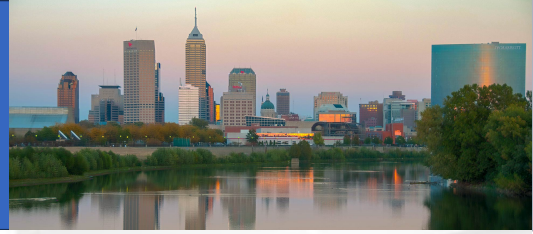
# Sterility Assurance & Quality Risk Management Conference


PDA®
Parenteral Drug Association
Midwest Chapter

PDA Parenteral Drug Association Midwest Chapter

Sterility Assurance & Quality Risk Management Conference

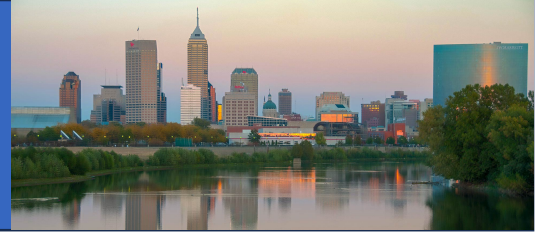
October 25th & 26th



# Sterility Assurance: Key Considerations to Maintain Compliance

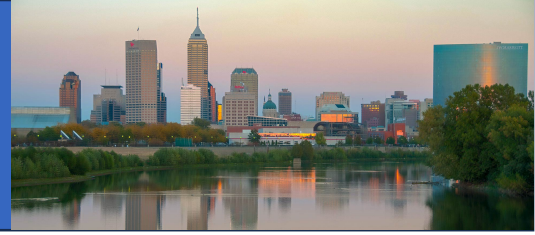
David Turner, Global Technical Consultant

ECOLAB®



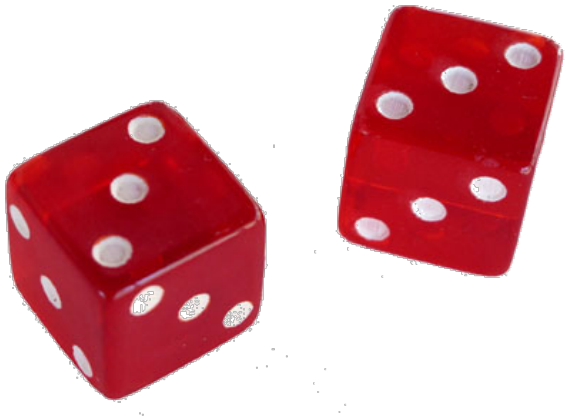
# Agenda

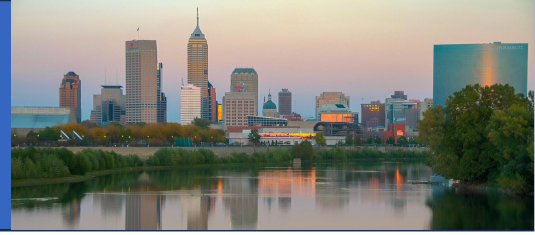
- Contamination control strategy and risk assessment
- Proven engineered and automated controls
- Integrating manual and automated approaches pragmatically
- Sterility assurance with holistic thinking



# Sterility Assurance & Probability

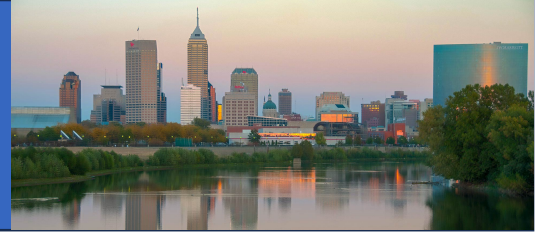
- Toss a coin
  - Heads = Sterile
  - Tails = Non-Sterile
- Roll a die
  - 1 – 5 = Sterile
  - 6 = Non-Sterile
- Probability of pulling the ace of spades



