Maintaining a Validated Cleanroom

Reducing Deviations and Contamination Events Through Effective Training

AZZUR GROUP

Shelley Preslar · September 2021

Agenda

- Section 1: Maintaining a Validated Cleanroom
- Section 2: Reducing Deviations and Contamination Events
- Section 3: Strategies for Success
- Section 4: Aseptic Gowning Qualification – A Case Study

AZZUR GROUP

Maintaining a Validated Cleanroom

Why Use a Cleanroom?

Cleanrooms are designed to minimize the introduction, generation and retention of non-viable particulates and viable microbiological contamination.

Key Characteristics of Cleanrooms

- Restricted Access
- Environmental Engineering Controls
- Personnel Flow Path
- Strict Cleaning Routine
- Windows/Interlocks
- Organized Workspace
- Visual/Audio Cues (lights, buzzers)
- Routine Environmental Monitoring

Cleanroom Regulations

CFR 211.42 (c)

"Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:

Cleanroom Regulations (continued)

CFR 211.42 (c)(10). Aseptic processing, which includes as appropriate:

i. Floors, walls and ceilings of smooth, hard surfaces that are easily cleanable

ii. Temperature and humidity controls

iii. An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar

iv. A system for monitoring environmental conditions

v. A system for cleaning and disinfecting the room and equipment to produce aseptic conditions

vi. A system for maintaining any equipment used to control the aseptic conditions

Cleanroom Certification

Once validated, a Cleanroom is certified to a required class of cleanliness aligned with intended use.

Classification requirements focus on air quality (particulate load in a cubic meter) and microbial load on surfaces (CFU recovered from sampling).

Monitoring and Control

Once fully certified, an environmental monitoring program must be established to ensure that the environment remains in a state of control.

Engineering Controls (Building Management Systems, In-line Testing Equipment, Trend Analysis) are in place to ensure mechanical systems are operational and effective.

However, personnel present several contamination variables.

Human Contamination

75% of contamination comes from people

- Total of 10 grams skin cells shed / day
- Shedding 1 layer of skin every 3-4 days
- SKIN – body part with most contact

Humans

- Host microorganisms and shed continually
- Transport dust & dirt

SKIN – major source of bacteria

AZZUR GROUP

Reducing Deviations and Contamination Events

Proper Cleaning Techniques

- Follow all appropriate gowning requirements.
- Start cleaning in the cleanest area, working your way out to the dirtiest area.
- Use a 3-step approach when cleaning:
    1. Clean all ceilings, walls, contacts surfaces, and floors with a surfactant.
    2. Clean all ceilings, walls, contact surfaces, and floors with a disinfectant or sporicidal agent. Leave the sporicidal agent on all surfaces for a minimum of 10 minutes.
    3. Rinse all ceilings, walls, contact surfaces, and floors with a sanitizer (i.e. 70% IPA).

    Note: Change mop heads between each step.

Proper Cleaning Techniques (continued)

- Clean from top to bottom, back to front in the following order:

  Ceilings→Walls→Contact surfaces (door handles, tables, chairs, etc.)→Floors

- Wipe in a unidirectional path utilizing appropriate mops or non-shedding wipes.

Losing Control

Losing control of your validated classified spaces will be evident in the monitoring data (personnel or environmental).

- Contamination Event Trends
  - Increased Personnel Recovery
  - Increased Environmental Recovery
- Product quality issues
  - SQUIPP Testing Failures

Where does it all come from?

Personnel Issues

Complacency Due to Redundant or Repetitive 'menial' tasks

- Lack of ownership / agency
- No motivation to improve
- Lack understanding of how critical their role is

High Turnover / Inexperienced Personnel

- Interpretation & Consistency Issues
- Increased downtime due to ongoing introductory training

ALL CONTRIBUTE TO INCREASED CONTAMINATION RISK AND CAN BE EFFECTIVELY MITIGATED BY TRAINING.

Contamination and Training Observations

Contamination Observation Examples

- Non-microbial contamination was observed in classified production area
- Material or supplies were not disinfected prior to entering the aseptic processing areas
- Aseptic processing performed outside certified ISO-5 area

Training Observation Examples

- Personnel donned gowning apparel improperly, in a way that may have caused the gowning apparel to become contaminated
- Hazardous drugs were produced without providing adequate cleaning of utensils to prevent cross contamination

Eliminating / Controlling Contamination

As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases.

To reduce this risk, it is equally critical for operators to be adequately trained in aseptic techniques and behaviors with a focus on understanding the underlying mechanics and theory.

TRAINING IS A VERY EFFECTIVE WAY TO REDUCE CONTAMINATION RISK.

