Aseptic Operations and Cleanroom Principals

PDA SoCal Chapter, Aseptic Processing and Sterilization Symposium

Presentation by: TAF Group LLC

Presenter: Paul Andrea

Date: 07Nov2019

Presentation Topics

- PDA WCC Chapter Information
- Aseptic Operations and Cleanroom Principals
  - Contamination Control Basics
  - Environmental Monitoring
  - Personnel Training
  - Gowning
  - Personnel Behaviors
  - Working in Isolator and RABS
  - QA Responsibilities
  - Guidance Documents

PDA West Coast Chapter

12
Events/year organized

9/10
Quality of our events

PDA Parenteral Drug Association
West Coast Chapter

22
Sponsors & Partners

1,500
Life-Science Professionals

Seize the opportunity

2019/2020 West Coast Chapter PDA Upcoming Events

12DEC19

PDA on the Bay

Vendor night & Life Science professionals holiday party to celebrate successful 2019

16DEC19

Aseptic Techniques

2 days of professional development and hands on practice on ATs

19FEB20

Gene Therapy

Executive from BioMarin, Novartis, Sangamo and Spark sharing the latest on gene-therapy

23APR20

21st century cGMP training

Training supported by Technology (like virtual reality, augmented reality, etc.)

18JUN20

Managing Projects in the Life-Science Industry

Best Practice and real-life stories from top notch Project Managers

20AUG20

5th Women in Life-Science

Career stories, challenges, and successes of inspiring women

01OCT20

OktoberFest Mixer

Celebrate the life science community of the SF Bay at Boehringer Ingelheim site

12NOV20

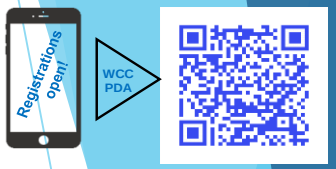
Artificial Intelligence in Life-Science

Application of Artificial Intelligence and Machine learning in Life-Science

Join us to strengthen your brand image, increase your visibility, and gain access to leaders of the San Francisco Bay Life-Science Community

West Coast Chapter of the PDA Sponsorship Opportunities

	Bronze	Silver	Gold	Titanium (Annual)	Platinum (Annual)
Exhibit Table	✓	✓	✓	✓✓✓	✓✓✓✓✓
Company logo in electronic and printed event-related material	✓	✓	✓	✓✓✓	✓✓✓✓✓
Complimentary tickets	2	4	8	18 (6 X 3 mtg.)	50 (10 X 5 mtg.)
Presentation Prime time	N/A	5min.	10min.	15min. (5 min. X 3 mtg.)	25min. (5 min. X 5 mtg.)
Company logo placement on National WCC PDA Webpage	N/A	✓	✓	✓✓✓	✓✓✓✓✓
Special recognition as Student Chapter Supporter	N/A	N/A	✓	✓	✓



Become a valuable Sponsor today by contacting us at:

rsvp@wccpda.org or +1 650-296-8044

Thank you to our 2019 Sponsors

Platinum Annual Sponsor

Genentech
A Member of the Roche Group

Titanium Annual Sponsor

BIOMARIN

Gold Sponsor

Boehringer Ingelheim
Govzilla
VALIDANT
VALSOURCE

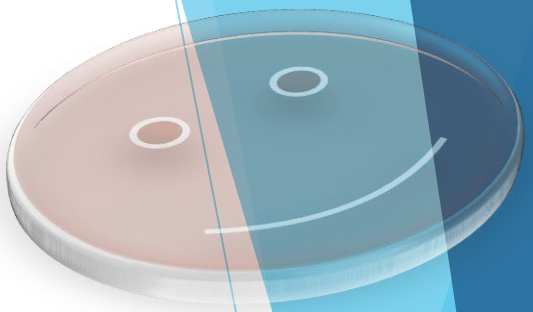
Silver Sponsor

BENCHMARK PRODUCTS
PBL Pacific BioLabs
CONTROLLED CONTAMINATION SERVICES
Prudential Cleanroom Services
ECOLAB
VALIDATION SYSTEMS
element
vai
VELTEK ASSOCIATES, INC.

