ENGINEERING PHARMACEUTICAL INNOVATION

Key Points to Consider in the Validation of Isolator Systems

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Presentation Outline

- Where do I start?
- Facility Design Considerations
- Regulatory Expectations
- BI Qualification
- Qualifying Isolators and Related Process Equipment

Where do I start? (The BIG Picture)

- Determine your requirements
- Specify your equipment
- Design your facility
- Purchase and build
- Qualify the equipment and the facility
- Validate the system (isolators and decontamination unit)
- Train and start-up

Facility Design Considerations

- Most sterility test isolator systems are currently based in standard labs
- The recent trend has been to place them in ISO 8 environments, but not classifying it
- Regulatory agencies expect them to be placed in controlled access areas
- Minimum air exchange and % fresh air make-up required for safety reasons
- Room temperature control critical for common decontamination processes
- Installation of proper exhaust system is critical

Regulatory Expectations
Aseptic Processing Guidance Document

- Maintenance – Focus is on Glove Integrity Testing
- Design
  - Closed vs. Open Isolators
  - Pressure Differential of 17.5 to 50 Pa common
  - ISO 8 (Class 100,000) background environment
- Material Transfer
  - Properly operated and maintained RTP systems are effective transfer mechanisms
  - Design of pass-through units must not compromise isolation via air ingress
  - Sufficient overpressure should be supplied and monitored continuously at mouse hole locations

Regulatory Expectations
Aseptic Processing Guidance Document

- Decontamination
  - Full exposure to all pre-cleaned surfaces
  - Must render inner surfaces free of viable contamination
  - Materials testing recommended
  - Robustness should be demonstrated to help overcome limitations
  - 4 to 6-log spore reduction can be justified (application dependent)
  - Breach of isolator integrity should lead to decontamination
  - Sterilant concentration monitoring encouraged in large isolators
  - Product contact equipment (stopper hopper) should initially undergo bioburden reduction

Additional Regulatory Expectations PIC/S Guidance Document

- Purpose of document is to provide guidance to GMP inspectors
- Focuses on reducing the risk of microbiological contamination arising from the environment
- Gas generators should not be assumed to be equivalent
- A minimum of 10 Pascal positive differential air pressure should be maintained
- Should seek a 6-log reduction of BI for isolator decontamination
- The resistance of the BI to the process being validated should be estimated

BI Resistance Testing - Why?

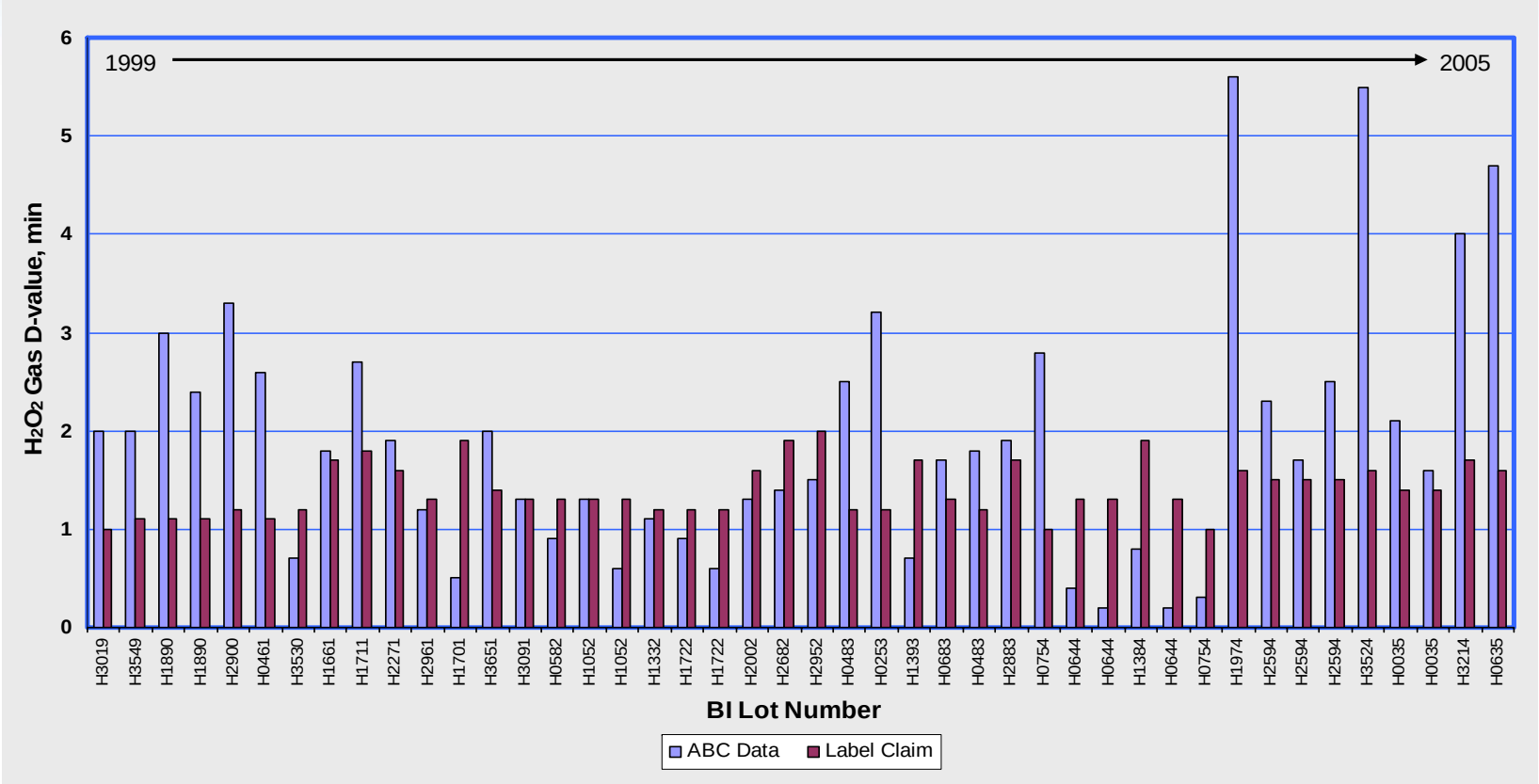
- Primary purpose for in-house testing is to compare lot-to-lot resistance against your internal standards
- The spore population and resistance of the BI must be determined <1208> and PIC/S
- The user should establish acceptance standards <1035>
- You can accept a vendor's D-value <1208>, but the label claim data may not correlate to results obtained in-house (not consistently higher or lower than data obtained in the field)