# Sterility Assurance

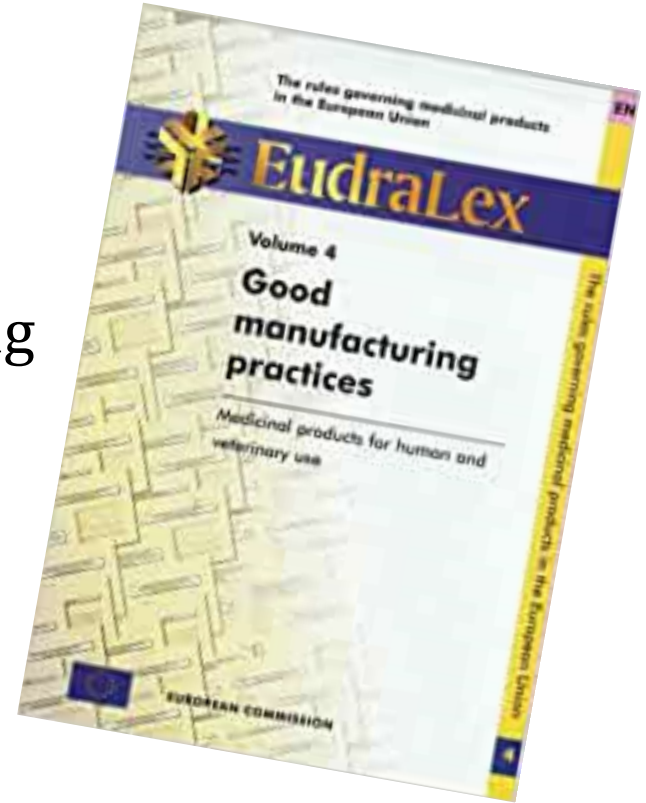

- Minimum probability of non-sterile: 1 in 1,000,000
- Sterility assurance is not an absolute; directly linked to changes in the controls, or the introduction of variables.
- Build into the manufacturing process as variables to the process must be understood and controlled
- Anything which moves the process away from its validated controlled state has the potential to impact sterility assurance

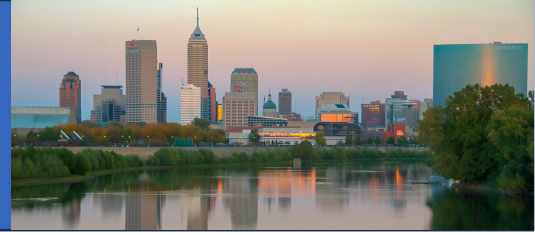


# Contamination Control Strategy

- Regulatory Requirements and Guidance
  - EC Annex 1 GMP for Sterile Products
  - PIC/S Good Manufacturing Practices
  - FDA Guidance GMPs for Sterile Products from Aseptic Processing
  - ICH Q9  Quality Risk Management

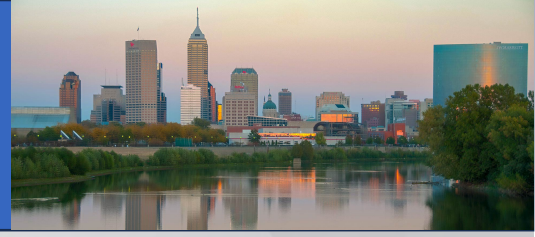
PIC/S
PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME



# Best practices approach

- Risk Assessment
  - Map all manufacturing areas, equipment and activities (including transfers) with relevant classifications
  - Identify risk of microbial intrusion
  - Develop understanding of microbiological bioburden and their decontaminants in each area
  - Determine frequencies of cleaning and decontamination based on activities, surfaces and risk



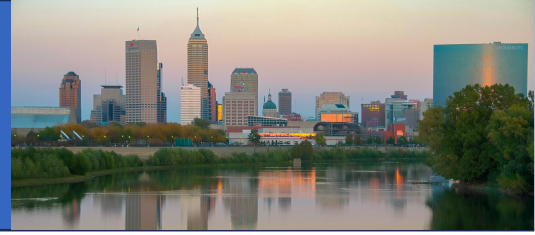
# Legacy approach

Control the aseptic core primarily

Courtesy of Pharmaceuticalonline.com

## INSIDE OUT

- ISO 5 Grade A/B classified areas – Aseptic Core
  - Engineered controls - HVAC, Pressure cascade
  - Full gowning and aseptic behavior expected
  - Airlocks and pass-throughs
- Risks
  - Contamination can still appear
  - Engineering controls taken for granted as 'enough'