Bronze Sponsor

ALG ANALYTICAL LAB GROUP
PMT
BOSCH Invented for life
RAININ Pipetting 360°
Northeastern University
SUEZ

My Journey– Paul Andrea



- *Hometown: San Mateo, California*
- *25+ years in GMP Manufacturing*
- *18+ years with Roche/Genentech*
  - *Cell Culture, Facility Management, Fill/Finish*
- *5+ years at Samsung Biologics*
  - *Drug Product Team Leader*
- *Principal Consultant at TAF Group LLC, BioPharma Services and Training*
- *Family: Wife and 2 teenage daughters, and Dexter*
- *Settled Back in the Bay*

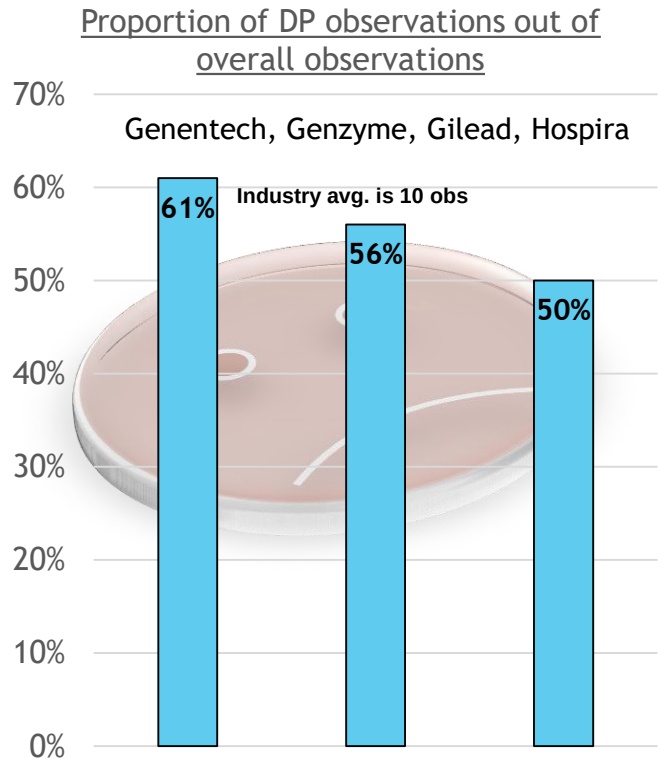
paul@tafgroup.us

Aseptic Operations and Cleanroom Principals

The Reality

FDA findings for poor aseptic practices are at a growing rate due to an increase in scrutiny in the manufacture of sterile product to ensure ***"the Safety, Identity, Strength, Purity, and Quality (SISPQ) are consistently maintained"***

