Utilizing EM Results to Improve Processes & Practices

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Who came up with this?

- **U.S. Railroad tracks are 4' 8.5" in width. That's a strange number… Where did that specification come from?**
- **Because that was the specific width of the English railroad tracks and the U.S. Railroads were built by English settlers (expatriates). But, why is that so?**
- **Because, in England, the railroads were built by the same people who made the original tramcars. They had used the same gauges as the tramcars, which had that specific spacing. But, why is that so?**
- **Because, the people who built those tramcars used the same tools as they did for building wagons. And the wagon axles had that specific spacing. But, why is that so?**
- **Because, the the old, ragged, roads in England had wheel ruts on the sides of the road. This specific spacing was needed to keep the wagon wheels from maneuvering out of the ruts and breaking on the rough surfaces. But, why is that so?**
- **Because, the roads where originally built by Imperial Rome and those ruts were dug over many years by their chariots. That was the specific width of the chariot wheels. But, why is that so?**
- **The Roman chariots were specifically spaced just wide enough to accommodate the rear ends of two horses.**

WHAT THE ???

So, the next time you are handed a specification/document/guideline and you are forced to wonder, "What horse's ass came up with this?", you may be right!

It may also be used to understand why "We have always done it this way".

Early microbiologists

Components of an EM Program

“System” Components

- **Contamination Control** is a proven system that prevents external contamination from entering controlled environments
- **Environmental Monitoring** tests that the system you designed is keeping your areas under control
- **Cleaning and Disinfection** corrects the inappropriate introduction of contamination

Areas of Control Within a Facility ("PEER")

- **Personnel**
- **Equipment**
- **Environment (Water, HVAC)**
- **Raw Materials**

What is Environmental Monitoring?

It Is:

- **Demonstrates Control of Aseptic Operations**
- **Identifies problems and trends in process and facilities**
- **Affects Cleaning and Disinfection selection/application and corrects the inappropriate introduction of contamination**
- **Provides data collection to support root cause analysis of excursions**

Is is Not:

- **A test for final preparation release**
- **An analytical test**
- **Highly reproducible or recoverable**
- **Always constant**
- **Always linked to the "smoking gun" (cause and effect)**
- **Total picture of control**

Regulations, Guidelines and Literature

Current Documentation

- **United States Pharmacopeia 39 (Unchanged for USP 40 - May 2017), <797> Pharmaceutical Compounding—Sterile Preparations**
- **Reference(s) to United States Pharmacopeia 39, <1116> Microbiological Control and Monitoring of Aseptic Processing Environments**
- **California Health & Safety Code – Division 104 (Environmental Health, Part 5 (Food, Drugs, Cosmetics), Chapter 6 (Drugs & Devices)**
- **Board of Pharmacy Regulations (January 2017) - California Code of Regulations Title 16 Section 1700 et seq.)**
- **FDA Guidance for Industry - Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (June 2014)**
- **ASHP Guidelines on Compounding Sterile Preparations (2014)**
- **CETA Application Guide for USP <797> Viable Environmental Sampling & Gowning Evaluation (January 2012)**
- **CDC Guidelines for Environmental Infection Control in Healthcare Facilities (2013)**

What is Current Status of USP <797>?

- **Originally Published in USP (2004), replacing chapter <1206>, Sterile Drug Products for Home Use**
  - **Changed from a guideline/advisory to an enforceable chapter**
- **Revised in USP 31 (June 2008)**
- **Additional revision proposed in 2010, initial revision published for public comment in Pharmacopeial Forum (PF) 41(6) Nov - Dec 2015 (comment period was from September 25, 2015 - January 31, 2016)**
- **USP Compounding Expert Committee received over 8,000 public comments and are currently reviewing all submissions.**

Determination of Sample Locations

Document	How to Determine Locations
ASHP	• Sampling plans should be detailed and include all high-traffic locations within the compounding area and any sites prone to contamination. • Turbulence caused by airflow disruption, such as within an ISO Class 5 LAFW or doorways, should be included in the testing plan, along with areas where garbing, cleaning, labeling, and staging occur. In segregated compounding areas, sampling should include locations within the ISO Class 5 PEC and other areas in close proximity to the PEC. • A specific plan detailing the location of each sample must be devised so that the same locations are repeated with each testing session.
USP <797>	• An appropriate environmental sampling plan shall be developed for airborne viable particles based on a risk assessment of compounding activities performed. • Selected sampling sites shall include locations within each ISO Class 5 environment and in the ISO Class 7 and 8 areas, and the segregated compounding areas at greatest risk of contamination (e.g., work areas near the ISO Class 5 environment, counters near doors, pass-through boxes).

Determination of Sample Locations (cont.)

Document	How to Determine Locations
CETA	Sites should be selected throughout the area. Areas that pose the greatest risk of contamination to the product must be included in the program. FDA Aseptic Guidance - "It is important that locations posing the most microbiological risk to the product be a key part of the program. It is especially important to monitor the microbiological quality of the critical area to determine whether or not aseptic conditions are maintained during filling and closing activities. • Air and surface samples should be taken at the locations where significant activity or product exposure occurs during production. • Critical surfaces that come in contact with the sterile product should remain sterile throughout an operation. • When identifying critical sites to be sampled, consideration should be given to the points of contamination risk in a process, including factors such as difficulty of setup, length of processing time, and impact of interventions." • Therefore, the number of sample locations is increased in areas where there is a greater potential for contamination to product.

Viable Monitoring Frequency

Document	Frequency		
	Parameter	**Monitored By**	**Frequency**
USP <797>	Surface sampling	Compounding or laboratory personnel	Periodically, as defined by compounding and infection control personnel, at least every 6 months or after significant changes in procedures or cleaning practices **Changed to Monthly in Interim Revision**
	Electronic device sample of viable particles	Compounding personnel or qualified certifier	Air sampling shall be performed at least semiannually (i.e., every 6 months) as part of the re-certification of facilities and equipment. **Changed to Monthly in Interim Revision**
CA CR	• Viable surface sampling shall be done at least every six months for all sterile-to-sterile compounding and quarterly for all non-sterile-to-sterile compounding. • Viable air sampling shall be done by volumetric air sampling procedures which test a sufficient volume of air (400 to 1,000 liters) at each location and shall be done at least once every six months. • Viable air sampling is to be performed under dynamic conditions that simulate actual production. • Viable surface sampling is to be performed under dynamic conditions of actual compounding.		

