Lessons Learned from Pharmacy Cleanroom Renovations

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Learning Objectives

1. Review recent compounding standards updates for facility design according to USP <797>, <800>, accrediting bodies, and FDA.
2. Discuss common engineering control and design flaws and best practices for pharmacy compounding cleanrooms.
3. What to look for when selecting vendors and equipment for a cleanroom construction project.
4. Case studies and lessons learned for the design and commissioning of cleanroom facilities.

Oversight and Inspection

- One of the most highly regulated spaces in a hospital
- State Board of Pharmacy - Licensed and inspected against USP <797>, <800>
- Joint Commission (other accrediting bodies)– inspects against USP <797>, <800>
- FDA inspects against Insanitary Conditions at Compounding Facilities *Guidance for Industry,* Nov 2020
- Department of Health
- CMS

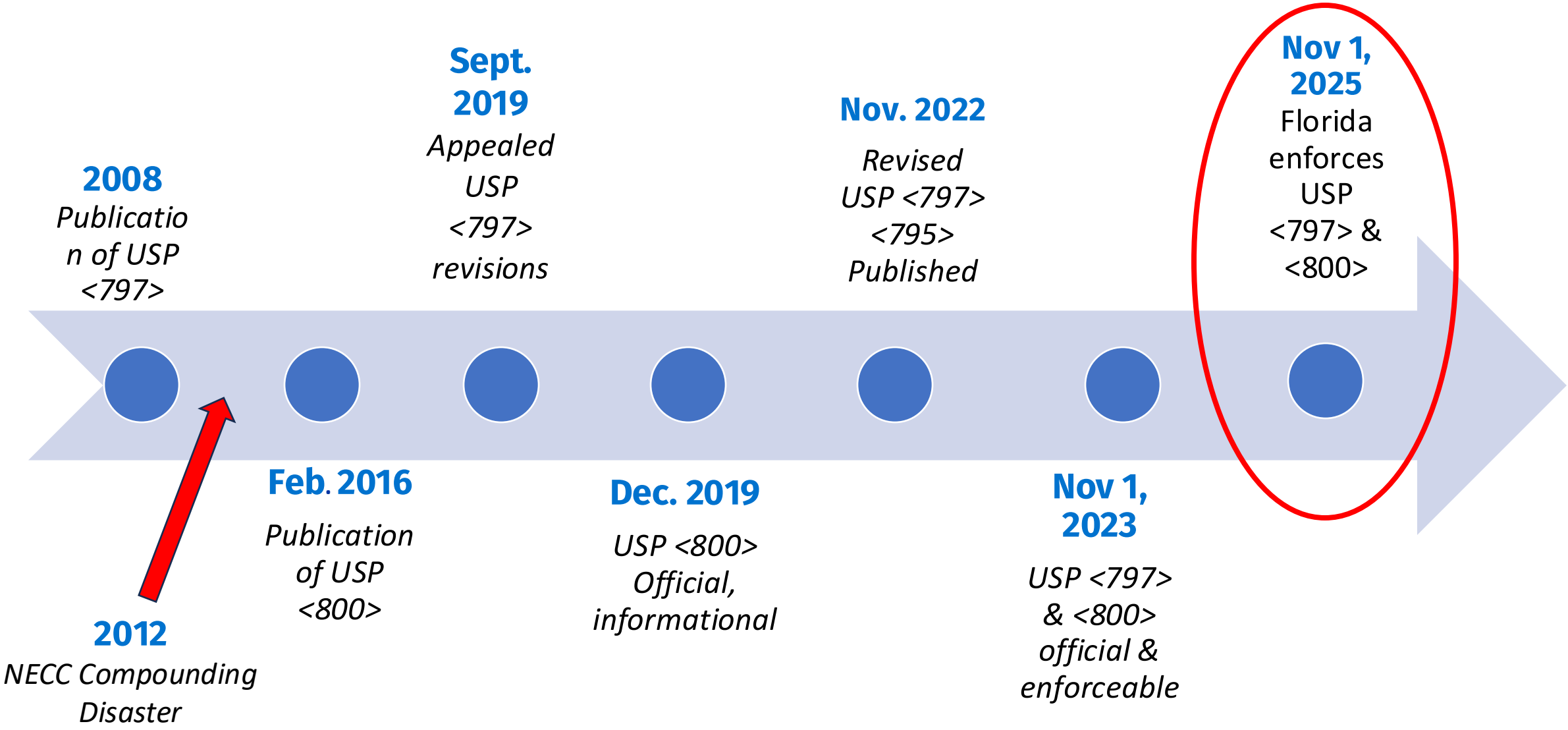
Oversight and Inspection

Pharmacy directors frequently share that what keeps them up most at night are issues related to **sterile compounding** and narcotic drug diversion

Cleanroom Facility Design Standards

- ISO 14644-1
- USP <797>, <800>, <795>, <1066>, <825>
- FDA – Insanitary Conditions; 503b Compounding Outsourcing Facilities
- State BOP Regs
- ASHRAE - 170-2017 – Ventilation of Health Care Facilities
- OSHA

Timeline for USP Chapter <797> & <800> Revisions



USP Engineering Control Requirements

- Temperature < 20°C/68°F
- Humidity < 60%; Risk of mold at RH > 60%.
- “Should” minimize dust collecting overhangs, “must” be easily cleaned
- Pass-through window doors “should” be interlocking
- Access doors “should” be hands-free
- No water sources inside ISO 7 buffer room
- Returns low on walls unless verified by a smoke study

USP Engineering Control Requirements

Summary of Requirements for Sterile Compounding			
COMPOUNDING AREA	**USP ACPH‡ REQUIREMENT**	***Best Practice ACPH Recommendation***	**USP Pressure Requirement**
Unclassified SCA* (non-HD)	No requirement	No requirement	No requirement
Unclassified C-SCA* (HD)	≥ 12 ACPH	≥ 15 ACPH	- 0.01 – -0.03” w.c.
HD Storage Room	≥ 12 ACPH	≥ 15 ACPH	- 0.01 – -0.03” w.c.
ISO Class 7 non-HD	≥ 30 ACPH	≥ 36 ACPH	+0.02” w.c.
ISO Class 7 HD or Ante	≥ 30 ACPH	≥ 36 ACPH	- 0.01 – -0.03” w.c.
ISO Class 8 Ante Room	≥ 20 ACPH	≥ 24 ACPH	+0.02” w.c.