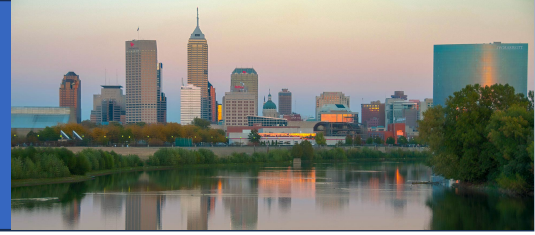
# Better approach

Control origins of contamination as well as the aseptic core

## OUTSIDE IN

- **ISO 5 cleanroom, isolator, closed instruments are not separate entities in a GMP environment**
- Pragmatic thinking of adjacent ISO 7-8 areas (Grades C-D)
- Consider control of CNC areas adjacent to cleanroom

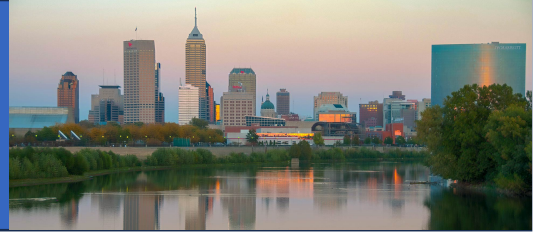
Miltenyi CliniMACS Prodigy



# Improvements to risk

## Outside In

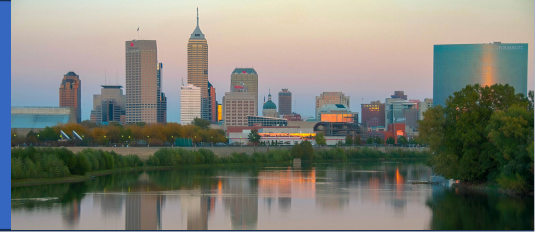
- Reduce source of contaminants
  People, materials, variability in cleaning and disinfection
- Influence reduction of cross-contamination
- Additive thinking for contamination control and reduction of human variability in cleaning and disinfection



# Engineered design to reduce risk

- Surface materials are cleanable, maintained in good condition
- HVAC calibrated and monitored
- Doors/seals checked and good condition
- Process equipment for containment, RABS or isolators (understand limitations)

Courtesy of Instant Cleanroom Solutions



# Approach for Selecting Manual Decontamination Agents

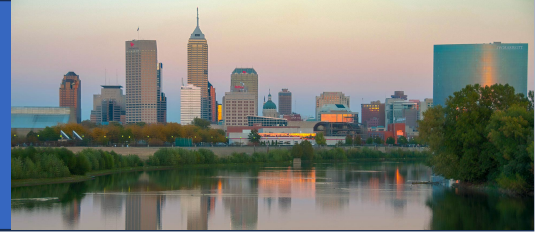
Identifying appropriate cleaning and disinfection agents

## Aseptic core and beyond

- Select appropriate cleaning agent: detergent, surfactants

- Select appropriate disinfectant:
  - ✓ Manual, broad spectrum rotated with a sporicide (automated $H_2O_2$ Vapor)

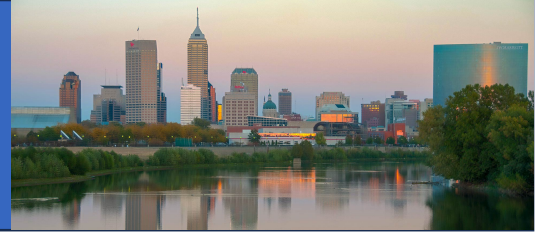
- Rinsing agents should be available: Water for Injection, IPA