Viable Monitoring Frequency (continued)

Document	Frequency
FDA – 503b	Environmental monitoring should consist of a well-defined program that evaluates the potential routes of microbial contamination of the human drug that could arise from the air, surfaces, process, operation, and personnel practices. The program should contain an appropriate detection component to verify state of control of the environment. In particular, the program should achieve the following: • Cover all production shifts and include monitoring during normal production conditions • Include at least daily monitoring of the ISO 5 zone during operations • Establish alert and action limits and appropriate responses to each • Describe use of sampling (e.g., contact plates, swabs, active air samplers), alert and action limits, and testing methods (e.g., media, plate exposure times, incubation times and temperatures) that are designed to detect environmental contaminants, including changes in microflora type and amount. • Be supported by an evaluation of the choice of the sampling locations and sampling methods

Viable Monitoring Frequency (continued)

Document	Frequency
CETA	Semi-annual basis as a minimum (twice per year). It is recommended to complete viable sampling after initial certification procedures but prior to recertification procedures to provide an "as found" result that compounding managers can utilize to show compliance for activities performed until the time of testing After any situation which may impact the normal operation of the cleanroom or PEC • after movement of equipment • after any servicing of facilities and/or equipment • after a patient incident in which the compounded material is suspect • after changes to the process that affect the cleanroom environment • after observation of incorrect work practices such as: gowning, technique, material flow, cleaning etc. • after identified problems with end product • After significant changes in work flow or addition of new procedures or equipment.

Viable Sampling Methods

Document	How to Determine Locations
ASHP	• Air: Electronic Active air, passive (settle plates) • Surfaces: Swabs and contact plates
USP <797>	• Air: Active air, passive (settle plates) • Surfaces: Swabs and contact plates
CA CR	• Air: Active air, passive (settle plates) • Surfaces: Swabs and contact plates
CETA	• Air: Active air, passive (settle plates) • Surfaces: Swabs and contact plates
FDA 503b	• Air: Active air, passive (settle plates) • Surfaces: Swabs and contact plates

While Passive/Settle plates are mentioned in the documentation, there is no specific recovery limit for them

Viable Limits – USP <797> (*harmonized*)

Table 2. Recommended Action Levels for Microbial Contamination*

Grade	Air Sample - CFU/1000L (m^3)
ISO Class 5	> 1
ISO Class 7	> 10
ISO 8 or Worse	> 100

* Guidance for Industry–Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice–US HHS, FDA September 2004.

Table 4. Recommended Action Levels for Microbial Contamination*

Grade	Fingertip Sample	Surface Sample (Contact Plate) (CFU per plate)
ISO Class 5	> 3	> 3
ISO Class 7	N/A	> 5
ISO 8 or Worse	N/A	> 100

* Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products Annexes PE 009-6, 5 April 2007.

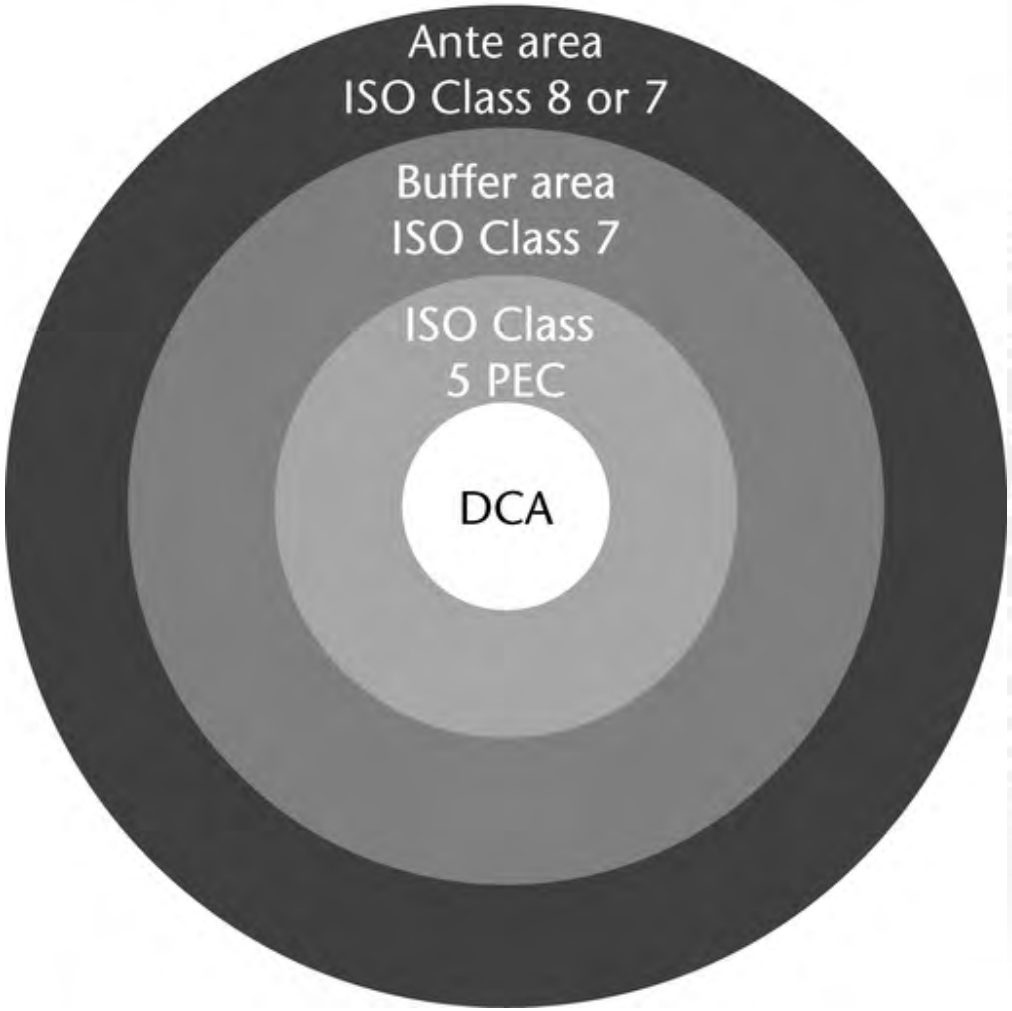
Media Selection & Incubation

Document	Microorganism	Incubation Conditions
ASHP	The growth medium should be incubated (outside of the sterile preparation area) according to the manufacturer's recommendations (huh!?)	
USP <797>	Bacteria, yeast, and molds	TSA: 35 ± 2°C for 2 – 3 Days MEA or other suitable fungal media: 28 ± 2°C for 5 – 7 Days
CA CR	• Media used must have demonstrated the ability to support and promote growth. Completed medium samples must be incubated in a manner consistent with the manufacturer's recommendations (again, what?) • Appropriate growth media, which are then incubated at a temperature and for a time period conducive to multiplication of microorganisms	
CETA	**Single plate method -** Sample each location using a general microbiological media such as tryptic soy agar. **Duplicate plate method -** Sample each location using a general microbiological media such as tryptic soy agar, then sample the same locations again using a general mycological media or a media capable of supporting growth of fungi.	

Personnel, Facility Design & Environmental Controls

Facility Layout

Conceptual representation of USP Chapter <797> facility requirements



"The patient in the next bed is highly infectious. Thank God for these curtains."

Only as Good as the People who Utilize it!

LFH/BSC – First Air Principle

Hint: Nope

Photos: www.rld.state.nm.us/pharmacy

A False Sense of Security?

How “Dirty” are my Personnel?

AREA	NUMBER OF MICROORGANISMS/cm^2
Scalp	1 million
Saliva and nasal fluid	10 million/gram
Back	100
Groin	1 – 20 million
Forehead	100 – 1000
Hand	10,000 – 100,000
Armpit	1 – 10 million
Feet	1 million

Gross! What Happens While They are…?