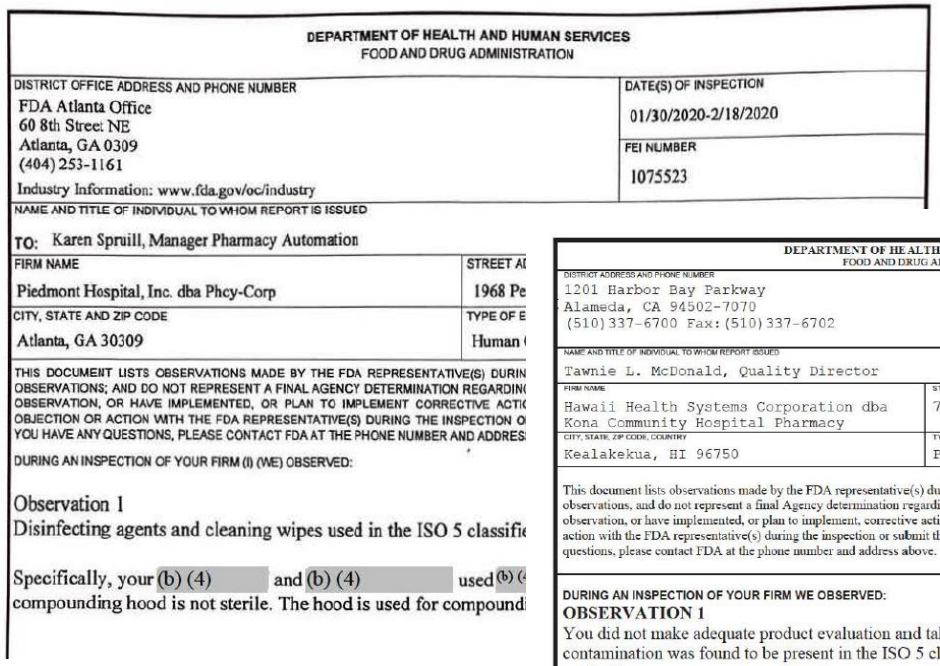
*Segregated Compounding Area / Containment Segregated Compounding Area

‡ At least 15 of total ACPH coming from HEPA/AHU

FDA Form 483 – Inspection Observations

- Remediation of Known **FDA Insanitary Conditions**:
  - **Scope** - The FDA's insanitary condition list is one of the quickest ways to find a hospital pharmacy under the purview of the FDA
  - **Observation** - If any of the following items were observed by an FDA inspector, sites may experience a thorough and drawn-out inspection lasting for weeks, months, or years. If one form 483 is issued, prepare for multiple form 483's to follow.
  - **Standards** – The broad scope of the FDA can lead to overreach with expectation to meet standards above 503A law (i.e., cGMP).
  - **Cost** – Years of oversight, lawyer fees, consultants, and building upgrades can become overwhelming to the budget when insanitary conditions are found.

FDA Form 483 – Inspection Observations



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
FDA Atlanta Office
60 8th Street NE
Atlanta, GA 0309
(404) 253-1161
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION
01/30/2020-2/18/2020

FEI NUMBER
1075523

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Karen Spruill, Manager Pharmacy Automation

FIRM NAME
Piedmont Hospital, Inc. dba Phcy-Corp

STREET AI
1968 Pe

CITY, STATE AND ZIP CODE
Atlanta, GA 30309

TYPE OF E
Human

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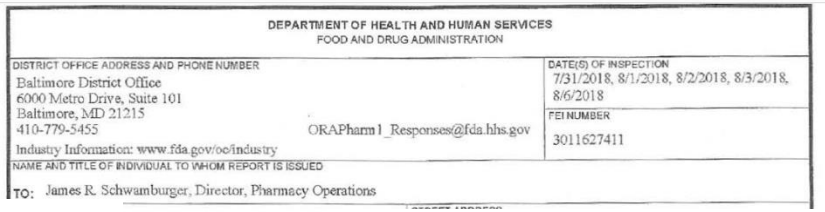
YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRES

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

Observation 1
Disinfecting agents and cleaning wipes used in the ISO 5 classifi

Specifically, your (b) (4) and (b) (4) used (b) (
compounding hood is not sterile. The hood is used for compound



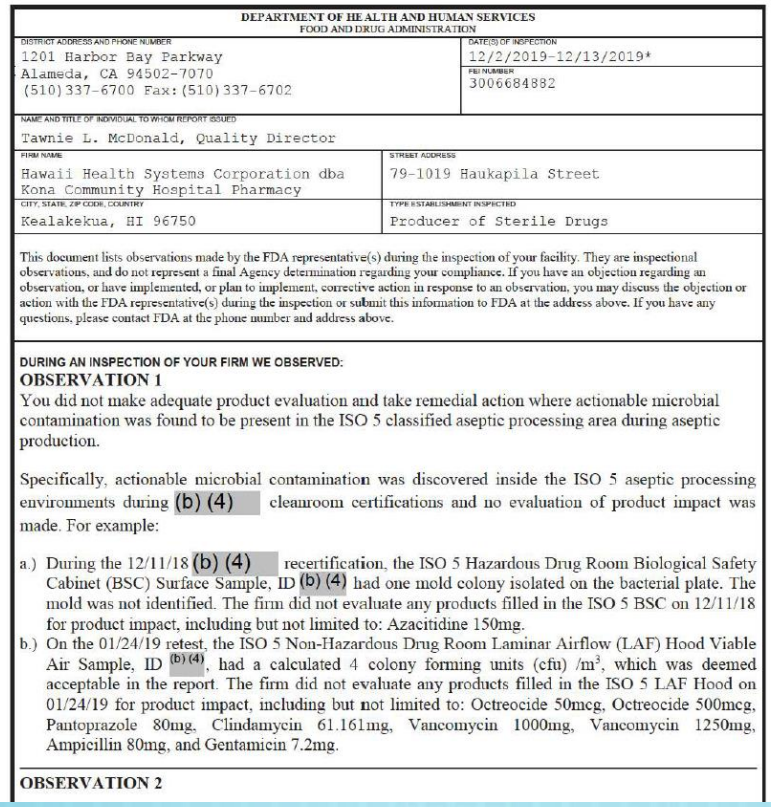
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
Baltimore District Office
6000 Metro Drive, Suite 101
Baltimore, MD 21215
410-779-5455
ORAPharm1_Responses@fda.hhs.gov
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION
7/31/2018, 8/1/2018, 8/2/2018, 8/3/2018, 8/6/2018

FEI NUMBER
3011627411

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: James R. Schwamburger, Director, Pharmacy Operations



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER
1201 Harbor Bay Parkway
Alameda, CA 94502-7070
(510) 337-6700 Fax: (510) 337-6702

DATE(S) OF INSPECTION
12/2/2019-12/13/2019*

FEI NUMBER
3006684882

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Tawnie L. McDonald, Quality Director