# Automated Approach to Contamination Control

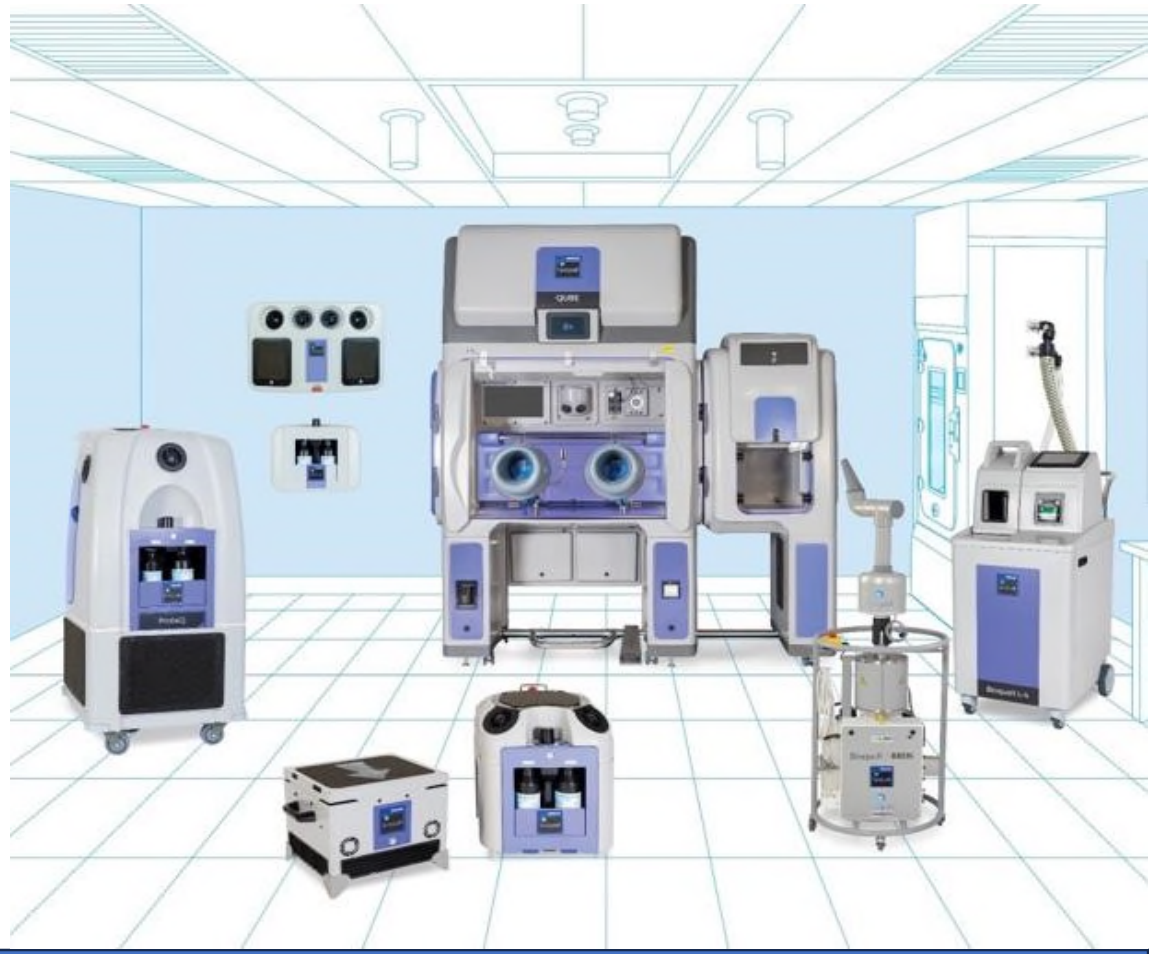
A choice for efficiency and consistency in controlling contamination

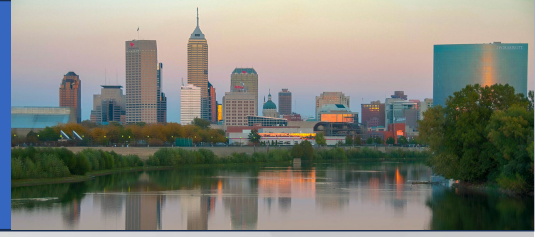
- Use of isolators/**closed** systems to reduce risk of contamination to process
- Use of automated room decontamination ($H_2O_2$ Vapor) to reduce variability from manual disinfection practices