Form 483s



The Aseptic Culture

- **For minimization of Regulatory Observations you must…**

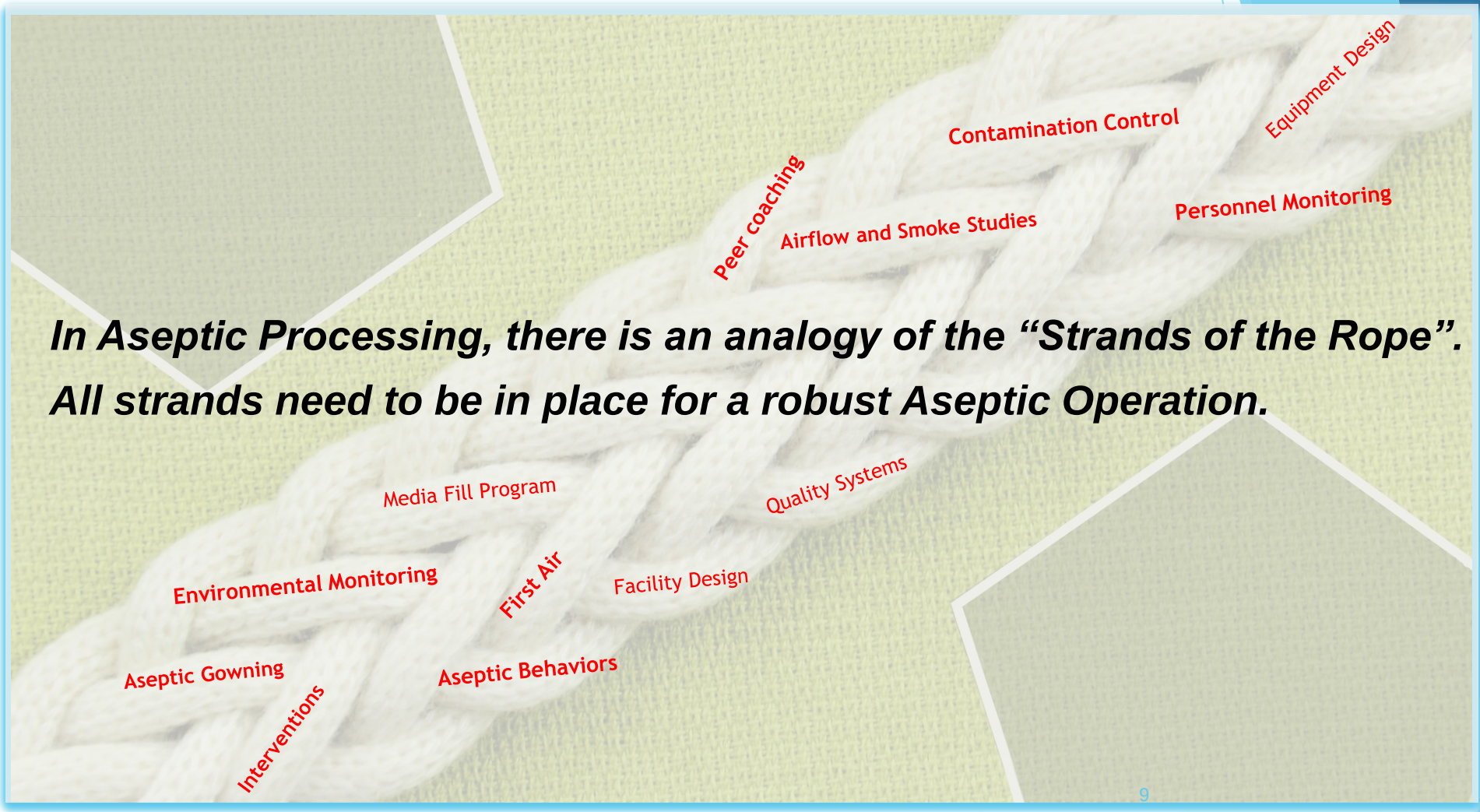
LIVE Aseptic

BREATH Aseptic

EDUCATE Aseptic

REWARD Aseptic

Strands of the Rope



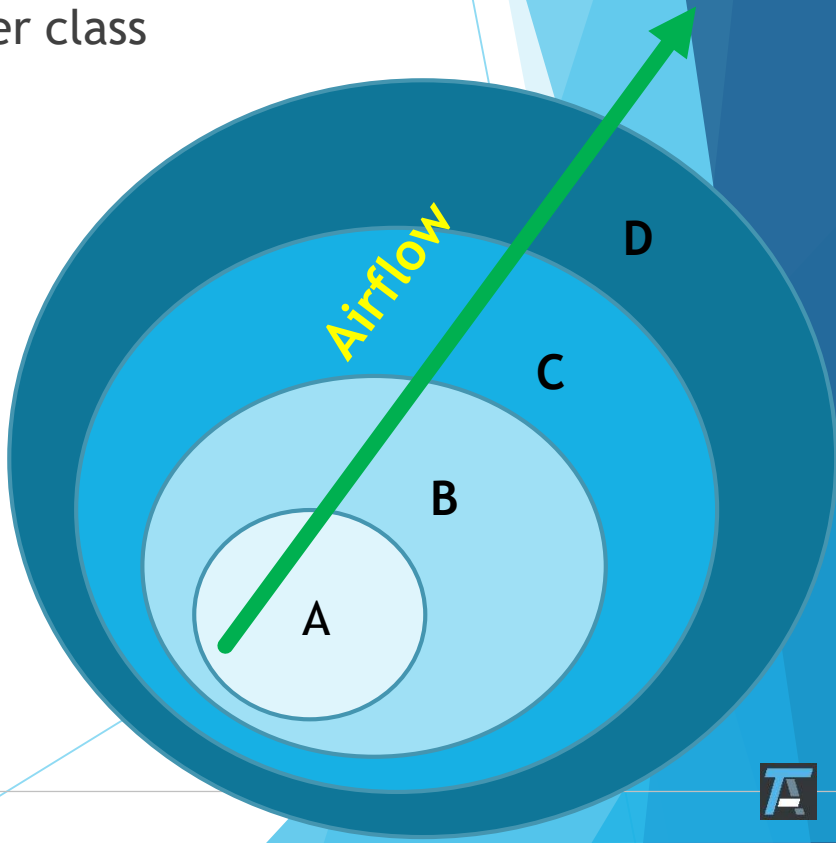
Contamination Control

Microbiological Risks

- Facility Design Principles
- Personnel and Cleanroom Behavior
- Aseptic Operations and Technique
- *Additional Considerations*
  - Aseptic Philosophies
  - Aseptic Processing Definitions
  - Sterility Assurance Level
  - General Facility Control
  - Cleaning and Sanitization

Facility Design and Protection of Critical Areas

- **Facility Design**
  - Cleanroom facilities are designed to go from lower class to higher class (less clean to more clean)
  - Each subsequent clean space requires additional controls to prevent ingress of undesired items
  - Goal is to make it more difficult for contamination to occur as you get cleaner
  - Minimize critical area space – contamination risk, cost, maintenance