Activity	Number of particles generated (0.5 micron and larger/minute)
Sitting or standing still	100,000
Sitting, small movement of arms or head	500,000
Sitting, moving arms, legs or head	1,000,000
Standing Up	2,500,000
Walking slowly	5,000,000
Walking normally	7,500,000
Walking ~ 5.5 MPH	10,000,000
Performing a workout	15,000,000 - 30,000,000

Viable Monitoring of Air

Portable Viable Air Samplers

- Sieve Impaction (many devices)
- Surface Air Sampler (SAS)
- Centrifugal Air Sampler (RCS)
- Slit to Agar Sampler (many devices)
- Sterilizable Microbial Atrium (SMA)
- Gelatin Filter Air Sampler (MD-80)

  - What makes them all different?

Isolator/RABS/Fixed Location Air Samplers

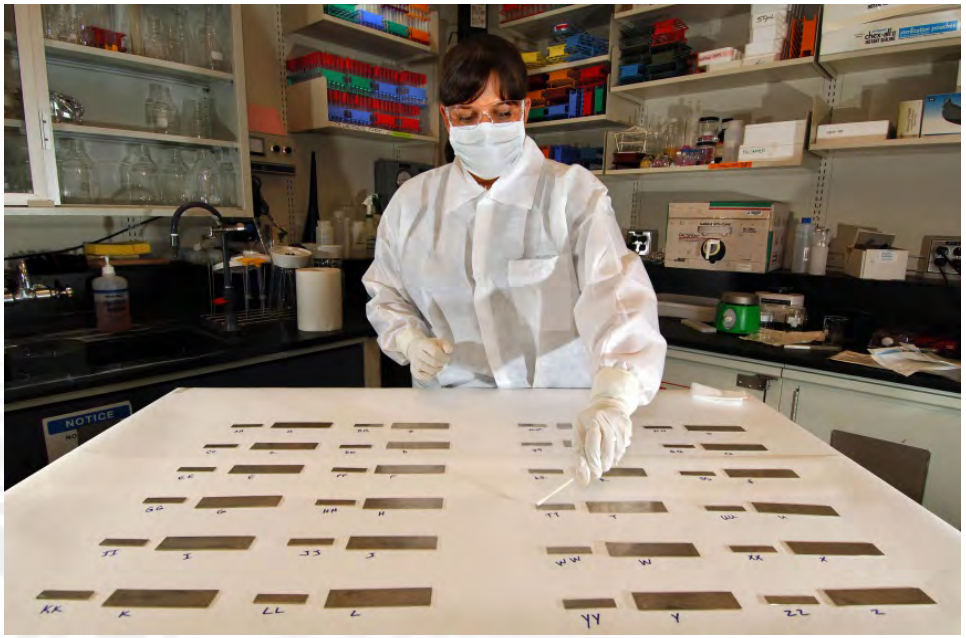
- Similar to their portable versions, however, these are designed so that the moving/active components (pumps, vacuums, electronics, etc.) are physically located outside of the barrier or room.

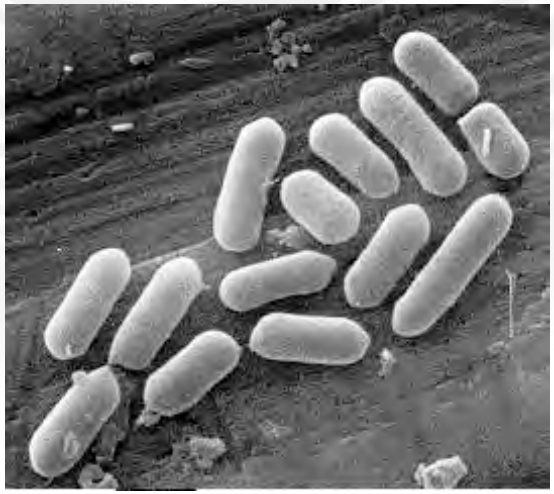
- It is generally NOT recommended to use a portable device inside an ISO 5 area for the following reasons:
  - Portable devices are NOT able to be fully sterilized
  - Portable devices generate particles
  - Portable devices disrupt unidirectional airflow

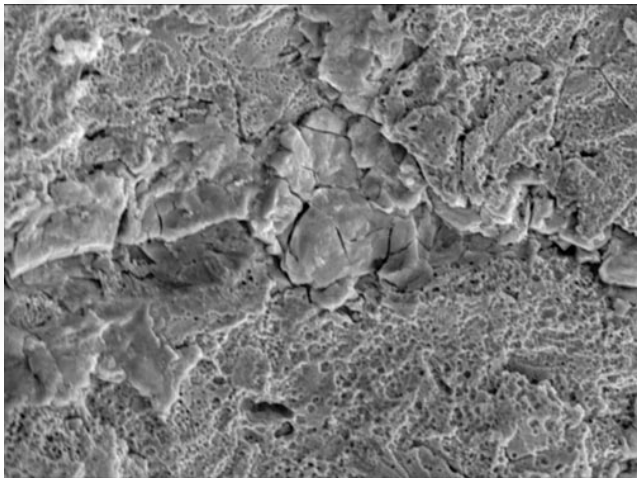
Viable Monitoring of Surfaces

Different Surface Types

- **Irregular Surfaces**
- **Residues**
- **Particulate and Viable particulates**
- **All may complicate monitoring and disinfection**

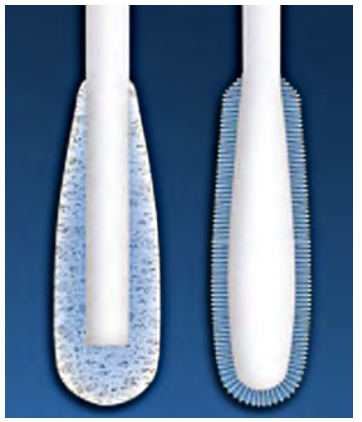


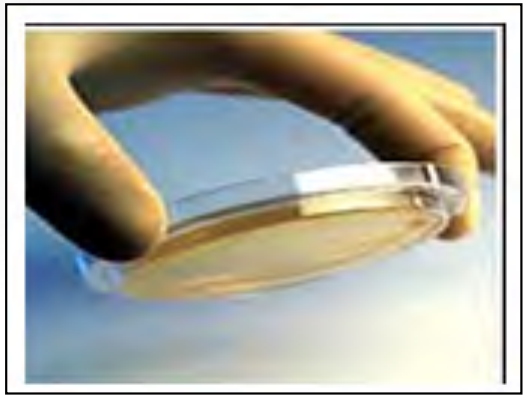




Sampling Methods

- Contact plates (RODAC) and swabs
- Contact Plate and Swab recovery studies
- Contact plates can offer “better recovery” than swabs and utilized more often (where surface and location permits)
- Flocked swabs offer “better recovery” than spun/cotton swabs due to physical composition
- Sampling done on equipment, work surfaces, floors, walls and product contact surfaces **after compounding is complete!**