Training Issues

- Dedicated training space reduces usable cGMP space
- Non-Dedicated training Space raises the risk of cGMP contamination
- Dedicated training personnel equals less headcount for production
- Non-dedicated training personnel overtaxed with the sometimes-conflicting tasks of performing their main duties and training while maintaining aseptic behavior

AZZUR GROUP

Strategies for Success

Challenge 1→ Changes in Personnel

Turnover is the expectation, but creates specific issues when it comes to operations personnel

- Inexperienced personnel may perform actions differently through lack of experience or unintentional SOP ambiguities.
- Individuals may interpret procedures and requirements slightly differently.
- Decreased productivity while veteran personnel try to perform double duty of production and training.

Challenge 2→ Personnel Motivation

Personnel training often focuses on how to perform a task without explaining why. Personnel often learn what to do without understanding the mechanics behind the process leading to:

- Lack of Ownership or Agency in the process. Without process understanding, operators lack nuance. The operator may notice something wrong but, lacking understanding, hesitates in correcting it.
- Lack of understanding criticality. People tend to rationalize when they're given a task without explanation. This can lead to assumptions that something "isn't that important"

Strategy - Developing Successful Training

- Evaluate current personnel capabilities and knowledge
- Identify gaps in personnel capability / knowledge
- Determine the key learning objectives
- Set trainees up for success by utilizing a variety of training methods / inputs to increase knowledge retention
- Share / Show / Do / Test

Evaluate

Understand where the trainees are now:

- Fresh Graduates / No Previous Industry Experience
- Industry transfers (technical but lacking in regulatory experience)
- Level of education / experience (Junior to Senior)
- Consider physical attributes (part of the onboarding process)
- Are they able to meet physical demands (flexibility, strength, endurance)?
- Will they be “ok” gowned up for several hours at a time?

Define Desired Outcomes

- What knowledge is required at the end of this training event?
- What skills must be acquired from this training event?
- Will graduates of this training go on to train others?
- Each lesson should target 1 or 2 objectives
- Teach one skill per objective
    - Avoid information overload (i.e., ”Drink from a firehose”).
      Maintain realistic expectations of the outcome

Learning Objectives

Drive Consistency

Trainees typically do not remember every detail the very first time they hear something.

Repetition is important in building consistency – it is so important that it is mentioned within the FDA regulations:

21 CFR 211.25(b) states in part that "Training in cGMPs 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."

Inspire Motivation

Provide the trainees with tools for success:

- Explain the “WHY”, reduce speculation and misinterpretation.
- Connect what personnel do directly to product outcomes, where possible show positive AND negative consequences.
- Empower individuals to “do the right thing” by instilling a ‘Quality First’ mentality.

Improve Retention: Acquiring Knowledge

There are three basic mechanisms for Humans to gain knowledge:

Visual: Watching, reading, observing, writing, seeing, drawing

Auditory: Listening, telling, discussing

Kinesthetic: Doing, moving, feeling, making, building, experiencing

WHEN YOU COMBINE ALL THREE, YOU CREATE A RECIPE FOR **SUCCESS** – PARTICULARLY WHEN YOU REFRESH KEY CONCEPTS ON A REGULAR BASIS.

Learning Pyramid

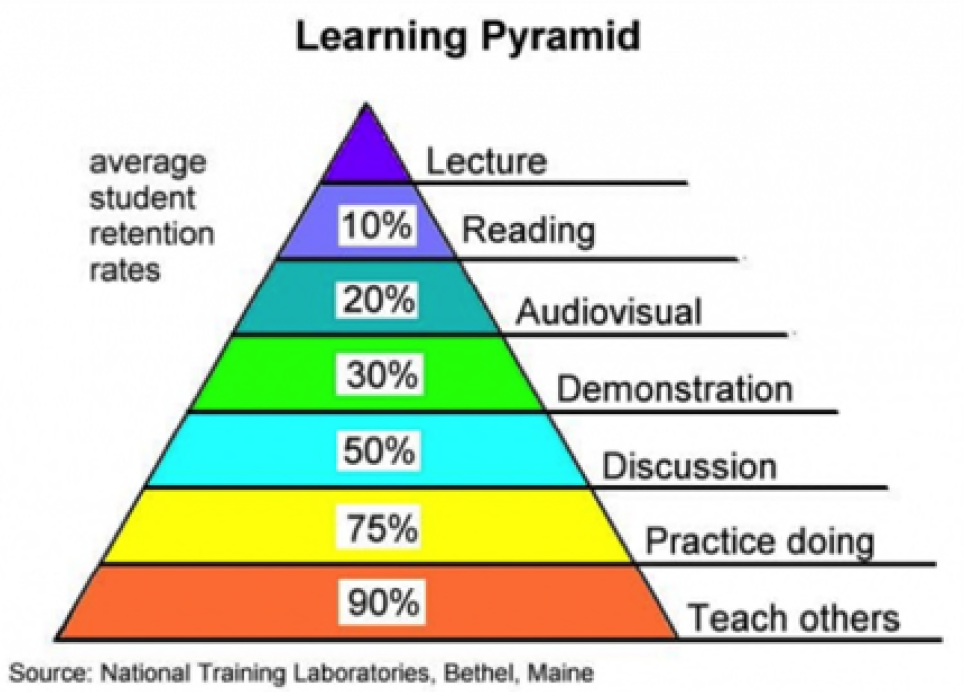
Visual – Read an SOP (read and understand) – 10%