Facility Design and Protection of Critical Areas

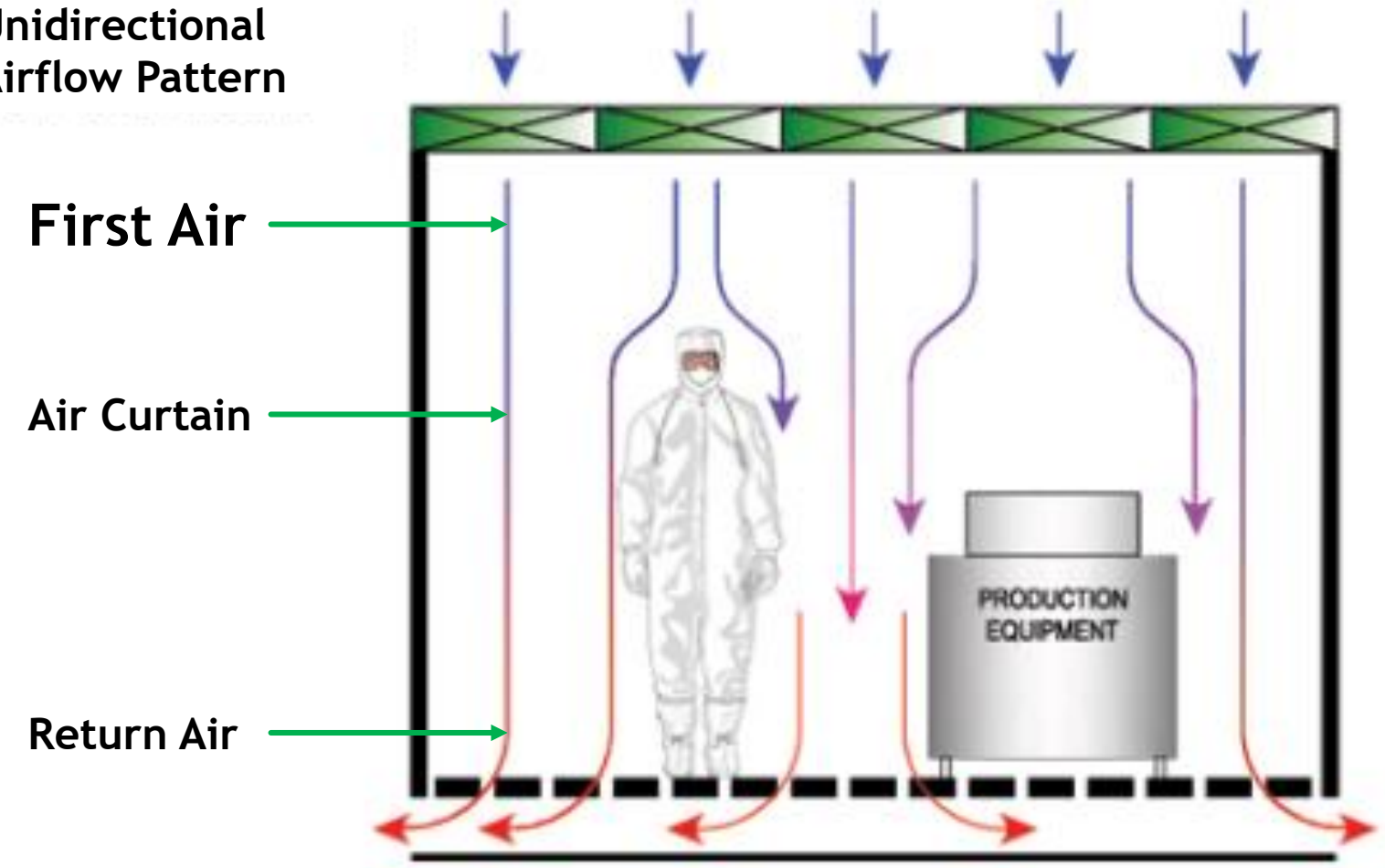
- Layout
  - Organization of Workflow
  - Minimize Critical Area
- Design
  - Cleanability
    - Smooth, continuous surfaces
- Pressurization
  - Force Airflow Away From Critical Areas
  - Smoke Tests

Facility Design and Protection of Critical Areas

- Maintenance
  - HVAC Systems
  - Certification of HEPA Filters
    - Flow Velocity
    - Aerosol Challenge for Integrity
  - dP Monitoring
- Sanitization
  - Cleaning/Disinfection Agents
  - Environmental Monitoring

Facility Design and Protection of Critical Areas

Unidirectional Airflow Pattern



EM Monitoring

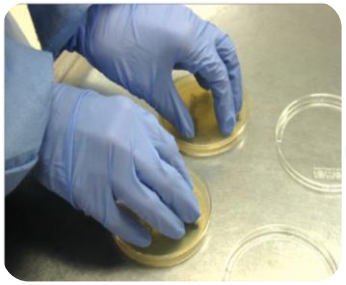
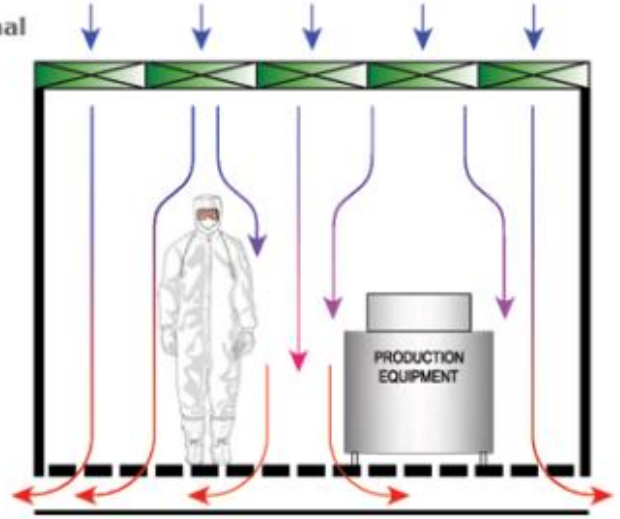