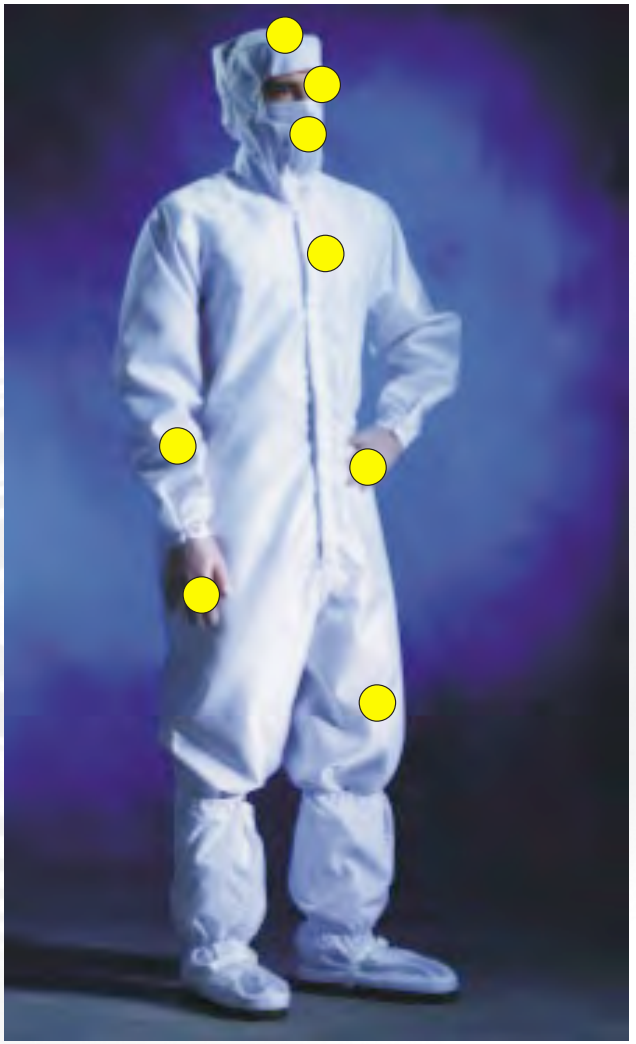
Viable Monitoring of Personnel

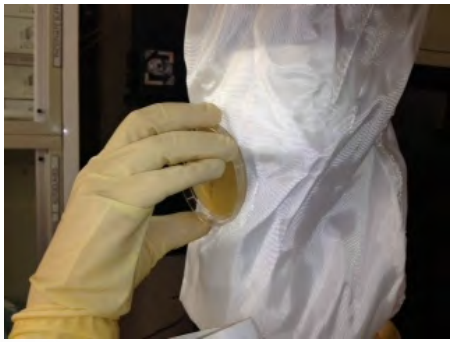
Viable Monitoring of Personnel

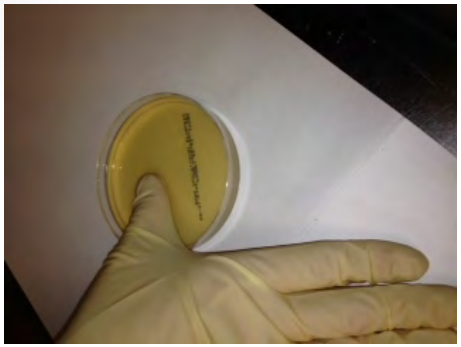
- **Personnel Monitoring:**
- Routine during compounding
  - Gloved fingers: underside where contaminants are most likely
  - Critical gown sites for aseptic operations
  - Contact plate testing of people leaving/exiting area
  - Routine failures on a person requires a corrective action (re-training and/or re-qualification)
- Gown Training Certification
  - Surface sampling of gown at key garment locations
  - Personnel MUST participate in a media challenge at least twice annually if they will be filling non-sterile to sterile preparations (annual if sterile to sterile)

Gowning Qualification/Testing

- Set strict limits (<1 CFU) for **qualification**
- Remove those who fail and retrain them
- Operators should not qualify or evaluate themselves
- Determine Qualification Test locations
  - **Examples: Hood, goggles, mask, zipper, sleeves, hands (both), thighs, fingers**
- Re-qualify on an every 6 month or annual basis







Establishing and Executing Alert & Action Levels

Establishing Alert & Action Levels

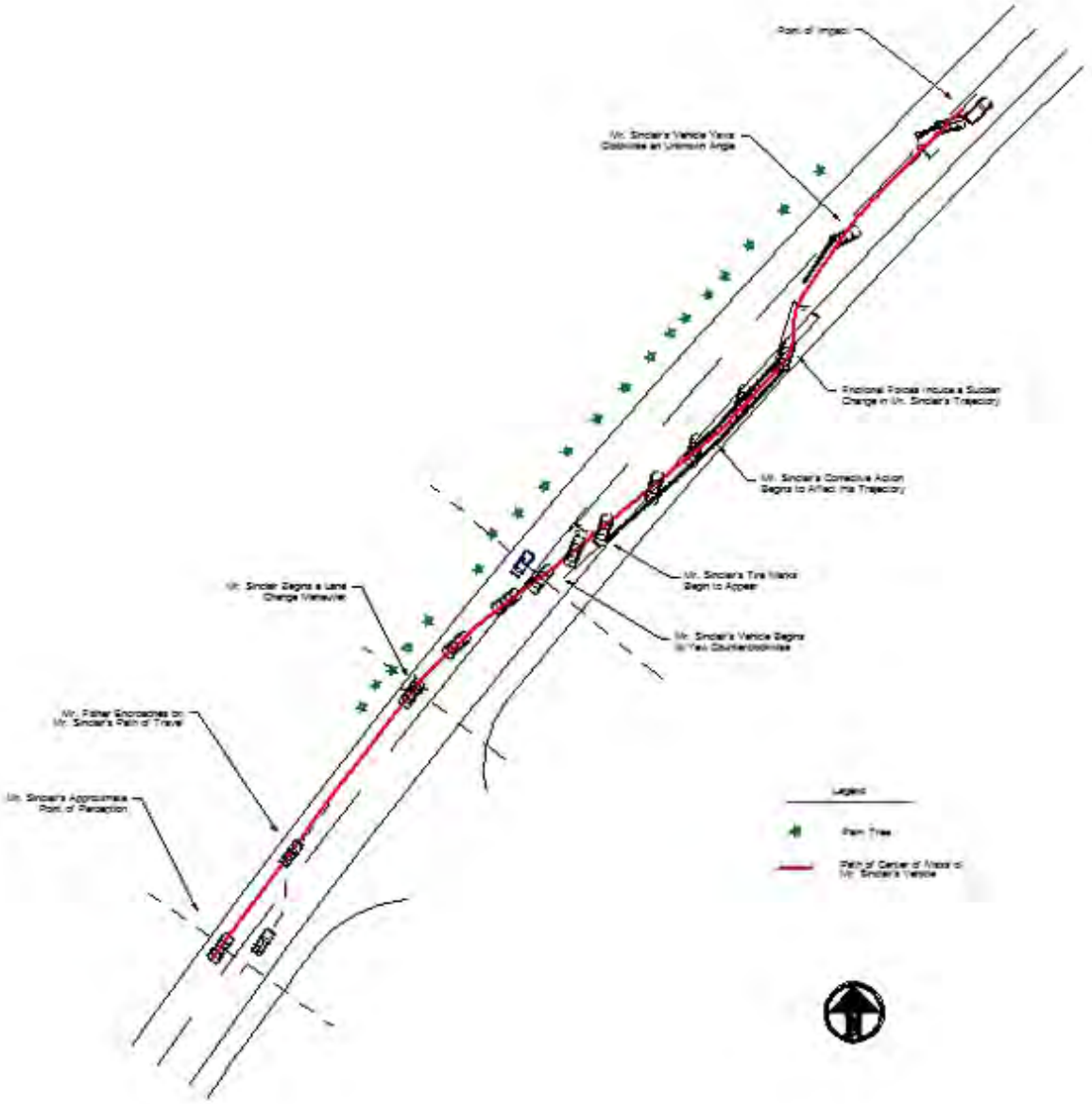
Document	Data Evaluation
ASHP	Sample data must be reviewed as a means of evaluating control of the compounding environment. Results above recommended action levels (see Table 7) should prompt reevaluation of work practices, cleaning procedures, and HEPA filtration.
USP <797>	• The value of viable microbial sampling of the air in the compounding environment is realized when the data are used to identify and correct an unacceptable situation. • Sampling data shall be collected and reviewed on a periodic basis as a means of evaluating the overall control of the compounding environment. • If an activity consistently shows elevated levels of microbial growth, competent microbiology personnel shall be consulted. • Any CFU count that exceeds its respective action level (see Table 2) should prompt a re-evaluation of the adequacy of personnel work practices, cleaning procedures, operational procedures, and air filtration efficiency within the aseptic compounding location. An investigation into the source of the contamination shall be conducted.
CA CR	Remediation shall include, at minimum, an immediate investigation of cleaning and compounding operations and facility management.