FIRM NAME
Hawaii Health Systems Corporation dba Kona Community Hospital Pharmacy

STREET ADDRESS
79-1019 Haukapila Street

CITY, STATE, ZIP CODE, COUNTRY
Kealakekua, HI 96750

TYPE ESTABLISHMENT INSPECTED
Producer of Sterile Drugs

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

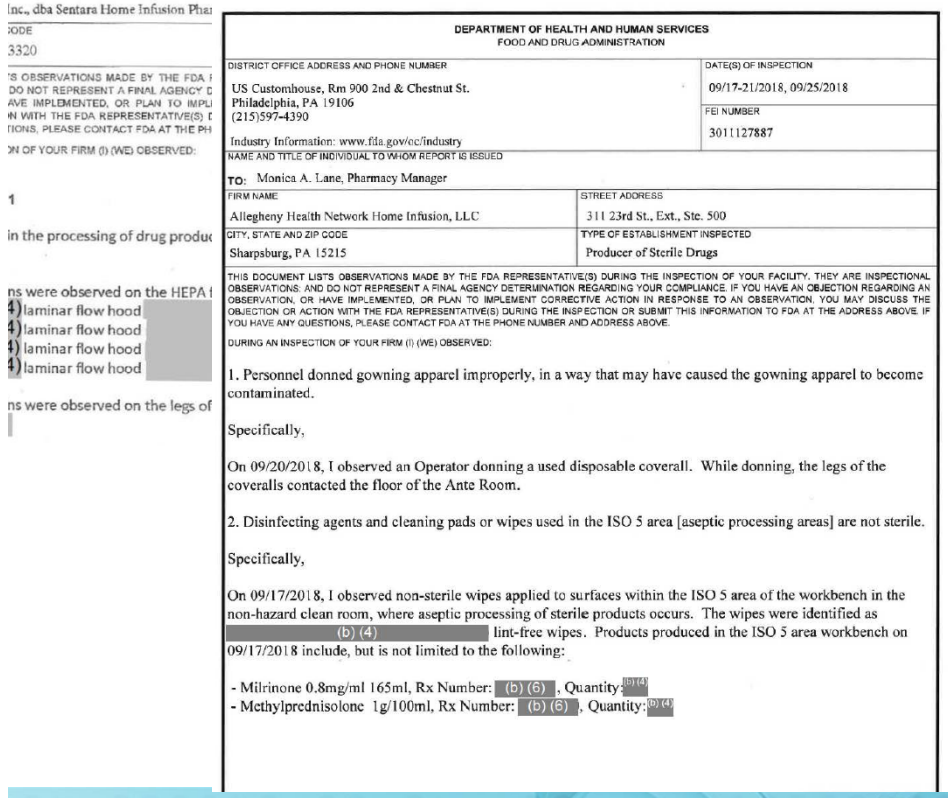
You did not make adequate product evaluation and take remedial action where actionable microbial contamination was found to be present in the ISO 5 classified aseptic processing area during aseptic production.

Specifically, actionable microbial contamination was discovered inside the ISO 5 aseptic processing environments during (b) (4) cleanroom certifications and no evaluation of product impact was made. For example:

a.) During the 12/11/18 (b) (4) recertification, the ISO 5 Hazardous Drug Room Biological Safety Cabinet (BSC) Surface Sample, ID (b) (4) had one mold colony isolated on the bacterial plate. The mold was not identified. The firm did not evaluate any products filled in the ISO 5 BSC on 12/11/18 for product impact, including but not limited to: Azacitidine 150mg.

b.) On the 01/24/19 retest, the ISO 5 Non-Hazardous Drug Room Laminar Airflow (LAF) Hood Viable Air Sample, ID (b) (4), had a calculated 4 colony forming units (cfu) /m^3, which was deemed acceptable in the report. The firm did not evaluate any products filled in the ISO 5 LAF Hood on 01/24/19 for product impact, including but not limited to: Octreocide 50mcg, Octreocide 500mcg, Pantoprazole 80mg, Clindamycin 61.161mg, Vancomycin 1000mg, Vancomycin 1250mg, Ampicillin 80mg, and Gentamicin 7.2mg.

OBSERVATION 2



Inc., dba Sentara Home Infusion Pha
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ON OF YOUR FIRM (I) (WE) OBSERVED:

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4) laminar flow hood
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4) laminar flow hood
4) laminar flow hood

ns were observed on the legs of

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
US Customhouse, Rm 900 2nd & Chestnut St.
Philadelphia, PA 19106
(215)597-4390
Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION
09/17-21/2018, 09/25/2018

FEI NUMBER
3011127887

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED
TO: Monica A. Lane, Pharmacy Manager

FIRM NAME
Allegheny Health Network Home Infusion, LLC

STREET ADDRESS
311 23rd St., Ext., Ste. 500

CITY, STATE AND ZIP CODE
Sharpsburg, PA 15215

TYPE OF ESTABLISHMENT INSPECTED
Producer of Sterile Drugs

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Personnel donned gowning apparel improperly, in a way that may have caused the gowning apparel to become contaminated.

Specifically,

On 09/20/2018, I observed an Operator donning a used disposable coverall. While donning, the legs of the coveralls contacted the floor of the Ante Room.

2. Disinfecting agents and cleaning pads or wipes used in the ISO 5 area [aseptic processing areas] are not sterile.

Specifically,

On 09/17/2018, I observed non-sterile wipes applied to surfaces within the ISO 5 area of the workbench in the non-hazard clean room, where aseptic processing of sterile products occurs. The wipes were identified as (b) (4) lint-free wipes. Products produced in the ISO 5 area workbench on 09/17/2018 include, but is not limited to the following:

- Milrinone 0.8mg/ml 165ml, Rx Number: (b) (6), Quantity: (b) (4)
- Methylprednisolone 1g/100ml, Rx Number: (b) (6), Quantity: (b) (4)

FDA Form 483 – Inspection Observations

Date	Location	Citation Detail
April 2022	Washington State	**Compounding workflows** and **building** is **not designed to prevent contamination**
January 2020	Georgia	**Nonsterile** disinfecting agents used in ISO 5 hood
April 2018	Minnesota	Failure of personnel to disinfect gloves frequently; **nonsterile disinfecting agents** used in ISO 5 hood
August 2018	Florida	Nonsterile disinfecting agents used in ISO 5 hood; **inadequate investigate** of **microbial contamination**
December 2018	Michigan	**Failure to disinfect** materials before entering aseptic processing area; **exposed skin** in ISO 5 hood
December 2019	Hawaii	Widespread **microbial contamination** findings; **poor facility design; poor air balance controls**; **dust collecting overhangs**; unsealed HEPA filters; **improper personnel gowning**
July 2018, Aug 2018	Virginia	**Brown stains observed on HEPA filter** of ISO 5 hood, nonsterile disinfecting agents used in ISO 5 hood
Sept 2018	Pennsylvania	**Improper personnel gowning;** nonsterile disinfecting agents used in ISO 5 hood

Isn’t a Pharmacy Cleanroom the same as an OR?

- Negative pressure cleanroom spaces are one of the most challenging areas to design and maintain

Requirement	Operating Rooms	Hazardous Drug (HD) Sterile Pharmacy Cleanroom	Non-HD Sterile Pharmacy Cleanroom
Pressure Flow Cascade	Positive	Negative	Positive
Inches w.c. pressure differential	> 0.01”	Must be between -0.01” and 0.03”	Must be at least ≥ 0.02”
Temperature	68 – 72F	Must be less than <68F (usually designed for 64 – 65F)	Must be less than <68F (usually designed for 64 – 65F)
Humidity	20% - 60%	<60%	<60%
Cleanliness	Not ISO Certified Must use MERV-16 filters at the air handler	**ISO 7** HEPA Filtration required at point of delivery in ceiling	**ISO 7** HEPA Filtration required at point of delivery in ceiling