Fig 2. Unidirectional Flow Cleanroom



Components of an EM Program

- Facility Design (Personnel/Material Flow, HVAC, Proper Room Cascades)
- Comprehensive Quality Risk Assessment (QRA/RA) for all Critical Areas – Evaluating Location, Methodology, Frequency and Equipment
- Building Management System (or another form of real time monitoring)
- Detailed Procedures that are easily understood
- Trained Personnel
  - Performing Sampling
  - Documentation
  - Reading plates

Components of an EM Program

- Clear Roles and Responsibilities (R&R)
- Robust Cleaning and Sanitization Program
- Personnel who understand the nature of EM and their overall impact to the Environment
- Trending Program
- Utility Program

Personnel Training

FDA Guidance for Aseptic Processing

21 CFR 211.25(a) states that “Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions…

…Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them

Training and Qualification Requirements

- For Aseptic Operators, must have a detailed, clear, and comprehensive training plan which includes
  - Aseptic behavior and Cleanroom training
  - Basic Microbiological Training
  - Gowning Qualification Program
  - Equipment Use Qualification
  - EM Qualification (if applicable)
  - Smoke Study Participation and/or Viewing
  - Process Simulation Execution

Training and Qualification Requirements

- For all personnel entering into Aseptic Core, one needs to understand their impact on the environment
  - Maintenance personnel
  - Cleaning Crew
  - QC
  - QA
  - Contractors and/or Equipment Vendors

Training and Qualification Requirements

- Qualification Maintenance
  - Gowning – 1x/year unless no entry for “x” months or if there is an EM failure
    - For EM failure, need to consider frequency, severity of failure, point of failure before determining appropriate action
  - Media Fills – Participate in at least 1 media fill/year
  - Interventions – Perform intervention at least 1x/year to maintain qualification. If proceduralized, can justify performing a subset of interventions rather then all
  - Continuing education on Aseptic concepts

Aseptic Gowning

Aseptic Gowning and Certification

- Importance of Gowning
- Aseptic Gowning Rules
- Guidelines
- *Additional Considerations*
  - *Aseptic Garments*
  - *Aseptic Gowning Certification Program*
  - *Demonstration of Aseptic Gowning*

Importance of Gowning

- GMP Requirement
  - FDA's CFR 211.28, Personnel Responsibilities
  - Described in applicable Regulatory Guidelines
- Provides a critical barrier between people and the product or the APA environment
  - Reduces microbiological ingress
  - Protects environment and product
- Part of entire Contamination Control Program

Aseptic Gowning

- **Guidelines**
  - Personal Hygiene is of utmost importance
  - Ensure all hair, including facial hair, is covered – NO SKIN
  - Sanitize hands following each step
  - Hand sanitization must include all parts of the fingers, palm, wrist, and forearm
  - Do not talk while gowning

Aseptic Gowning

- **No Cosmetics**
  - Cosmetics consist of individual particles
  - Viscous or greasy based material
  - Captures and traps microorganisms against the skin
  - Adds to the organic matter and oil on the skin
  - Presents an avoidable source of contamination
  - Includes makeup, hair spray, artificial nails, nail polish, etc.