Establishing Alert & Action Levels

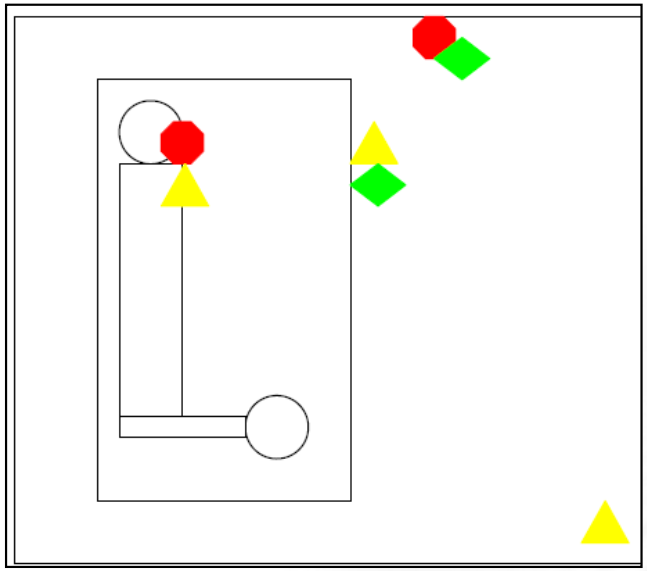
Document	Data Evaluation
CETA	• Pharmacy personnel are responsible for reviewing and analyzing the data generated by the environmental sampling program periodically and evaluating for trends. • Pharmacy personnel must analyze the data periodically (usually yearly) and set appropriate alert and action levels based on the data generated by the program. These levels may differ from the USP suggested levels but may not deviate significantly.
FDA – 503b	• Calls for an investigation of results that exceed the established levels or demonstrate an adverse trend, a determination of the impact on the sterility assurance of finished products intended to be sterile, and the development and execution of appropriate corrective actions

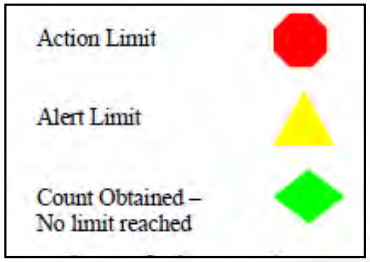
Do I Take Enough Samples?

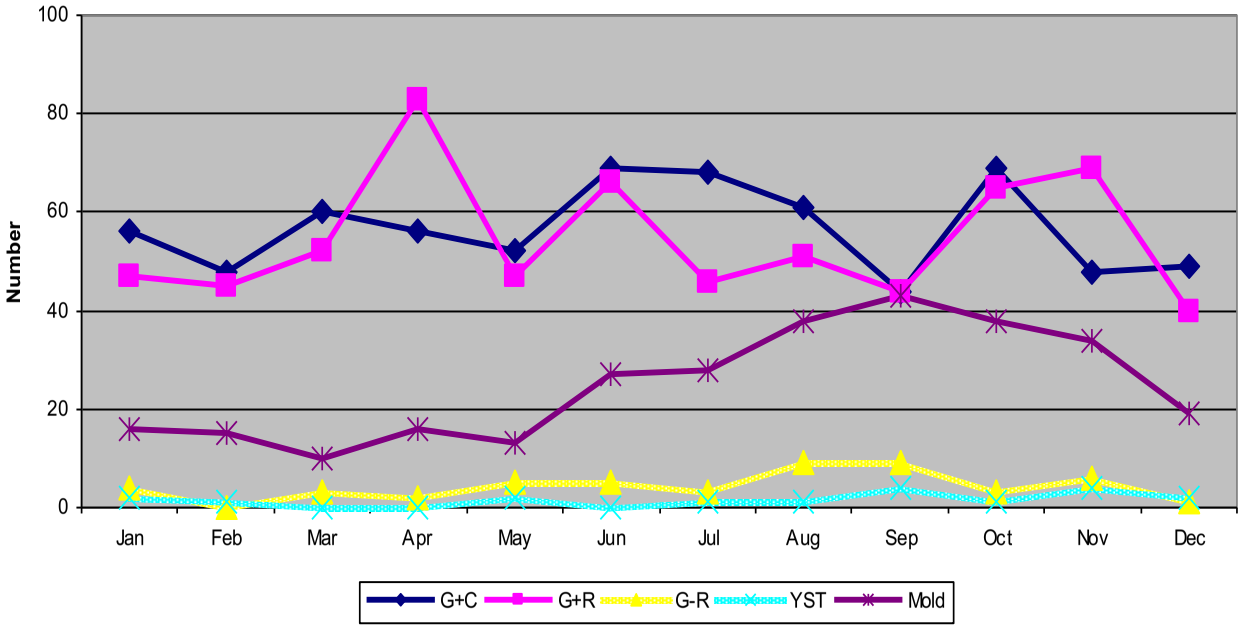
- **Once is chance**
- **Twice is coincidence**
- **Third time is a pattern**



Establishing Alert & Action Levels







Executing Alert & Action Levels

- **Regulations require:**
  - **Immediate follow-up**
  - **Identification of microorganisms**
  - **Corrective actions/preventive actions (CAPAS) if appropriate**

