

THE CLEANROOM OF THE FUTURE

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MOLLY PICKETT

- **Survey Question**

- What is new in cleanrooms and environmental monitoring?

OTHER INDUSTRIES

- Other regulated industries have more readily adopted new technologies and rapid methods.
- Some are fully automated.
- Some manufacture Just in Time with Real Time Release.
- Some even do continuous manufacturing.

GOWNING AND CHANGING ROOMS

- **Dedicated Shoes**

- Do you have plant issued shoes?
- Where do you wear them?
 - Cafeteria or outside picnic benches
 - Out to smoke
 - Meeting rooms
 - Offices
 - Manufacturing/laboratory areas
- How do they get cleaned and disinfected?
- When does this occur?

GOWNING AND CHANGING ROOMS

- **Shoe covers are not enough.....**
 - If your shoes are dirty, you will contaminate other surfaces, including the hands of the person putting on the shoe covers.
- **If you clean the shoes....How do you do it?**
 - How often?
 - What methods are best?
 - Should we wear rubber boots?
- **Can the shoes withstand the chemical processes used in the plant? Should they be sterilized?**
- **How often are they replaced?**

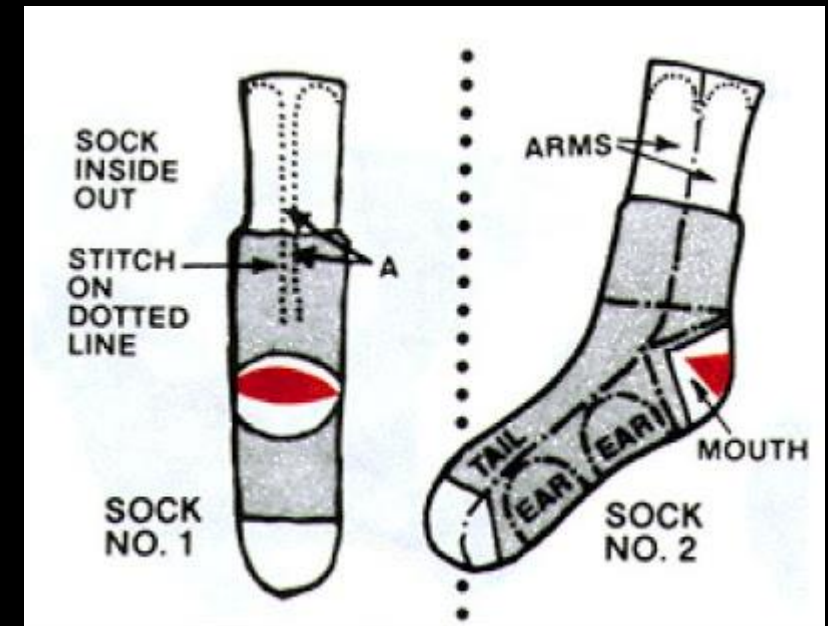
CHANGING AND GOWNING ROOMS

- **Dedicated shoes are NOT bad! It is a good idea, but may need some control.**
- **What can you do with dedicated shoes?**
 - Periodic chemical sterilization, sterilization, or sanitization
 - Chemical baths
 - Hose them down with a chemical sterilant or disinfectant
 - Gas, radiation or steam sterilization
 - Cover them up
 - Have procedures for covering up the shoes when they go into “contamination zones”
 - Wear a boot type product over the shoes in some risk areas
 - Replace them at a specified frequency, but.....
 - Use the Asian method of changing shoes for each area, but..



SOCKS

- There are many company-issued socks for cleanroom programs.
- Typically, they are a basic white cotton.
- Today many new materials for socks are available:
 - Antibacterial
 - Antifungal
 - Keep the moisture in
 - Keep the moisture out
 - Keep the moisture away from the body, but not in the environment
 - Stain proof
 - Different sizes and fits
 - And so forth



GOWNING MATERIALS

- **Some advances in gowning are beginning to be adopted in companies, e.g.:**
 - pre-folded in a way that makes the gown easier to don
 - some have sensors/chips to identify how many times the uniform has been washed to determine when it should be taken out of circulation.
- **Why does the gown need to be made in one piece?**
 - Wouldn't other designs be easier to don without the risk of contamination???
 - Aren't there ways to keep the entire body covered, without having to be a one piece torture chamber?