Types of Biological Indicators

Pre-packaged BI

User Prepared BI

5-Year Review of In-House vs. Apex Labs BI D-value Data



BI Resistance Data - Conclusions

- BI manufacture is part science and part art (inherent lot-to-lot variability)
- Manufacturer's label claim resistance data obtained at 2 mg/liter may not coincide with what is determined in your isolator
- In-house resistance data is not consistent in it being less than or greater than the label claim
- The purpose of in-house testing is not to verify the label claim (not an "apples-to-apples" comparison)
- Goal should be to establish base-line validation data, to provide a means of accepting or rejecting future lots, or to assist in troubleshooting generator problems

Key Validation Steps - IQ

- Equipment / System Specifications Review
- Purchase Order Review
- Equipment Drawing Verification
- HEPA Filter Installation Verification
- Equipment Manual Verification
- Instrument Identification and Calibration Verification
- Utilities Verification
- Maintenance / Preventive Maintenance Review
- Recommended Spare Parts List
- Safety Department Inspection Notification
- Software Version Installation Verification
- Input/Output Tests

Key Validation Steps – OQ

- Alarms Tests
- Start-up Sequence / PLC Function Verification
- Isolator PLC – Phase Parameters, Phase Changes, and Password Protection
- Basic Function and Loop Checks (all modes)
- Leak testing (pressure drop vs. ammonia)
- Interconnectivity of equipment
  - Controls & handshaking with decontamination equipment
  - Measure isolator exhaust airflows when attached to active exhaust system
- Pressure Maintenance

Key Validation Steps – PQ

- Development of an optimized decontamination cycle
- Temperature and gas distribution tests (TC/BI) using minimal exposure time
- Aerate and exhaust tests using normal (production) exposure time – typically 20% longer
- Equivalency testing
- Residue effects testing

Developing & Qualifying Optimum Decontamination Cycles

- Development calculations utilize known (volume) and estimated (temperature) variables
- Parameters obtained from Cycle Development Guide
- Goal is to optimize the cycle based upon actual data and then proceed with the PQ cycles
- Surface temperatures in the isolator should be documented along with the room air temperature
- Gas distribution can be verified or optimized with Chemical Indicators (CIs) – use only for development
- Total kill analysis of BIs establishes exposure time

How Many BIs Should We Use?

- Many locations throughout the isolator, including difficult to reach areas (FDA)
- PDA TR 34 suggests 5-10 BIs per m^3
- Base it on load size & volume of the enclosure
- Number can range from a few to hundreds

25-30 BIs is typical

265 BIs were used below

Importance of Temperature Distribution Studies (H_2O_2 Gas)

- The maximum allowable H_2O_2 gas concentration is based upon the humidity level and the minimum surface temperature within an isolator
- The coolest point in an isolator represents the location at which condensation would first occur when an excessive H_2O_2 gas concentration is used
- Temperature has been shown to indirectly affect sterilization efficacy in that an increase will lower the percent saturation and half-life of the gas, both of which can require longer exposure times

Aerate/Exhaust Validation Tools

- Understand limitations of the tools (RH & Temp effects)
- Permissible Exposure Level (PEL) & aerate levels are not necessarily equivalent
- Document exhaust airflow rates at pre-filter or in exhaust pipe during OQ
- Product stability testing may be warranted

Decontamination Cycle Equivalency Testing

- Cannot assume that identical isolators and/or generators are equivalent to each other (PIC/S)
- Must provide data to demonstrate that the validated cycle works for any isolator with any generator
- Perform a minimum of a single BI and a single aerate test for each piece of equipment

Residue Effects Testing

- USP <1208> states that tests must be performed using actual test articles that have been exposed to all phases of decontamination
- Studies need to be performed on each type of test container and environmental monitoring device
- This test will verify that residues on or around articles will not lead to a “false negative”
- Use triplicate samples for each test organism during a single decontamination cycle

Revalidation Studies

- Perform at least annually
- D-value determination on new lot of BIs
- Single BI and Aerate test per isolator and sterilant generator (this can be done for isolator/generator equivalency tests during original validation)
- Confirm sufficient exhaust airflows
- Verify room temperature is still within acceptable limits
- Reside effects testing on any new product configurations out of the validated matrix

Questions?

- Where do I start?
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- Regulatory Expectations
- BI Qualification
- Qualifying Isolators and Related Process Equipment