- **Indicates potential deviation from normal operational conditions**
- **Document and follow-up**
- **Additional or modified sample plan**
- **Designed to allow appropriate capability of reaction before reaching Action level**

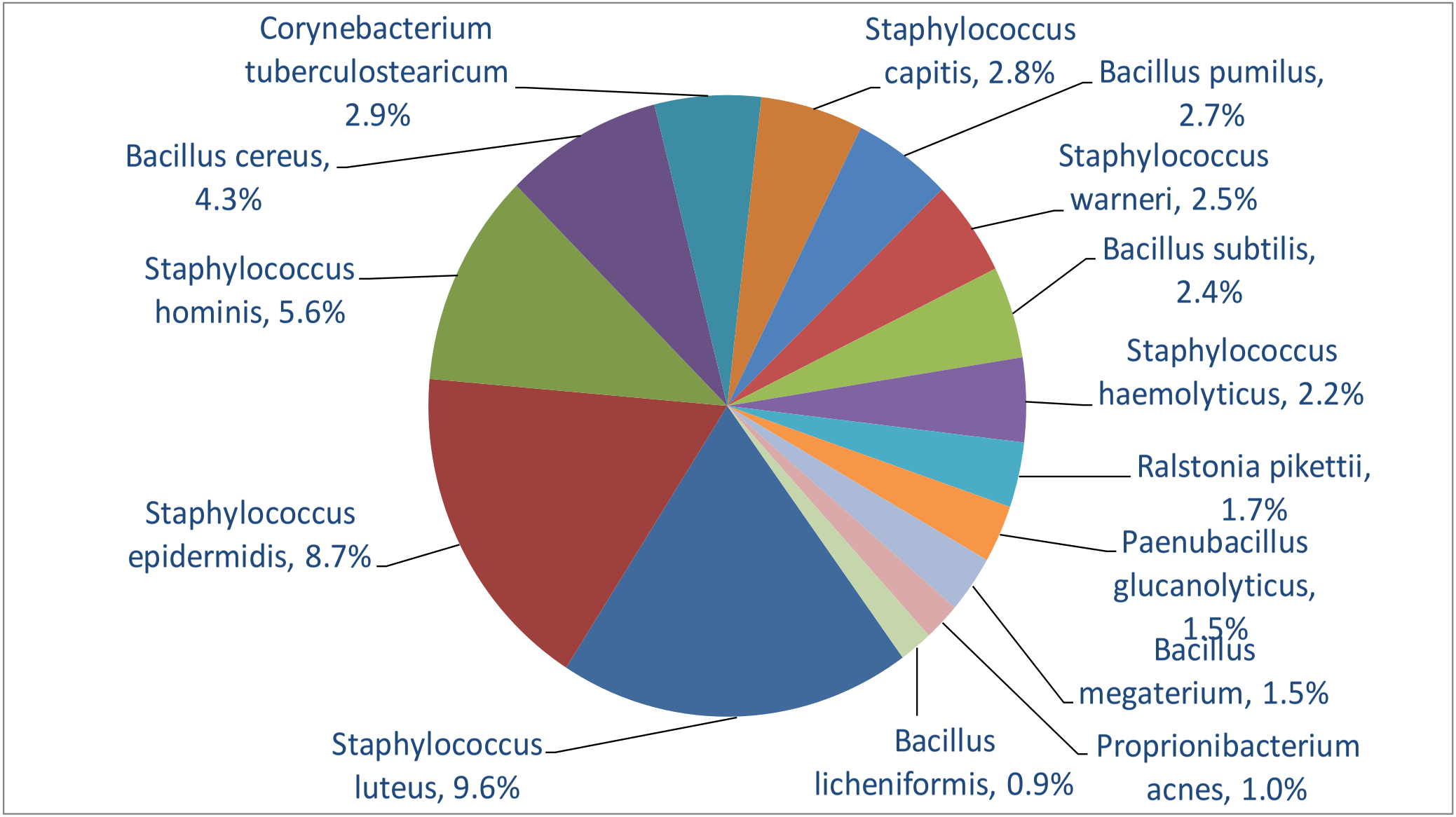
- **No actions required**

Identification of Microorganisms

Identification of Microorganisms

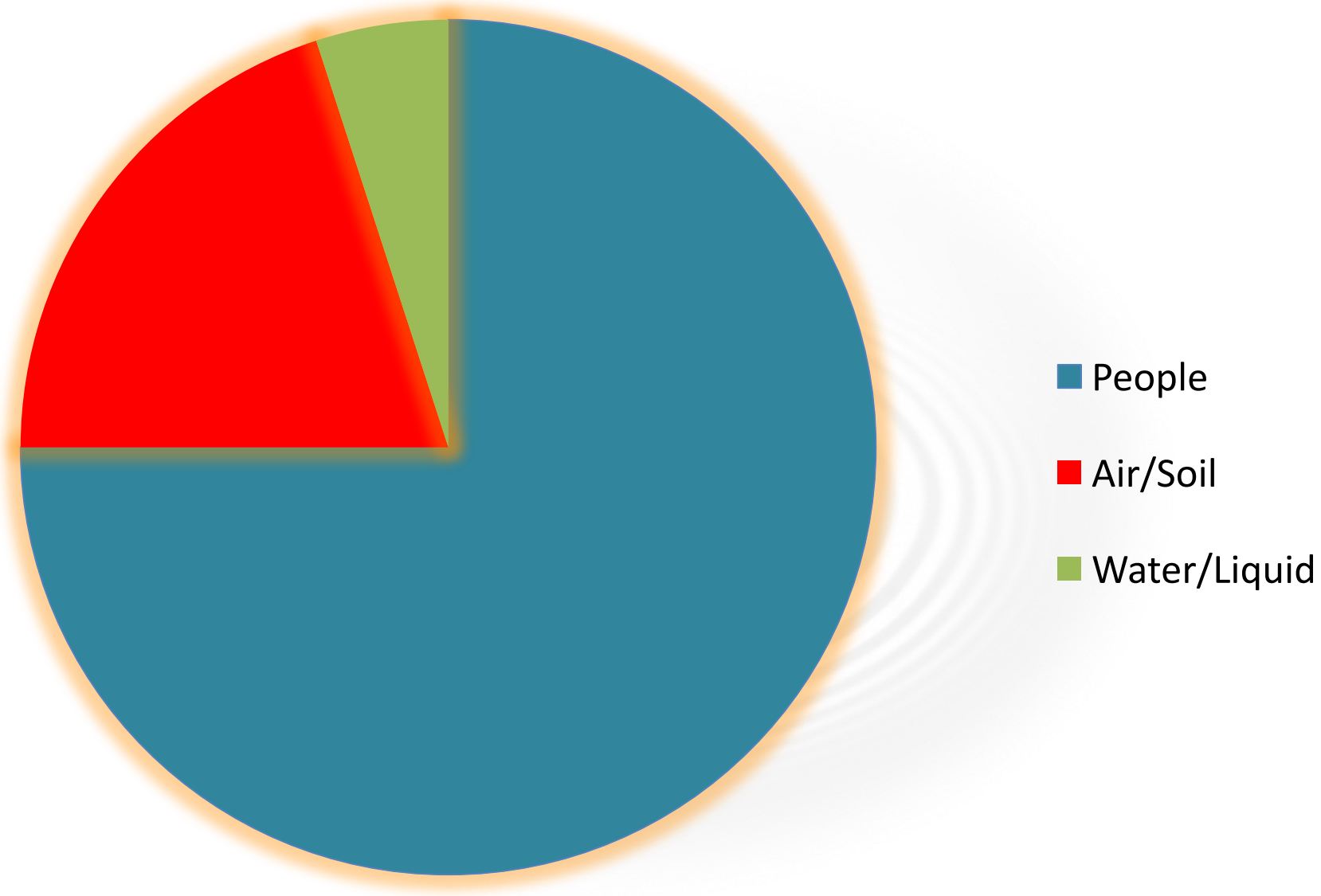
Document	Microorganism
ASHP	Any microbial growth that results from viable environment sampling must be identified to the genus level by microbiology personnel. If any highly pathogenic organisms (e.g., gram-negative rods or yeasts) are identified, infection control specialists should immediately be consulted to assist in formulating a response to the situation.
USP <797>	• Further corrective actions will be dictated by the identification of microorganisms recovered (at least the genus level) by an appropriate credentialed laboratory of any microbial bioburden captured as a CFU using an impaction air sampler. • Highly pathogenic microorganisms (e.g., Gram-negative rods, coagulase positive staphylococcus, molds and yeasts) can be potentially fatal to patients receiving CSPs and must be immediately remedied, regardless of CFU count, with the assistance of a competent microbiologist, infection control professional, or industrial hygienist.
CA CR	When the environmental monitoring action levels are exceeded, the pharmacy shall identify the CFUs at least to the genus level in addition to conducting an investigation pursuant to its policies and procedures.
ASHP	• test results indicating any presence of mold, gram negative rod, yeast or coagulase positive staphylococcus • identification of all recovered organisms at least to genus level must be completed by the laboratory for all risk levels