GOWNING MATERIALS

- **Numerous new materials are available for gowning materials.**
 - Keep moisture in
 - Keep moisture out
 - Antibacterial
 - Antifungal
 - Water proof or water-resistant
 - Easier to breathe fabrics, i.e., keeping better temperature control
 - Neutralizes odors
 - Stain-proof or stain-resistant
- **Need to control the number of washings to ensure that the gown is capable of performing its function. By the way, this number is probably much lower than you think!**

GOWNING MATERIALS

- **Laboratory Coats**
 - They constantly look “dirty” or “stained”.
 - Few companies have programs that have clean coats for each day of the week due to costs.
 - Many of the new fabrics available could significantly improve this, e.g.,
 - Wrinkle-free
 - Stain-proof or stain-resistant, yes there are even some that resist malachite green
 - Neutralizes odors
 - Antibacterial
 - Antifungal
 - Keeping moisture in or out or trapping moisture
 - And so forth

GOWNING MATERIALS

- **Goggles and Safety Glasses**

- **Methods of Sterilization/Sanitization**

- Ultra violet is most commonly used, but is only a surface sanitizer. If it doesn't come in contact with all areas of the goggles, they aren't sanitized. Few validation protocols evaluate all areas of goggles in the cabinet.
 - Liquid phase sterilants and gas sterilants can be more effective and actually sterilize the goggles between uses but you need to select ones that have no issues with residues or do not destroy the goggle materials. Some examples are hydrogen chemically activated water (electro activated water), ozonated water, ozone gas, chlorine dioxide, nitrogen dioxide, and others.

- **Foggy / Moisture Loaded Goggles**

- Learn from the Self-cleaning windows
 - Nanotechnology coatings that make the moisture "rain off" the surface



FACILITIES

- **Isolators and Restricted Area Barrier Systems (RABS)**



From the Skan Images File on Bing

FACILITIES

- **Why is the USA so slow to implement the use of isolator and RABS systems?**
 - **They significantly reduce human intervention in the process.**
 - Humans are the greatest source of contamination!
 - **Initial Facility Costs** (*Agalloco, Akers, Madsen*)
 - Typical cleanrooms have well-defined costs for set up and are high
 - RABS can have higher costs and have higher equipment costs
 - Isolators can be more expensive for initial installation
 - **Qualification** (*Agalloco, Akers, Madsen*)
 - Typical time for cleanroom, RABS, and isolators are 6-9 months
 - RABS can take less time than an isolator.
 - Longer times for isolators reflect technical burdens, not complexity in validation.

FACILITIES

- **Operating Costs** (*Agalloco, Akers, Madsen*)
 - RABS and Isolators can be more expensive to operate than conventional cleanrooms, but there can also be cost savings:
 - Gowns
 - Supplies
 - Environmental monitoring
 - Isolators may have additional cost for the sterilants used for biodecontamination of the isolator.

FACILITIES

- **Environmental Conditions** (*Agalloco, Akers, Madsen*)
 - Most isolators are smaller than conventional cleanrooms. Airflow inside the isolator is filtered in an absolute manner. The used air inside the isolator has to be filtered for dust and airborne aerosols.
 - The elimination of people in the environment also eliminates the contamination carried in by the operators. This may provide for a lower number of air exchanges in the isolator. The authors recommend a minimum of 20 exchanges/hour. Note: This may be contested by some regulators since the Aseptic Guidance has this rate of air exchange for a lower classification area.
 - One needs to consider temperature and relative humidity conditions on the biodecontamination process and its' efficiency. The isolator conditions may not favor the growth of microorganisms during production.

FACILITIES

- **Biodecontamination** (*Agalloco, Akers, Madsen*)
 - Not all areas in the cleanroom are classified the same way. Some areas may only be sanitized, not sterilized. Operators can intervene and unfortunately be a source of contamination.
 - The isolator is completely biodecontaminated. Only the manufacturing materials brought into the isolator come into contact with the processing system. This results in less microbial contamination. Cleanrooms are sanitized and have the potential for controlled contamination.

FACILITIES

- **BUT.....**
 - If our process is based upon risk, isn't the risk of contaminated product lower for an aseptic process using an isolator??
 - What is more important, patient risk or cost of initial construction??
 - Why don't we want to implement these systems??
- **Note:** The issues are different for terminally sterilized products, as the terminal sterilization process itself delivers a probability of a non-sterile unit that is so high. The other potential risks of using a cleanroom for processing can be negligible.