Common Pharmacy Cleanroom Failures

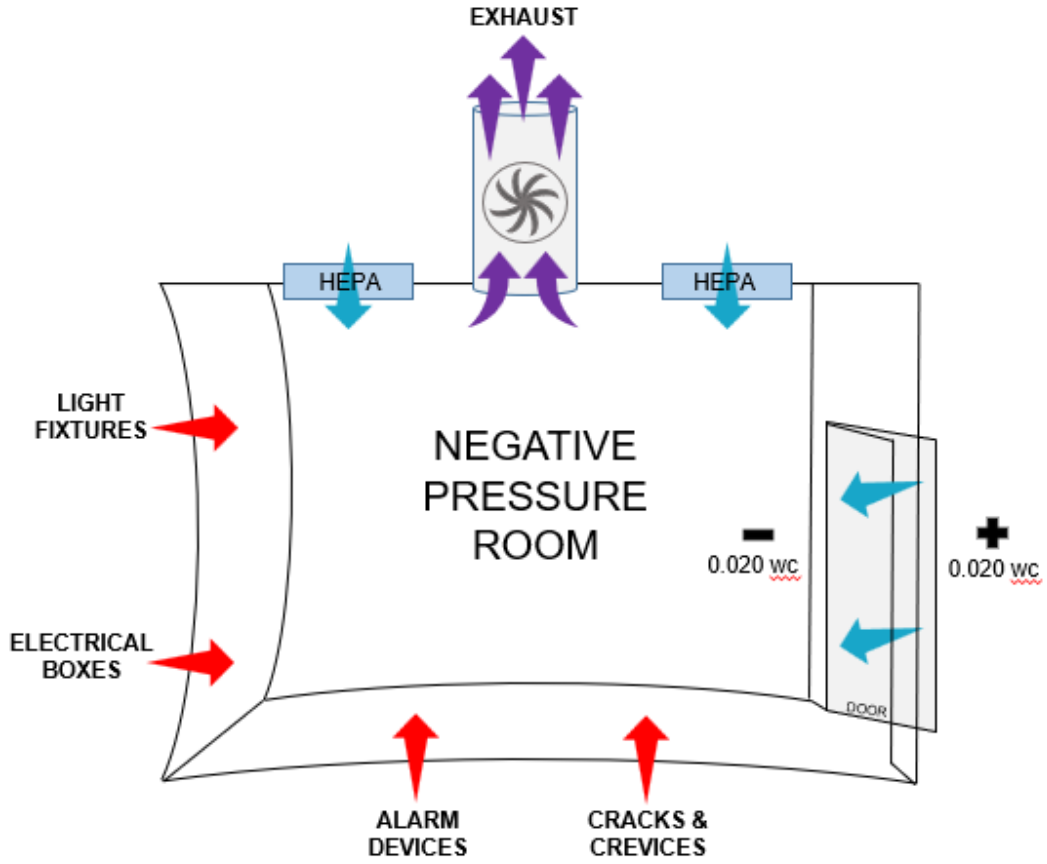
- Differential air pressure
- ACPH below minimum acceptable level for ISO classification
- Temperature
- Relative humidity
- Design and layout
- HEPA filter leaks
- Elevated particle counts

Differential Air Pressure Reversals

- Entry of viable contaminants (e.g., bacteria, fungus) into positively pressurized cleanroom
- Ingress of viable contaminants into overly negative space
- Release of hazardous agents, materials from negatively pressurized cleanroom, occupational exposure

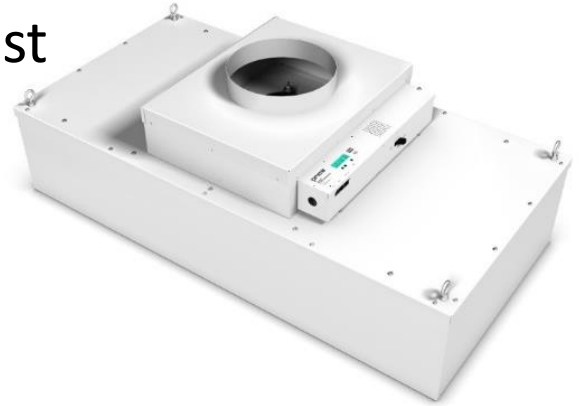
Differential Air Pressure Excursions

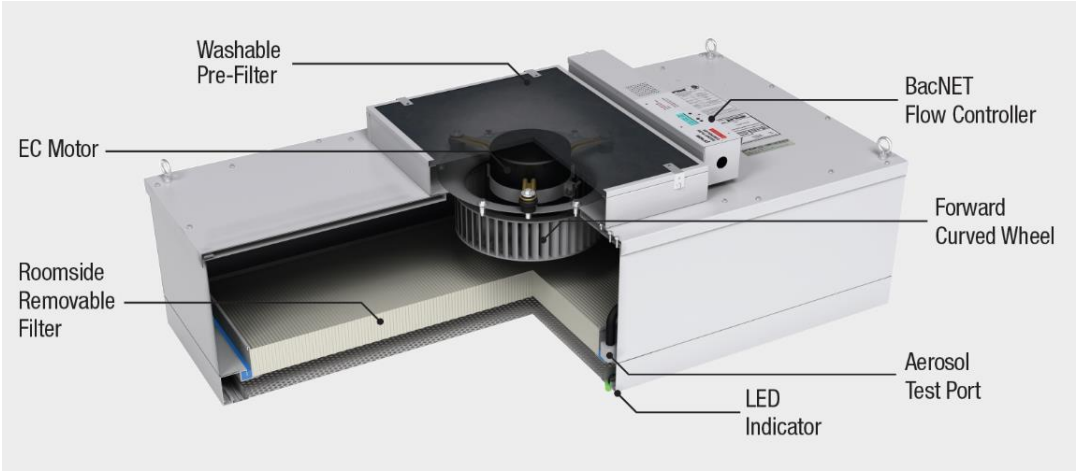
- Improper equipment selection, undersized AHU, airflow design
- DP is affected by primary air originating from AHU



Impact of Equipment Selection on DP

Fan Filter Unit (most common)



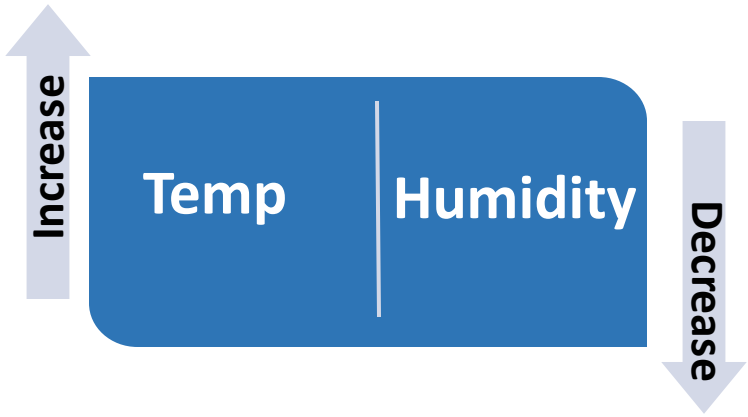


HEPA Filter Diffuser (uncommon)

No fan, all airflow will be from Air Handling Unit

Image source: www.priceindustrustries.com

Temp/RH: RH vs. Dew Point



- Relative humidity is the amount of water vapor that exists in the air compared to the total amount that can exist at its current temperature.
- Dew point temperature is the temperature the air needs to be cooled to in order to achieve a relative humidity (RH) of 100%
- AHU should be sized to deliver supply air at a sufficient dew point
  - AHU discharge air temperature - This cooling coil leaving air temperature sets the upper limit of dew point for the space
- Use dew point when troubleshooting humidity issues in the space.

Temperature and Humidity Failures

- Systems that do not run 24/7
- Shared temperature control zones are problematic. Ensure each space a thermostat and heating source for temperature control.
- Only designing to the USP temperature recommendations of 68°F / 60% RH.
- Standard HVAC systems are specified
  - 66°F / 55% RH is a dew point of about 49.4°F. This requires non-standard HVAC systems with a higher capacity

Temperature/Humidity Failures

- Inadequate capacity of AHU cooling coils
- If using chilled water as the cooling source, must ensure that the chilled water temperature is always cool enough and ***does not*** reset to warmer temperatures at some times of the year.
- Know the chilled water temperature at the point of use. E.g, plant may output 42°F water, however AHU is very far away and water is 45°F when it gets there.