Identification of Microorganisms



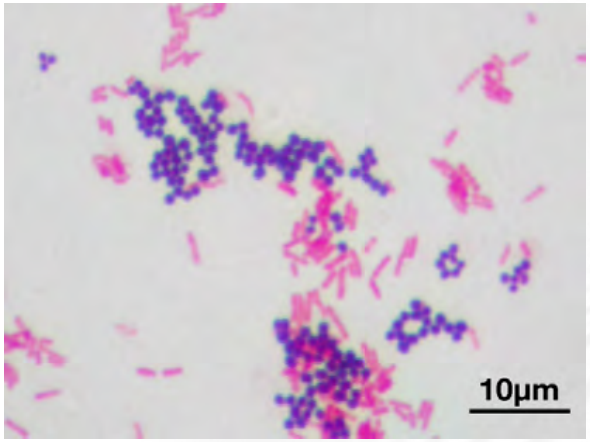
Source: Bacteria Most Often Submitted for Identification Testing During 2010, Barry A. Friedman, posted May 17, 2011

Distribution of Microorganisms

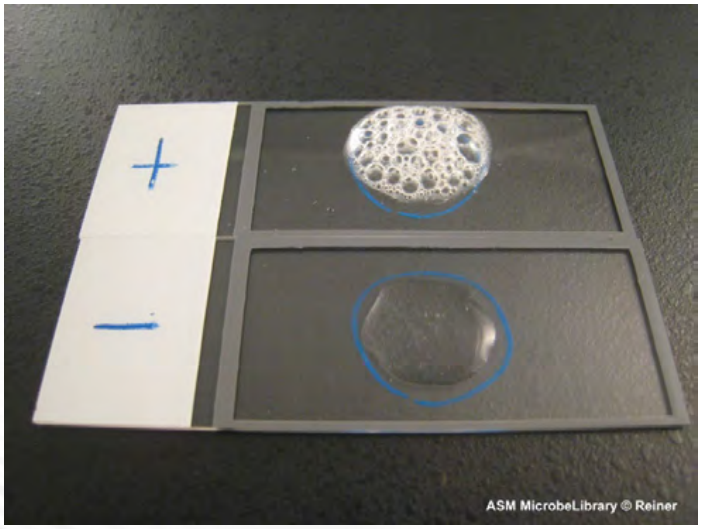


Microorganism Identification (DIY)