# Hydrogen Peroxide Vapor Technology

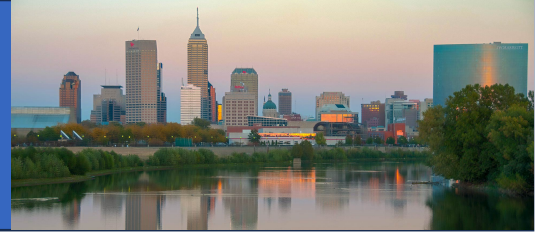
- Bio-decontamination cycles in as little as 30 mins in isolators
- Validated, 6-log sporicidal kill* on exposed surfaces, verified with *Geobacillus Stearothermophilus*
- Compatible with sensitive materials and products
- Breaks down into oxygen and water vapor with no additional wipe downs needed
- Efficacy against a wide spectrum of microorganisms





# Automated bio-decontamination can replace human intervention

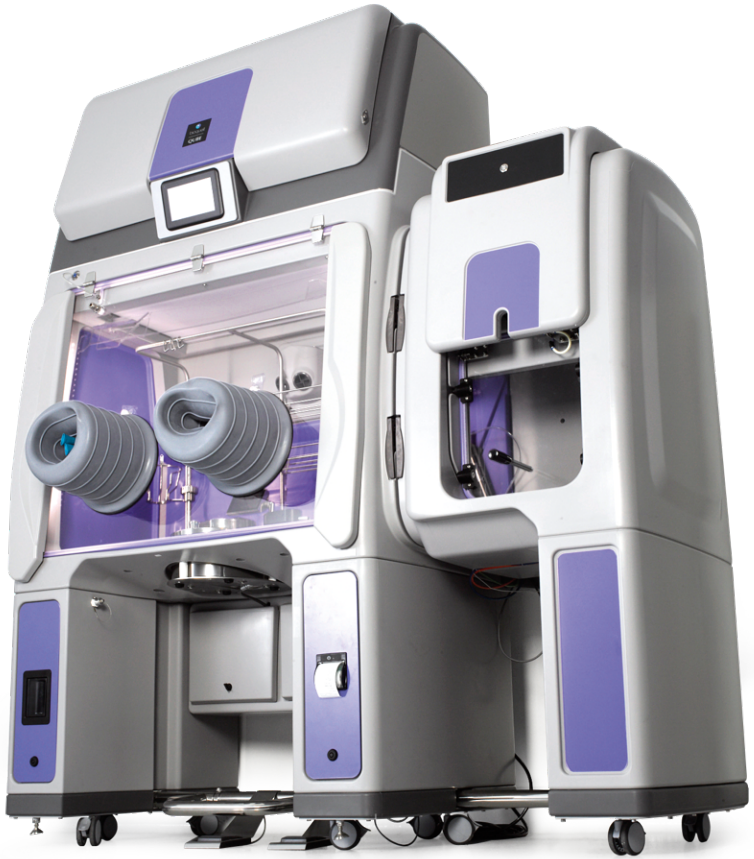
- Any room decontamination with hydrogen peroxide vapor replaces manual activity with mops, wipes and spray
- Consistent, validated, efficient, cGMP
- Pass-thru or MAL decontamination
- Aseptic core, ISO 5, containment with built-in $H_2O_2$ system
- $H_2O_2$ Vapor Technology can be contracted or performed internally

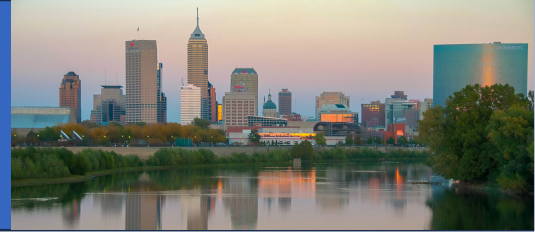


# Isolator Systems vs Biological safety cabinets

Environments for aseptic processing

vs





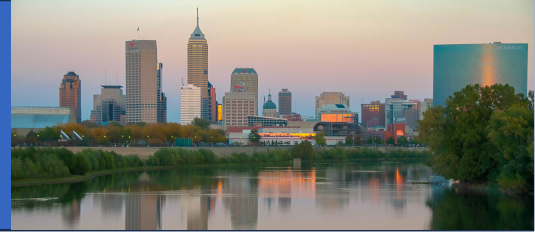
# Biological Safety Cabinets Overview

## ADVANTAGES

- Provides some protection for a critical process
- **Lower capital cost** compared to most isolator systems