Cooling Sources - Chilled water vs. DX

- Chilled water usually preferred; cooling output is easier to control the water flow with a control valve.
- Direct expansion (DX) systems use refrigerant inside a cooling coil to cool and dehumidify the supply air.
- DX systems (compressors) can create dew point/humidity control challenges due to compressor cycling when temperature set points are achieved.
- If DX is necessary, the design engineer must understand the need for consistent supply air dew point control and specify equipment that alleviates the issue of compressor staging.

Impact of Equipment Selection on DP

- Placement of service items (valves, dampers) in accessible areas outside of cleanroom space
- FFU speed adjustments and fan speed control methodology
- Designing with a variable air setpoints for a pharmacy cleanroom. Should be fixed set points for supply and exhaust.

Impact of Equipment: Class II Type A2 vs. B2 BSC

- A2 cabinets recirculate 70% of their HEPA-filtered air back into the room and approximately 30% is exhausted.
- B2 cabinets require a hard-ducted building exhaust connection to draw the exhaust from the cabinet. 100% exhausted.
- B2 cabinets require higher pressure exhaust systems, use more energy, costlier ductwork, operational challenges for maintaining room differential pressures.
- During facility downtime or device failure, entire room goes out of compliance and pressure reversals can be experienced

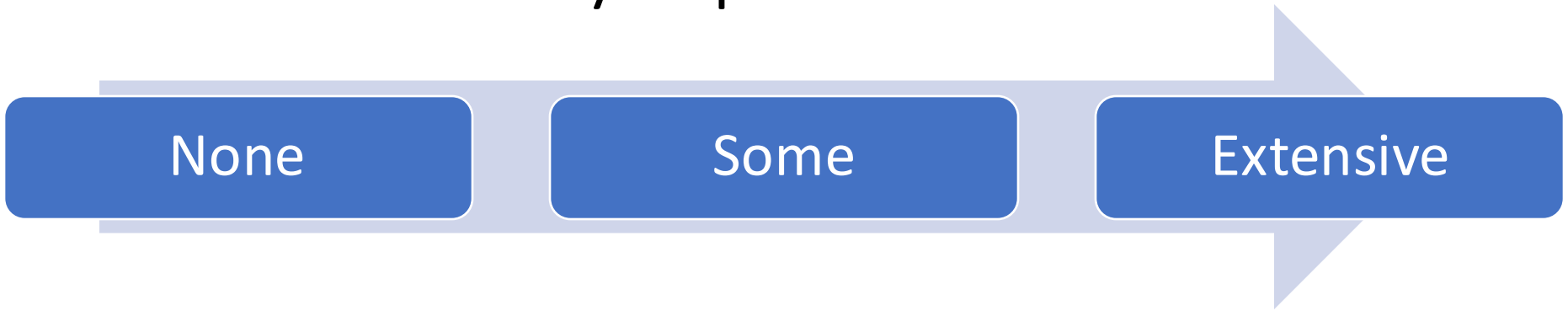
Other HVAC Failures

- Designing to minimum air changes
- Overdesigning – ACPH too high – impact Temp/RH
  - Minor changes in leaving air temp of primary air at AHU can impact temp/RH
  - ACPH – ISO 7 spaces – ACPH > 36 not necessary unless very specific equipment (multiple freezers within cleanroom with large heat load)
- Not having a dedicated AHU or exhaust fan
- Humidification systems - usually not recommended; require constant maintenance; proper water source (clean steam); no copper components

Improper HVAC Exhaust Design

- Recirculation of low wall exhaust in hazardous compounding room prohibited by USP <800>
- Lack of low wall exhaust (only using BSC)
- Lack of low wall exhaust behind cold storage

HVAC Redundancy Options

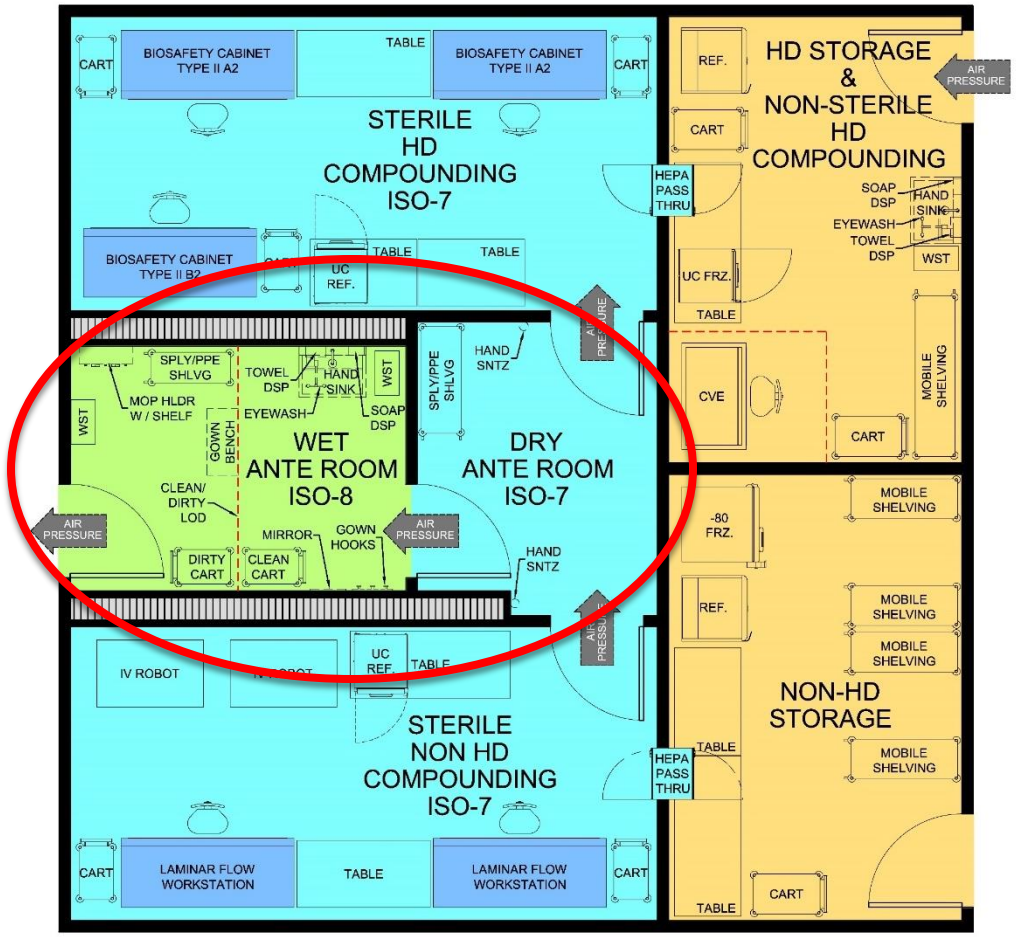


(Clinic or independent office cleanroom setting) Single exhaust fan, single RTU	(Hospital setting) Single AHU - fan array with N+1 supply fans 2 exhaust fans	(Hospital/Large Academic Center) Dual AHU Package dx unit - 2 sets of refrigeration circuits - compressor

Design Features

- Layout:
  - Single ante room vs.