FACILITIES

- **Isolators and RABS**

- Complementing these technologies with robotic arms or robot systems can make them almost 100% free of human intervention.
- **Note:** One concern with robotic applications – most of these systems generate particulates and you may need to qualify the area for classification under static conditions as the dynamic conditions may generate particulates.

FACILITIES AND PRODUCTION

- **Single-Use Technologies**



From GE Lifesciences Website

FACILITIES AND PRODUCTION

- **Single Use Technologies**

- Disposable, single-use technologies are being introduced into the biopharma industry.
- They allow for elimination of cleaning validation steps, since new sterile bags are used for each manufacturing lot.
- Some believe that they offer a significant cost and time savings. (depends upon the process)
- These technologies continue to evolve even as we speak.

FACILITIES AND PRODUCTION

- **Single Use Technologies**
 - **An example was given in *BioProcess Online Magazine*:**
 - ***A single-use facility,***” is equipped with disposable seed and production bioreactors. In addition, all media and buffers are prepared in single-use bag systems consisting of powder transfer bags, disposable bags with a disposable internal agitators, external mixing systems, a weighing station, and a disposable path (pump, tubing, filters, and so on) for transfer of prepared media or buffers into another disposable bag system for storage. When necessary, buffers would be prepared in concentrated solutions to accommodate transport in disposable bags at a maximum volume of 500 L, which is a typical volume limitation for longer-distance transport within a facility. In-line dilution skids are placed at point of use for concentrated buffers.”

FACILITIES AND PRODUCTION

- **Single Use Technologies**

- One benefit is that the bags can be disposed following the production and in effect are dedicated equipment for each batch.
- Could hold the bags until after batch release to aid in potential contamination investigations.

- **Some concerns:**

- Is this a cost effective methodology for small molecule drugs?
- Could a generics company even consider the use of single use technologies?

FACILITIES

- **Structures**

- Antifungal and antibacterial paints can be used on the walls, lockers, and other non-stainless components of the room design to prevent microbial growth.
Note: There is little published data to tell you how long the paints are effective for microbial and fungal control. Many of these products utilize silver nanoparticles.
- There are antifungal solutions that can be sprayed, fogged, or wiped on surfaces to prevent mold growth. These sprays are comprised of natural ingredients commonly used in foods and cosmetics. The ingredients are on the GRAS list, as generally recognized as safe. These solutions are effective for a year or more, depending upon how you clean and what you use as cleaning agents.
- There are wipes available that renew surfaces to their original pristine condition, e.g., removing black, brown and rust like particles. These can also be useful.

FACILITIES

- **Antifungal Paints and/or Solutions**
 - Should always be considered for ductwork.
 - Mold spores are ubiquitous and are difficult to remove.
 - Ducts are notorious for being harbors of mold spores.
 - HEPA filtration does **NOT** remove all mold parts. Research data has shown that some mold parts go through HEPA filters and grow up to be full-grown mold.

FACILITIES

- **Incorporate real time and/or near real time methods for laboratory testing in your cleanrooms, e.g., RMMs, in-line chemistry tests**
 - Today, you can have inline results for TOC, conductivity, microbial counts, and ozone concentration. You can have near real time results for endotoxin. There is no real reason to use WFI or other grades of water “at risk” or while awaiting results.
 - There are numerous RMMs for air testing, bioburden testing, product testing, identification of samples, LAL testing and the like. Other than LAL and identification methods, we have been slow to adopt many of these methods.

FACILITIES

- **Eliminating Paper-based Documentation in the Production and Laboratory Areas**
 - **GO PAPERLESS**
 - Touch screen pads designed for use in the cleanroom and laboratory
 - Transmit the data wirelessly to the appropriate system, e.g., batch records, lab records, investigations, etc.
 - Use biometrics or advanced security systems to ensure data integrity
 - RFID chips can be placed on equipment, incubators, etc. and with a wand document the equipment used.
 - Automated batch records were already approved by FDA in 1980, Why don't more people utilize them??
 - Track samples with bar codes and/or RFID chips.