## DISADVANTAGES

- **Open** to the environment/operator, putting critical process at risk of contamination
- Must be located in grade B cleanroom, **increasing running costs**

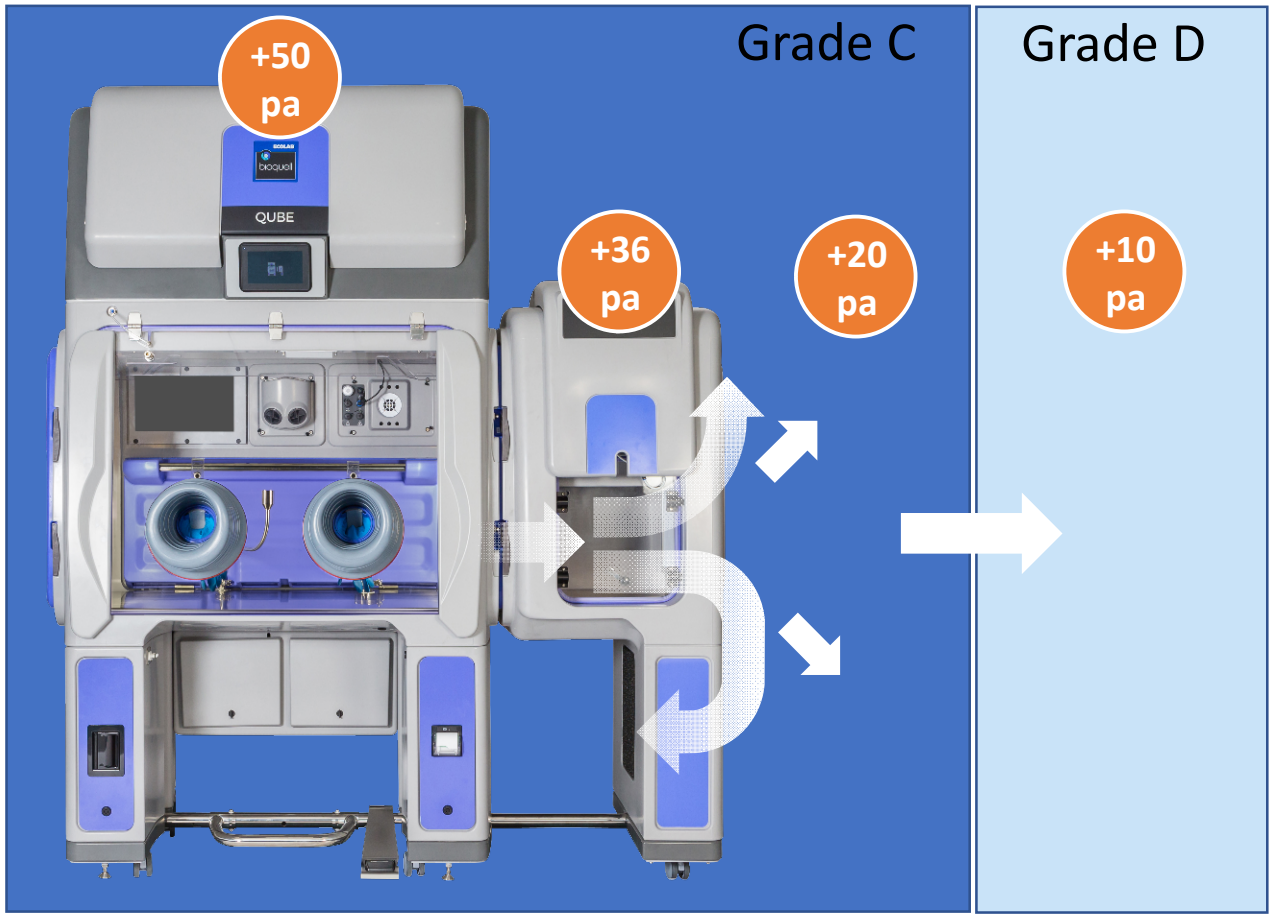


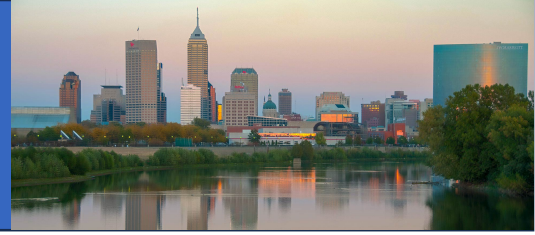
# A Systems approach to contamination control

