor Supplied	Collectis/CRB Purchase	Ship to vendor site for mock-up	Ship to vendor site for FAT	Isolator location	Gas Supply	Electrical (electrical receptacle to be vendor provided)
<b>Upstream Isolator ISO-001 &amp; 002</b>							
CO2 incubator	Yes	No	N/A	N/A	integral to isolator	CO2/CCA	Integral to isolator
Centrifuge	Yes	No	N/A	N/A	Integral to isolator	N/A	Integral to isolator
Manual Plasma Extractor	No	Yes	No	Yes	Inside process chamber	N/A	N/A
Scale (5 kg)	No	Yes	No	Yes	Inside process chamber	N/A	Plug connection outside isolator
Tubing sealer	No	Yes	No	Yes	inside process chamber	N/A	Plug connection outside isolator
Tubing Welder	No	Yes	No	Yes	inside process chamber	N/A	Plug connection outside isolator
Electroporator	No	Yes	No	Yes	Pod inside / controls outside	N/A	Plug connection outside isolator
Microscope	No	Yes	No	Yes	Inside process chamber	N/A	Plug connection outside isolator
<b>Cell Expansion Isolator ISO-003 &amp; 004</b>							
Xuri W25 rocking bioreactor (quantity - 4)	No	Yes	No	Yes	inside process chamber	CO2/CCA	Plug connection outside isolator
Tubing Sealer	No	Yes	No	Yes	inside process chamber	N/A	Plug connection outside isolator
Tubing Welder	No	Yes	No	Yes	inside process chamber	N/A	Plug connection outside isolator
<b>Downstream Isolator ISO-005 &amp; 006</b>							
CO2 incubator	Yes	No	N/A	N/A	Integral to isolator	CO2/CCA	Integral to isolator
Centrifuge	Yes	No	N/A	N/A	Integral to isolator	N/A	Integral to isolator
Manual Plasma Extractor	No	Yes	No	Yes	Inside process chamber	N/A	N/A
Scale (5 kg)	No	Yes	No	Yes	Inside process chamber	N/A	Plug connection outside isolator
Tubing Sealer	No	Yes	No	Yes	Inside process chamber	N/A	Plug connection outside isolator
Tubing Welder	No	Yes	No	Yes	inside process chamber	N/A	Plug connection outside isolator
Xuri W25 rocking bioreactor	No	Yes	No	Yes	inside process chamber	CO2/CCA	Plug connection outside isolator
Microscope	No	Yes	No	Yes	inside process chamber	N/A	Plug connection outside isolator
Miltenyi CliniMACS (or Prodigy)	No	Yes	No	Yes	Inside process chamber	CO2/CCA	Plug connection outside isolator
Benchtop cooler (2 - BC)	No	Yes	No	Yes	Inside process chamber	N/A	Plug connection outside isolator
<b>Filling Isolator ISO-007</b>							
Aseptic Technologies Crystal L1 Automated Vial Filler	No	Yes	No	Yes	Inside process chamber	N/A	Plug connection outside isolator
Orbital oscillator	No	Yes	No	Yes	Outside process chamber	N/A	Plug connection outside isolator
Scale (top loading, 100gm)	No	Yes	No	Yes	Inside process chamber	N/A	Plug connection outside isolator

# Upstream Isolator: Dual chamber w/ airlock

## Upstream Isolator System

- Modular Design
- Rapid Airlock
  - 20 minute H2O2 Decon
  - Bypass cycle for sensitive materials
- Integrated Incubators on Right Side and Rear
- Centrifuge in floor (centered in left chamber)

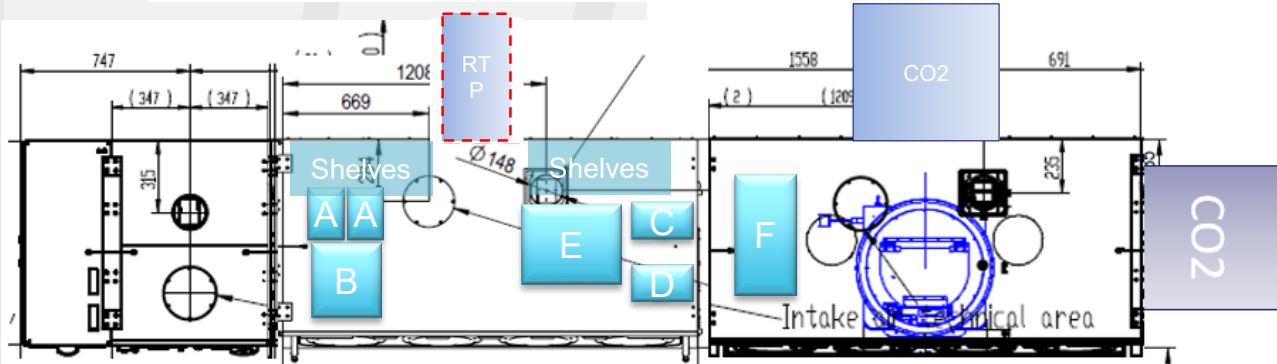
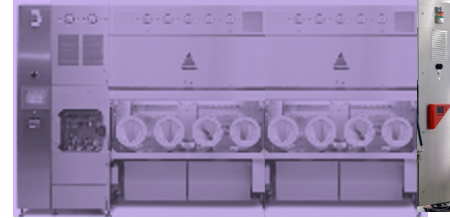