  Wet & dry ante room
  - Prevents incoming contaminants
  - Conflicting regulations, standards, and best practices do not always align for contamination control

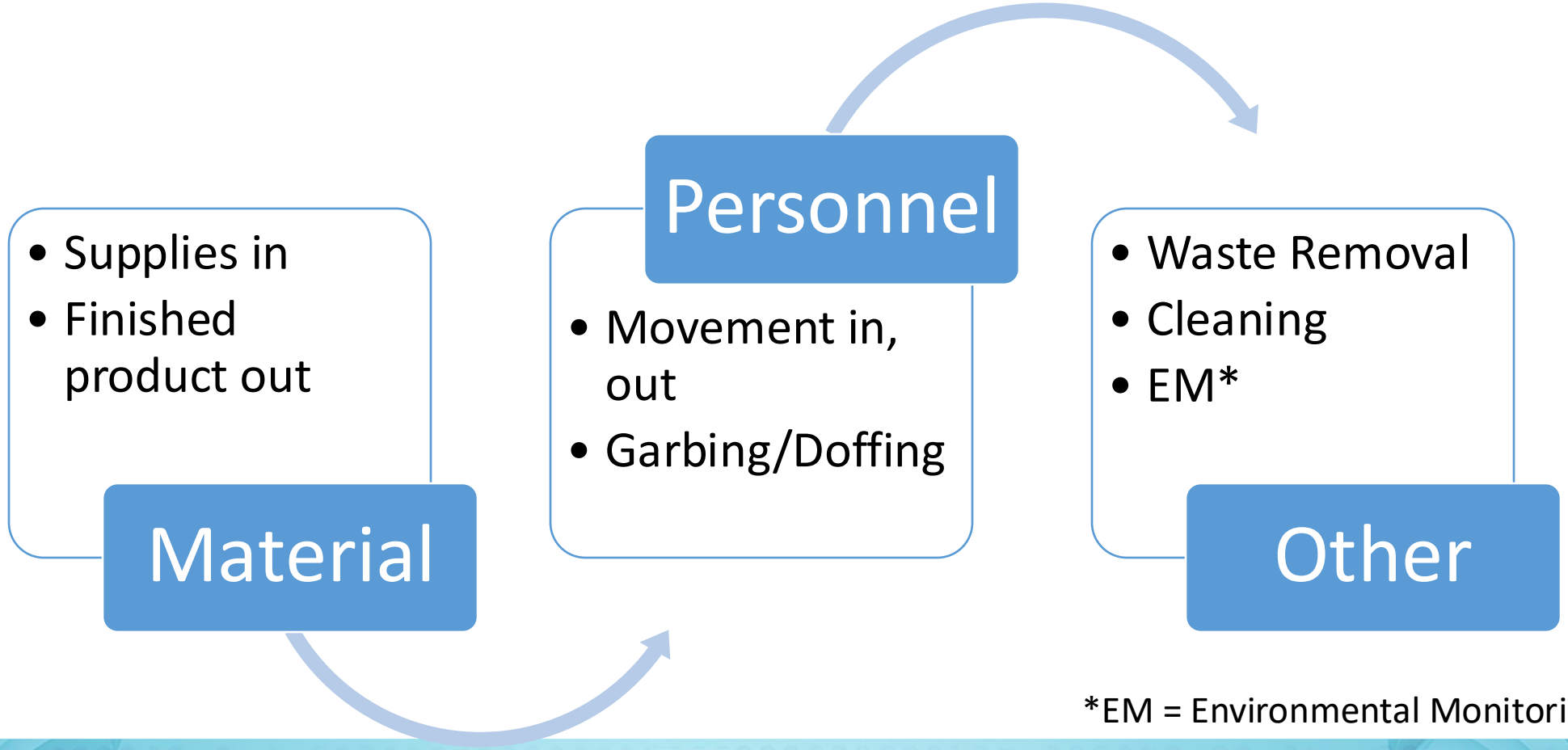


Design Features

- Sink location –
- In single ante room design – sink proximity; too close to HD room; shallow sink; proximity to PPE
- Integral eye wash
- Implement sink drain and p-trap cleaning program (No copper drain components – sporicides dissolve)
- HEPA ceiling filter location conflicts with PECs
- Proper placement of returns/exhaust especially in ante rooms… **don't block!**

Design Features

- Lack of defined program or workflow can result in poor design



*EM = Environmental Monitoring

Design Features

- Finishes: Walls, floors, ceiling, sealant
- Exhaust/return: blade style vs. egg-carton style
- Envelope and containment
- HEPA vs. non-HEPA powered pass-through between classified and non-classified spaces
- Furniture/Storage: examine grade of stainless (304 vs. 316)
- Recommend casters to prevent rust

Design Features

- Location of PEC
- Avoid installation of BSC adjacent to wall
- Avoid placement of BSC near doorways, pass-throughs
- Access panels – lack of gasketing
- Ledges (e.g., ensure sloped top door openers, pass-through)

Design Flaws

- Doors – swing vs. slide – interlocking – direction of swing
- Select and install door without seal/gasket

PHARMACY SEALANT LOCATIONS

WALLS: All locations where a device or material creates a joint with the wall must be sealed.

- Perimeter of electrical devices
- Perimeter of door frames and windows
- Pass-Through Units – Flange to PT joint and flange to wall joint
- Perimeter of Fire Alarm devices
- Perimeter of Access Control devices
- Perimeter of HVAC devices – Tstats, RH, and DP sensors
- Perimeter of exhaust/return grilles
- Top of integral floor cap
- Perimeter of hand wash sink
- Perimeter of wall hung accessories – Dispensers for soap, towels, booties, etc.
- Perimeter of wall mounted door stops
- Perimeter of wall protection devices
- Perimeter of Tele/Data devices

FLOORS: All locations where materials form joints with the flooring must be sealed.

- Cove base joint where floor meets the base of the top cap
- Base of door frames
- Integral floor cove to door frame joint

CEILINGS: All locations where a device or material creates a joint with the ceiling must be sealed.

- Perimeter of electrical fixtures – lights, exit signs, etc.
- Perimeter of Fire Alarm devices
- Perimeter of sprinkler head penetrations (**NOT Covers**)
- Perimeter of duct penetrations
- Perimeter of supply air filters

DOORS: All locations where a device or material creates a joint with the door must be sealed.

- Perimeter of window lites
- Perimeter of hardware – levers, bottom seals
- Perimeter of door protection devices

Cleanroom Vendors & Equipment

- Modular vs. stick build
  - Ensure no ledges (no storefront system)
- Flooring
- Ceiling Selection / suspension system selection
- Hoods (limit powder coated metal; type of s.s.)
- Pass through unit
- AHU (appropriate modulation capabilities)
- Test and Balance Team expertise
- Certification firms