HEPAS

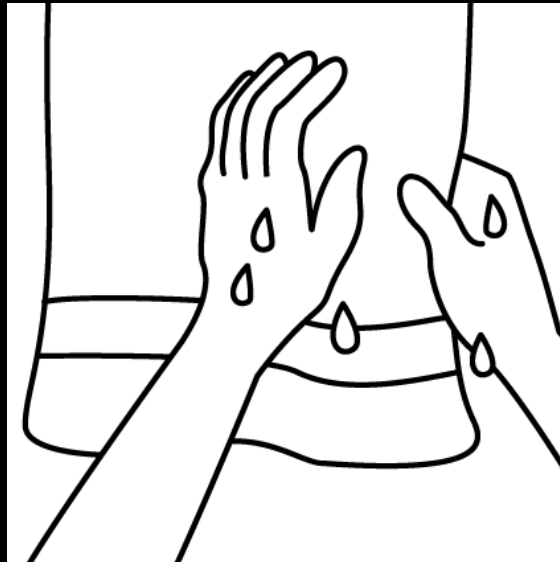
- There are numerous chips and technologies available to monitor velocity, temperature, humidity, etc.
- Why don't we install them on every filter face?
- This technology was conveyed to FDA as existing when they were drafting the Aseptic Guidance. Industry fought to not have to retrofit all equipment, but why aren't we considering them for new facilities????

HANDWASHING

- **Handwashing is a critical component of gowning.**
- **Case Study:**
 - Professionals trained in how to properly wash their hands
 - They were evaluated to show they knew how to properly wash their hands
 - They Knew they were being watched during handwashing and still over 75% did not properly wash their hands.
- The procedure and time required to properly wash your hands is rarely followed by employees
- Consider newer technologies, e.g., ozonated water, that works at ambient conditions and quickly reduces the microbial population. This has been used in the food industry for many years and is recognized by FDA.

HAND DRYING

- This is always a topic of discussion. What is better – air drying, hot air drying, paper towels, or cloth towels.
 - Need to carefully assess the risks/benefits to your process and use appropriately.



PRODUCT PROCESSING

- **Glass vials**

- Some manufacturers have developed an outer casing that virtually makes the glass break proof – similar to a shatterproof safety glass.
- This can have real value for tubing glass or other easy to break glass formulations

- **Stoppers**

- There are new innovations on stoppers, how they are sterilized, how they are coated, formulations of stoppers, shapes of stoppers, etc.
- Be sure to pick the best stopper formulation for your product.

CLEANING, SANITIZATION, AND DISINFECTION

- **We tend to stay with the products we have always been using.....**
 - Some leave residues on the surfaces
 - Some people believe that these residues continue to disinfect
- **Today there are many more options that may have specialty application or may be used for routine operations and/or for responses to contamination events.**
 - Hydrogen chemically activated water
 - Ozonated water and/or ozone gas
 - Chlorine dioxide gas
 - Nitrogen dioxide gas

CLEANING, SANITIZATION, AND DISINFECTION

- If you do have residues on stainless steel or glass surfaces, there are a variety of wipes with microfibers, that can be used to remove the residues from the surfaces and leave the surfaces looking brand new.
- Nanotechnology derived towels are also available. They allow you to wet the towel with water, wipe it on the surface, and then wipe with a dry towel. They claim to remove residues, inks, crayons, markers, and the like.

ENVIRONMENTAL MONITORING

- **Numerous rapid microbiological methods are available for air and water monitoring.**
- **Some rapid microbiological methods are available for surface monitoring (less data published)**
- **BUT.....**
 - Our industry continues to be afraid to fully adopt them due to regulatory concerns. This is in spite of FDA personnel recommending these types of methods from the podium at PDA meetings.
 - They do tend to use them for gowning training, are considering them for water monitoring, and use them for investigations

ENVIRONMENTAL MONITORING

- **Collecting, reviewing, and storing data**
 - Computerized systems available from about \$25K to over \$100K
 - Some people still use spreadsheets and home grown data bases.
 - You can look at data from simple control charts and scatter plots to using contamination rates and higher levels of statistics.
 - Ideally, you want a paperless system with as little operator intervention as possible.
- **If these programs are really risk-based, why do we continue for years collecting EM samples in Grade A/ISO 5 areas that have years of data with all zeros?**

THE CLEANROOM OF THE FUTURE

- **Since all of these technologies are available today, why aren't we investigating and using them???**
- **The future is today!**

QUESTIONS



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