# Upstream Isolator: Dual chamber w/ airlock

## Upstream Isolator Equipment

- Process equipment

- A. Manual plasma extractor
- B. 5 kg weigh scale
- C. Tubing sealer
- D. Tubing welder
- E. Electroporator (electrode handle and tip only)
- F. Inverted microscope

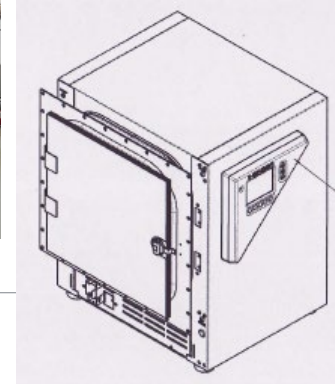


TOP VIEW

# Incubator and Centrifuge Interface

## Upstream Isolator System

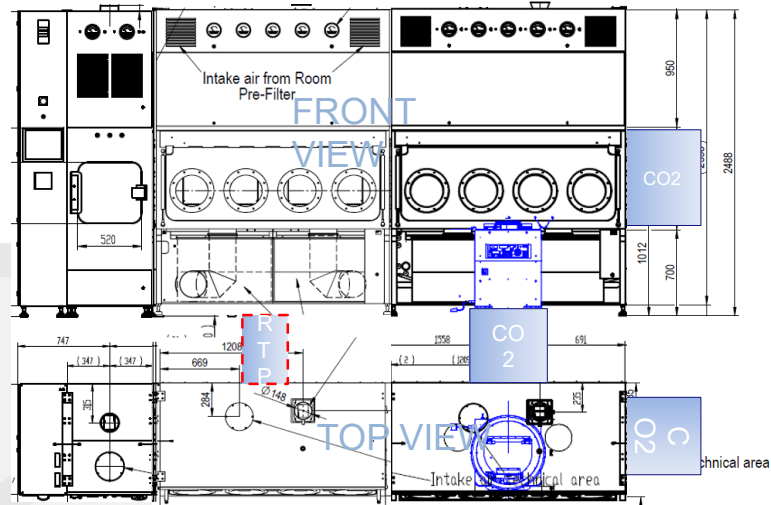
- Integrated Incubators on Right Side and Rear
- Centrifuge in floor (centered in left chamber)



# Incubator and Centrifuge Interface

## Upstream Isolator System

- Integrated Incubators on Right Side and Rear
- Centrifuge in floor (centered in left chamber)



# Downstream Isolator: Three chamber w/ airlock

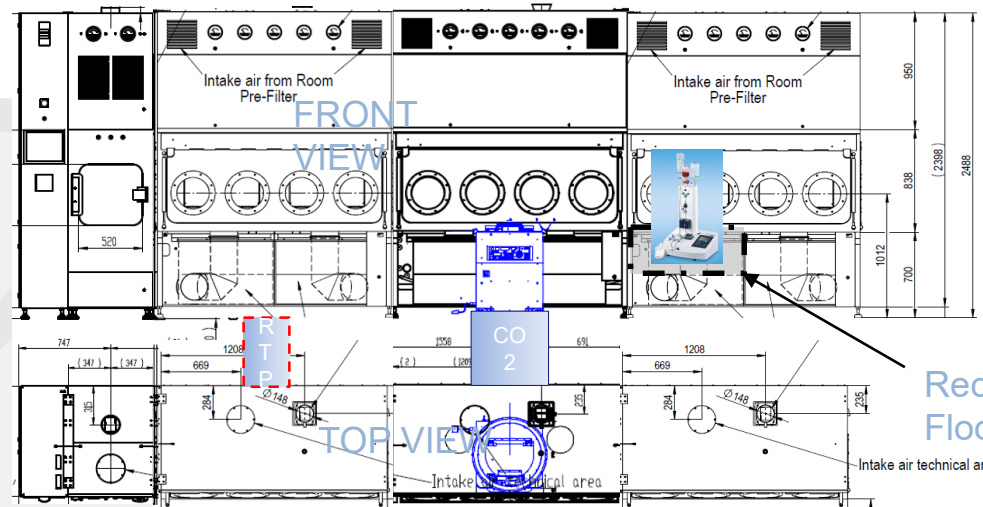
## Downstream Isolator Equipment

- Process equipment

- A. Benchtop 2-8 °C cooler
- B. 5 kg weigh scale
- C. Manual plasma extractor
- D. 2L rocking bioreactor
- E. Tube sealer
- F. Tube welder
- G. Temperature-controlled centrifuge (integrated) or stand-alone LOVO
- H. Inverted microscope
- I. CliniMACS cell separation system
- J. Orbital oscillator (located within incubator)

**Not shown**

- Particle counter (isokinetic probes)
- Viable air sampler



# Aseptic Vial Filling Isolator + Sterility Test

## Closed Vial Filling System

- Aseptic Technologies (AT) closed vial filling system w/ robot
- Stäubli TX40 Stericlean
- Peristaltic pump
- Weighing scale
- AT-Port for drug product
- Caps sorting bowl
- Tray holder







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# Aseptic Vial Filling Isolator: Video

# Aseptic Filling Common Alternatives

## Bulk or Nested Vial Filling System

- Various scale / speed vial, syringe or other container filling systems
- One or two module systems common.





# Summary and Conclusions

- As lab-based processes are introduced for clinical and GMP production, increased controls are required.
- Closed systems are effective for increasing sterility assurance and overall quality.
- Isolator technology is a natural next step to increase process and quality control.
- Challenges in ergonomics and transfers must be addressed, including decon practices.
- **End goal is not necessarily perfection, but improved aseptic quality.**
- Great example of the “c” in cGMP...are you staying current?