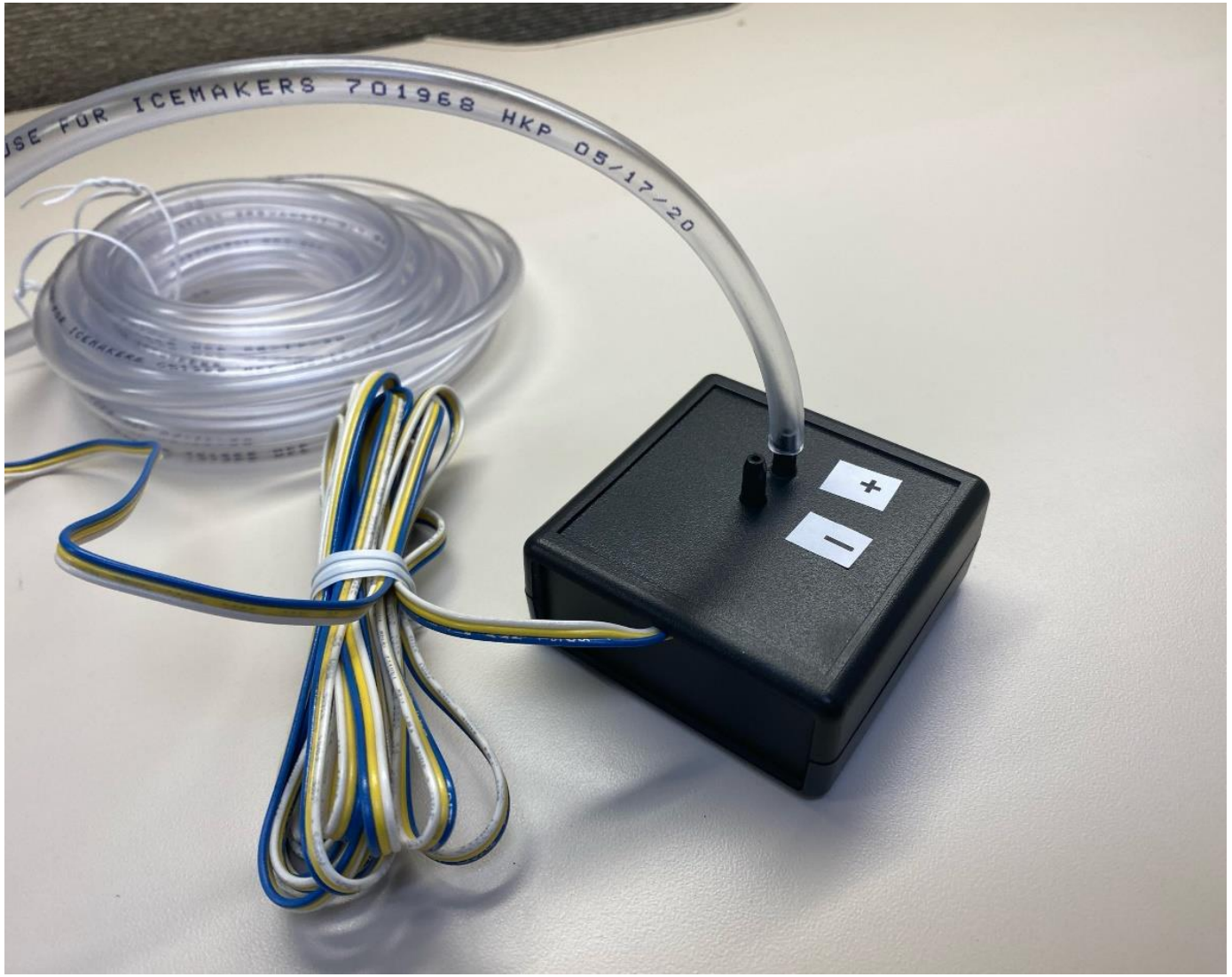
Equipment Lessons Learned

- Refrigerator – ensure heated condensate pan is present and HD rooms – required exhaust
- All in one HEPA diffuser fan and cleanroom light combination (space saver)
- Avoid HEPA pass through with recirculating air
- Emergency power considerations
- Supply and exhaust interlocks

Case Study 1

- GMP biologics manufacturing program
- DP out of range and room certification failed
- No DP alarms had gone off

Case Study 1



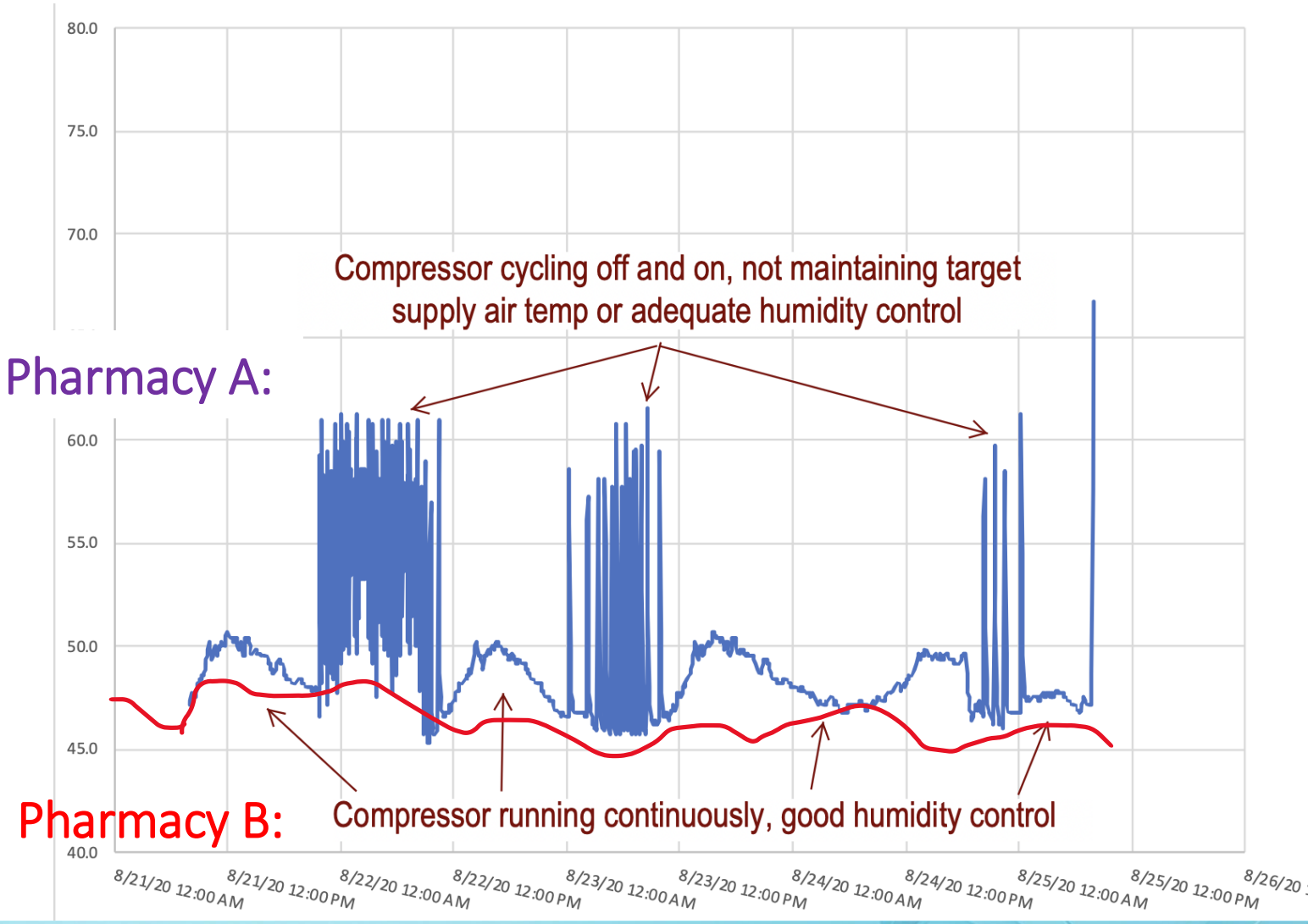
Case Study 1: Investigation

- Pressure sensor tube/valve malfunction
- No DP alarms → no alarms had been programmed
- Pressure sensor tube corrected and DP alarms set

Case Study 2:

Pharmacy A:
compressor cycles on and off – inadequate temp/RH control

Pharmacy B:
Compressor runs continuously



Case Study 2 Question:

What are some reasons for the RH excursions in Pharmacy A?