Aseptic Gowning

- **No Jewelry**
  - Harbors microorganisms
  - Harbors particles and body oils
  - Creates abrasions
  - Generates flaking of skin cells
  - Rings can damage gloves and create holes
  - Presents an avoidable source of contamination

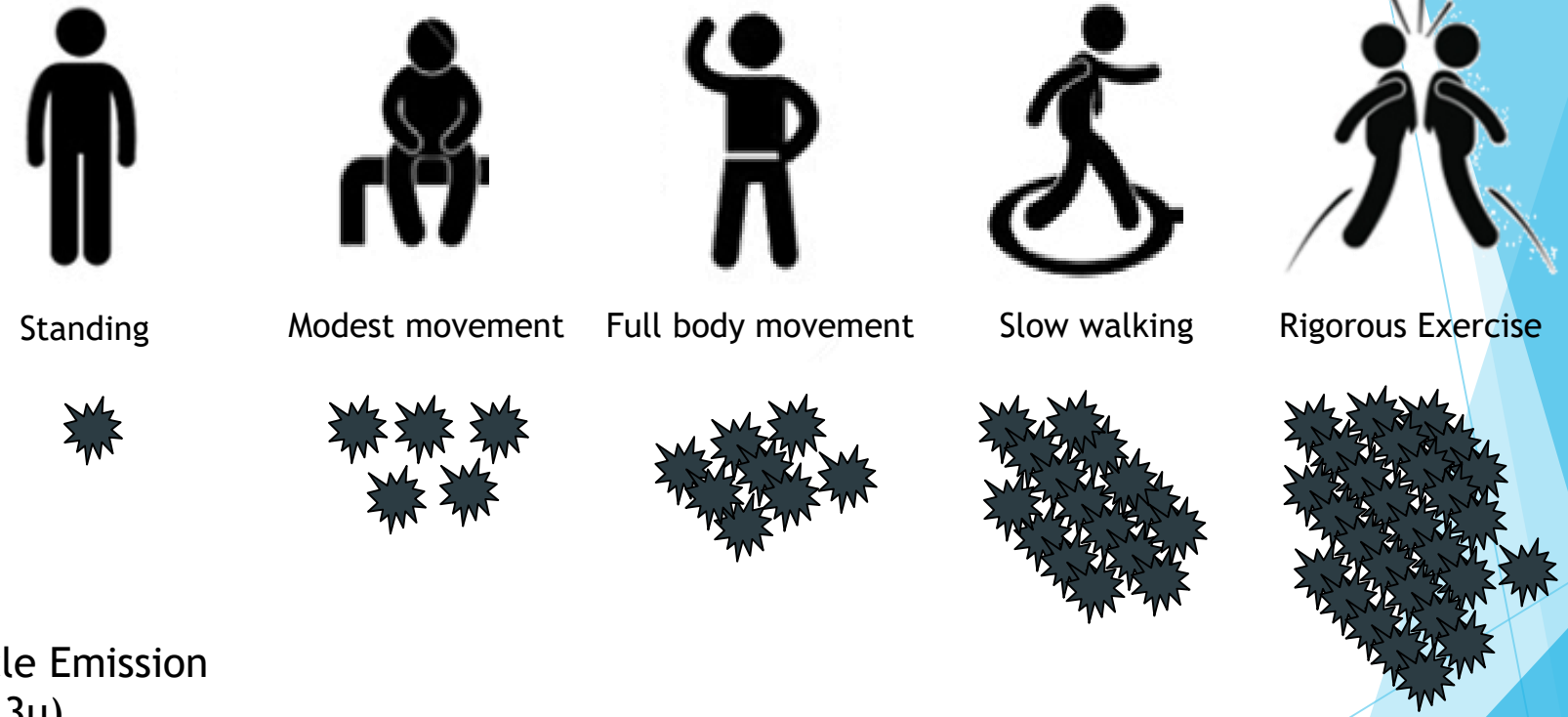
Personnel and Cleanroom Behaviors

Who is this???

YOU !!!