A choice for efficiency and consistency in controlling contamination

## Use of isolators/closed systems

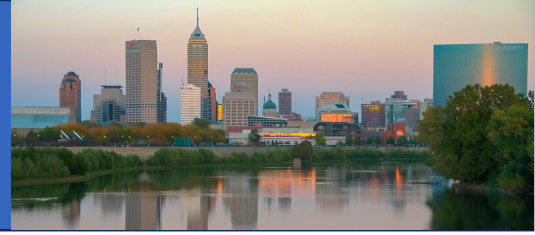
- A **complete barrier** eliminates risk of **environment/operators** contaminating process
- **Pressure cascades** prevent entry of 'dirty' air into isolator
- Note: EU GMP Annex 1 requires '**open'** isolators to be in grade **C** cleanroom, but '**closed'** isolators can be in grade **D**





# Use of Isolators for Sterility Testing

- Must be performed to release **all** sterile medicines and products to the market
- Failed test due to a false positive results in unnecessary investigation, halting production, loss of product
- Isolators should be used to protect process from environmental contamination
- Minimising the risk of false positives

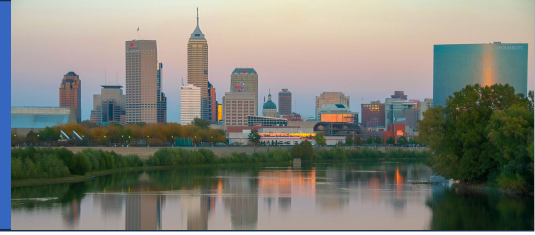


# Best Practice

## All manufacturing-related areas

- Develop a full facility control approach based on risk assessment of adjacent areas and potential for cross contamination
- Clean areas based on risk
- Automate disinfection for consistency and fit for manufacturing schedule
- Combining automated and manual approaches in a robust, efficient plan
- Train and maintain personnel aseptic practices in any classified area

How can you drive contamination control?



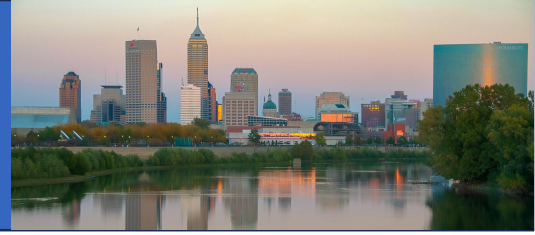
# Significance of infrastructure control

Infrastructure and people

**Adjacent to aseptic core**

- Maintenance
- Cleaning
- Disinfection
- Operator traffic flow and restrictions
- Physical controls for manufacturing rooms
  - Diff. pressure
  - Temperature
  - Humidity
  - Air changes

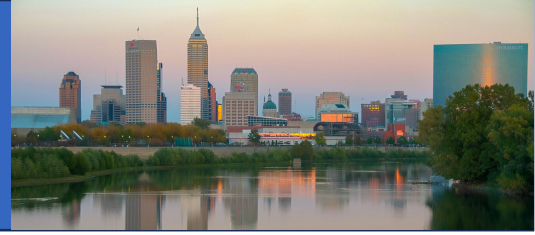
Courtesy of Class One Cleanroom Systems Inc.



# Monitor and observe contamination control

**Consistency is key!**

- Monitor engineered controls from Grade A to CNC
- Observe facility design and personnel aseptic behavior, skills and gowning
- Training ongoing
- Material decontamination and transfer



# Your Bio-decontamination Program

## Summary

- Holistic contamination control
  Integrated across your facility and processes

- **Pragmatic cleaning with combined automated and manual decontamination meets your needs for efficiency and consistent, effective facility control**

- Impact your key parameters of concern:
  - reduced chemicals, reduced residues
  - validated processes
  - efficient and effective labor (resources)
  - more production 'run time'

# Thank you!

# Any questions?