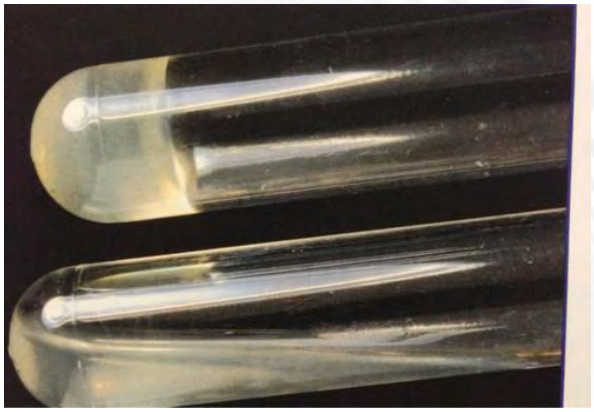
- **Biochemical (Selective Assays)**



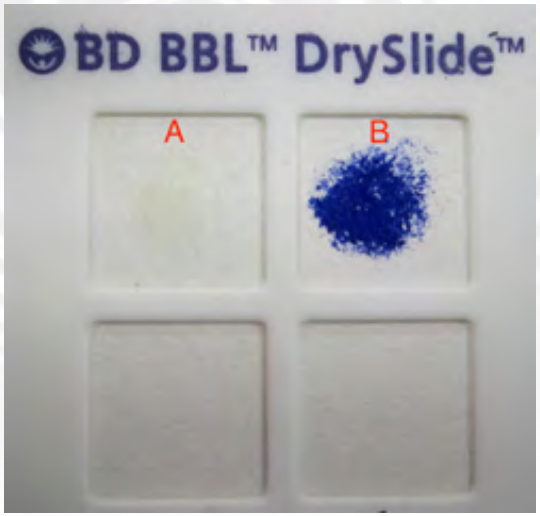
Gram Stain



Catalase Test



Coagulase Test

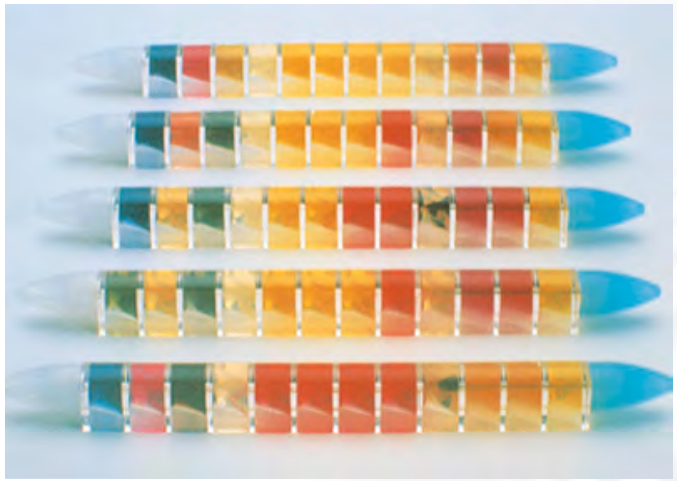


Oxidase Test

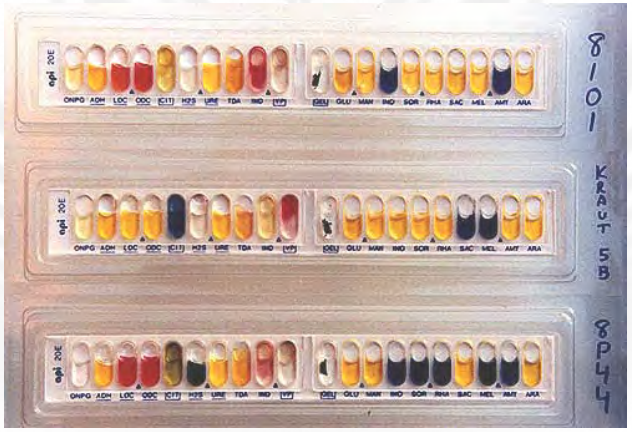
Indole Test

Microorganism Identification (DIY, Still…)

- **Phenotypic Identification** (incorporates reactions to different chemicals or different biochemical markers)



BD BBL™ Enterotube™ II



BioMerieux API® Strips

BD BBL™ Crystal™ ID Panels

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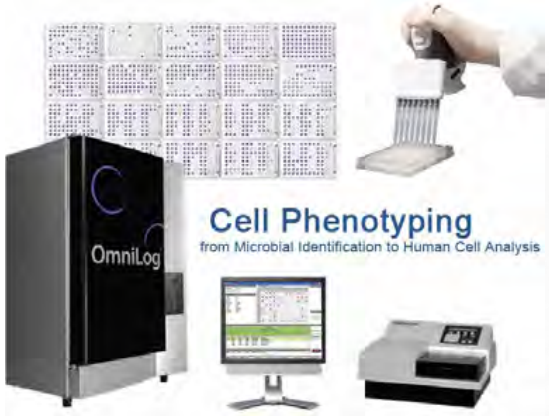
Microorganism Identification (Fancy!)

Phenotypic Identification



Biolog GEN III OmniLog ID® System

BioMerieux Vitek® 2 System

Genotypic Identification

DuPont RiboPrinter®

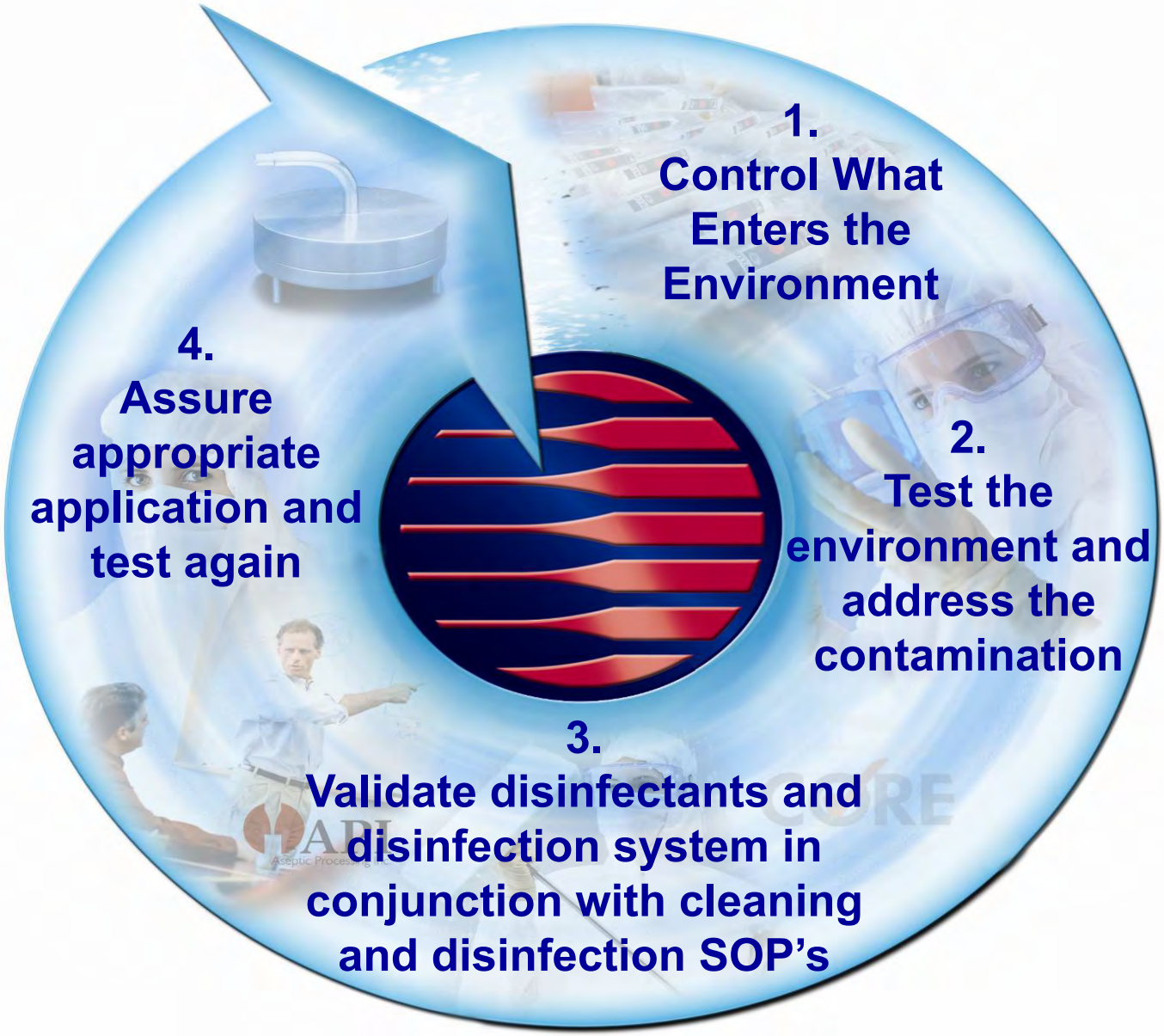
Thermo Fisher Scientific MicroSeq®

Proteomic Identification

BioMerieux Vitek® MS System

Bruker MALDI Biotyper

The “System” is a Cycle



In Conclusion…

- **Understand Environmental Monitoring because it can be a very unique and daunting task**
- **The guidelines are just that, guidelines. Establish a well-justified and validated program that works for you and meets the various recommendations**
- **A good EM program also controls the introduction of contamination**
- **Cleaning and disinfection are critical aspects to contamination control**
- **Monitoring systems should not affect final preparation or environments**

Any Questions?