Personnel Behavior

Body Emission Related to Activity



Particle Emission
(>0.3μ)

Standing	Modest movement	Full body movement	Slow walking	Rigorous Exercise
100,000	500,000	2,000,000	5,000,000	30,000,000

Clean Room Behavior – MUST be detailed in SOPs

- Minimal Communication
- Keep movements slow
- Maintenance of aseptic gown
- Don’t lean against the wall
- Don’t pick items up off the floor
- Don’t huddle
- Maintain Control when you encounter a problem
- Frequent glove sanitization
- Keep sterile articles continuously bathed in direct, unobstructed, uninterrupted, HEPA-filtered air or “first air”
- FEEDBACK FEEDBACK FEEDBACK

Working with RABS/Isolator

Aseptic Operations

- Aseptic Practices
- Cleaning and Sanitization
- Interventions
- QA Oversight
- EM Procedures

Working in RABS or Isolators

- Aseptic Practices

- Generally speaking, you want to enter Grade A as MINIMAL as possible during operations
- When required to enter RABS through gloves
  - Clear the line whenever possible
  - Sanitize gloves before placing into RABS glove
  - NEVER reach over product contact parts – remember **“first air”** concept
  - Always use sterile tools (forceps, hemostats, mechanical, etc)
- Use the “clean person”/”dirty person” concept
- Follow your intervention procedures exactly, if you need to do something differently, consult with your QA team

Working in RABS or Isolators

- Cleaning and Sanitization

- Cleaning should be performed pre/post operations. Cleaning procedures should be detailed as to where to start and end, using uni-directional motion, use of detergents and wipes, etc.

- After performing an intervention, properly sanitize impacted area with sterile, pre-saturated, IPA wipes. If a “sterile” item is compromised, replace it

- Ensure entire doors are wiped when performing open door intervention

Working in RABS or Isolators

- Interventions

- Intervention needs to be documented based on classification and in REAL TIME
- Detailed procedures should direct you on how to clean
  - product spill, open door, glass breakage, vial jam, etc
- Procedures need to address type of monitoring performed after intervention (additional, personnel, etc)
- DO NOT reach over product contact space so to interrupt First Air
- For any unqualified intervention, SOP must provide guidance on path forward

Intervention Management

- All interventions must be captured in a QRA
- Best practice is to categorize between Routine/Non-routine
  - Routine – stopper/cap addition, fallen vial, EM, etc
  - Non-routine – broken vial, open door, major mechanical adjustment, change part removal, power outage, etc
- Each intervention should have detailed instructions as to how they are performed and what actions are taken before, during, and after intervention
- New interventions should be qualified as soon as possible as to when they were performed (and added to QRA)

Intervention Management

- Regs state that interventions MUST be qualified through media fills
- General standard is that routine interventions are performed every media fill and non-routine are performed at least 1x/year
- Current trend is that interventions are performed at maximum frequency as worse case production batch
- QA oversight is highly recommended during non-routine interventions
- DO NOT ever justify a bad practice through an intervention, even though you passed MF
  - Using non-sterile items
  - Having to pass items over product contact surfaces/open containers
  - Others?

QA Oversight

- All companies need to have a QA Oversight program
- Especially important for Fill and Finish Operations as this is the expectation of Regulatory Agencies
- Procedures should detail R&R, expectations, frequency, identification of anomalies, escalations, documentation
- At the very least, QA should view all production operations and documenting aseptic behaviors (good and bad)

Useful References…

1. Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
2. EudraLex The Rules Governing Medicinal Products in the European Union – Annex 1 Manufacture of Sterile Medicinal Products
3. ISO 14644-1: Cleanrooms and Associated Controlled Environments, Classification of Air Cleanliness.
4. Technical Report No. 36, “Current Practices in the Validation of Aseptic Processing," Parenteral Drug Association, Inc., 2002.
5. Parenteral Drug Association: www.pda.org
6. Google
7. Youtube!

???’s