A. Undersized AHU
B. Compressor is designed to cycle on and off
C. ACPH set too high
D. Class II Type B2 unit selection vs. Type A2 BSC

Case Study 2 Question:

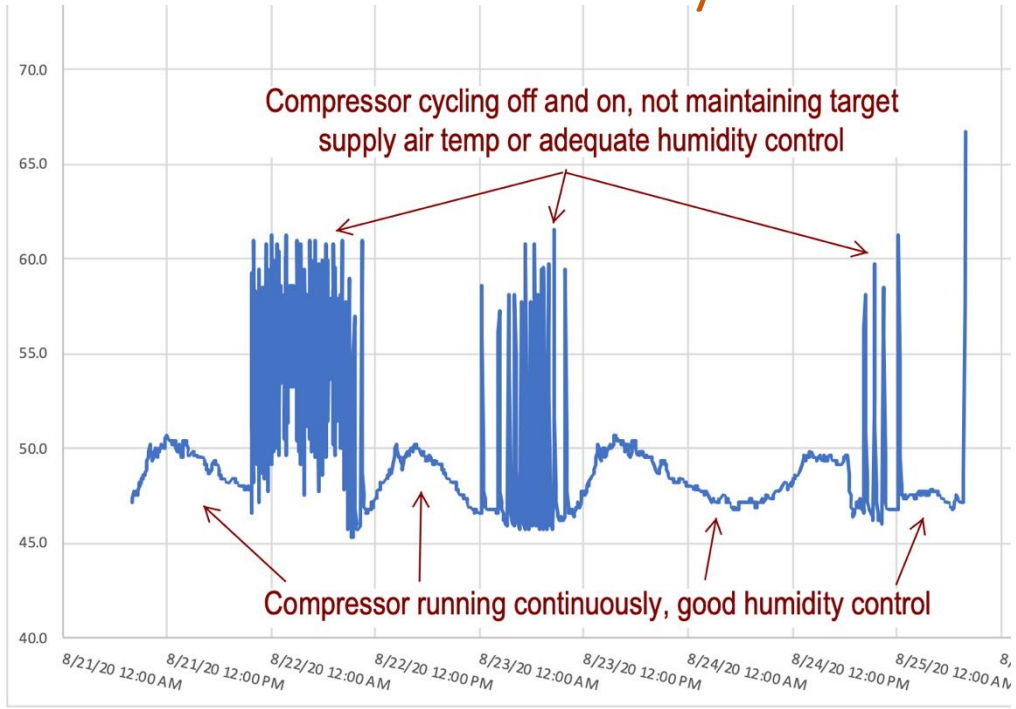
What are some reasons for the RH excursions in Pharmacy A?

A. Undersized AHU
B. Compressor is designed to cycle on and off
C. ACPH set too high
D. Class II B2 unit selection vs. Class II A2 unit

Case Study 2: Investigation

- Direct Expansion (Dx) Compressor Cycling
- Normal Dx unit has compressor that cycles on and off
- To overcome – unit will need to be outfitted with hot gas bypass

Relative Humidity control



Case Study 3: Excursion

- Hospital system recently renovated the oncology office building with a new small cleanroom suite containing 2 BSC, 1 LAFH, wet-dry ante room.
- Due to cost containment, the existing Dx unit servicing the office building was used for the cleanroom suite. The cleanrooms were installed using ceiling mounted HEPA filter diffusers

  Initial certification results:

ISO 7 HD room	**ACPH: 23**
ISO 7 non-HD room	**ACPH: 27**
ISO 7 dry Ante room	**ACPH: 30**
ISO 8 Wet Ante room	**ACPH: 21**

Case Study 3 Question

What is your initial hypothesis for the decreased ACPH in the new cleanroom?

A. Inappropriate cleaning regimen
B. Existing Direct Expansion Unit was not sized for the necessary air changes for the facility
C. HEPA diffuser boxes were installed rather than HEPA fan filter units
D. B & C

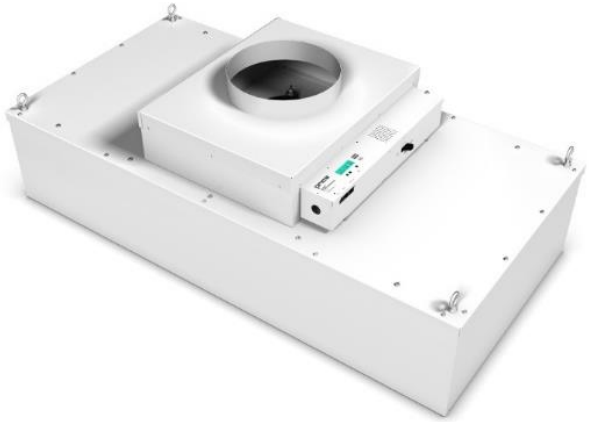
Case Study 3 Question

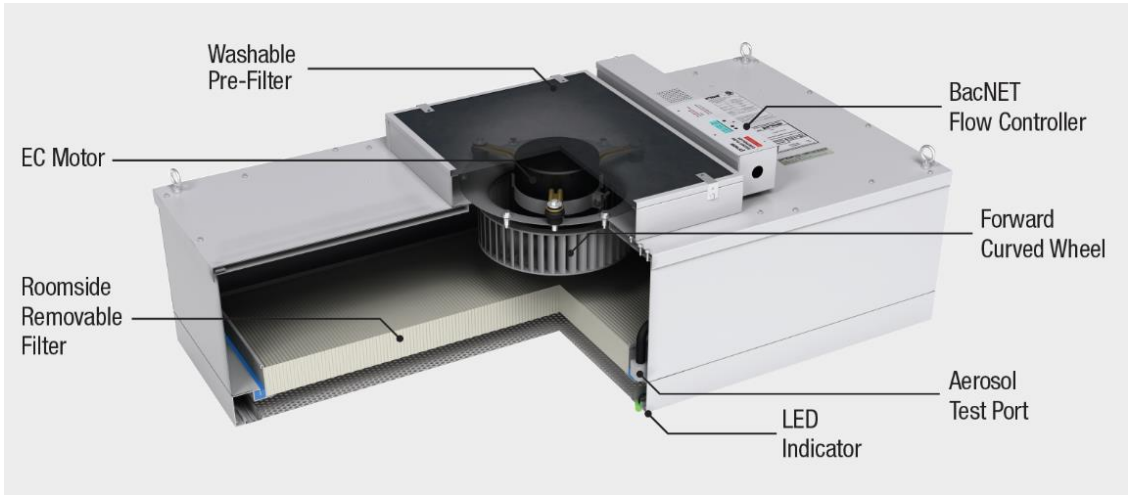
What is your initial hypothesis for the decreased ACPH in the new cleanroom?

A. Inappropriate cleaning regimen
B. Existing Direct Expansion Unit was used rather than a dedicated AHU for the cleanroom
C. HEPA diffuser boxes were installed rather than HEPA fan filter units
D. B & C

Cast Study 3: Excursion Example

Fan Filter Unit (most common)





HEPA Filter Diffuser (uncommon)

With insufficient capacity from Dx AHU, the HEPA diffuser was not sufficient

Image source:
www.priceindustrustries.com

Case Study 4: Identify what is wrong?

Identify what is wrong with the image shown on the next slide


STERILE COMPOUND
CAUTION

Questions?