Audiovisual – Hear a lecture, listen to a PPT, watch a video, VR – 20%

Kinesthetic – practice / perform a physical exercise – 75%+

Gowning – trainees practice prior to qualification

Process / Technique – often doesn't happen until in cleanroom



MORE INPUTS = STRONGER RETENTION

Step 1 - Share

Provide the knowledge:

- Start with WHY, uncover the underlying mechanics.
- Educate on general concepts as well as specific technical content
- Connect daily activities directly to patient outcomes

WHAT IS THE ULTIMATE REASON WE DO WHAT WE DO????

PATIENTS

Step 2 - Show

- Demonstrate the desired activity
- Walk through step-by-step
- Answer questions along the way
- Establish what **SUCCESS** looks like, then demonstrate it

Step 3 - Do

- Provide time and materials for trainees to **practice, practice, practice** - prior to entering cleanroom
- Evaluate their capability to perform the action
- If they are not capable – don't force it. Physical limitations can usually be overcome with alternative methods

Step 4 - Test

Provide ample time for trainees to practice as much as needed for them to be comfortable with the process.

- **Practice, practice, practice**
- Coach, mentor, and encourage along the way.
- Surround them with trained personnel to answer questions and support them through the process.

Strategy – Training Methods

Traditional Model:

- Utilizes critical personnel to train job specific requirements (gowning, aseptic processing, etc.)
- Requires the use of manufacturing space to train personnel
- Contamination can shut down manufacturing areas temporarily
- Trainees learn site specific knowledge with exact materials

Strategy – Training Methods (continued)

Virtual Reality (VR)

- Has been utilized in multiple locations
- Provides background knowledge and familiarity with spaces, instruments, etc., (Requires specific setup)
- Gives the ability to see and interact with a virtual replica of your specific environment
- Does not provide actual hands-on experience with actual equipment, tools, materials used in the cleanroom – utilizes some sort of hand-held controller.
- Muscle memory from gained in VR can be counterproductive to learning real-world actions once in the cleanroom

Strategy – Training Methods (continued)

Outsourced Training Partner:

- Train partner personnel on your internal procedures – certified trainers
- Provide your specific SOPs for the training activities
- Off-site classroom and cleanroom available to provide actual hands-on experience
- Your site SMEs continue to do their "day job"
- Contamination events during training will not impact your manufacturing areas
- Personnel are trained and qualified on your procedures. Returning to work ready to work*.

**Applicable EM Data can take up to 7 days to receive.*

Formula for Success

With a well thought out training strategy, your team will be on the path to reduced deviations and contamination events.

By providing the general philosophies, concepts, and underlying mechanics with the specific requirements of your organization you will create a **POWERFUL** formula for success.

AZZUR GROUP

Aseptic Gowning Qualification – A Case Study

Project Overview

Situation: Union personnel contract negotiations

Problem to solve / risk: Keep the plant running in the event of a walk-out

Solution: Deliver a large number of qualified personnel in a very short time

Knowledge Components: GDP/GMP, Contamination Control, Aseptic Techniques and Gowning

Objective: Each trainee must meet Grade A gowning qualification requirements (3 x 8)

Challenge: MOST of these trainees had little to no pharma experience, let alone aseptic processing experience or knowledge…

Project Delivery

Phase 1: Train the Trainer

- Our team, on-site becoming trained in required SOPs
- Go through Qualification Process
- Fully signed off (client system) as “Trainers”

Phase 2: Set Up Operations Off-Site

- Set up classrooms and cleanroom space
- Logistics (gowning supplies, test materials, computers)

Project Delivery (continued)

Phase 3: Time to Train

- 12 Qualified Trainers covering 3 sites
- Class size of up to 24 for 3 days
- Three Classroom locations, 1 cleanroom
  - A = Classroom and Cleanroom
  - B & C = Classroom only

Trainees were moved back and forth as needed to run through qualification process

Successfully Qualified 91 individuals in 12 (very long) days

Training Schedule Example

General Concepts

- 16-hour days
- 10 active trainers
- 4 trainees through 3x8 in 2.5 hours

Day 1	Day 2	Day 3
GDP/GMP Part 1	Aseptic Techniques Part 3	Gowning Eval 9-12: Practice 13-16
Break	Break	
GDP / GMP Part 2	Gowning Training	Break
Lunch	Lunch	
GDP/GMP Part 3	Gowning Practice 1-4	Gowning Eval 13-16: Practice 17-20
Break	Break	Break
Aseptic Techniques Part 1	Gowning Eval 1-4, Practice 5-8	Gowning Eval 17-20: Practice 21-24
Dinner	Dinner	Dinner
Aseptic Techniques Part 2	Gowning Eval 5 - 8 : Practice 9 - 12	Gowning Eval 21-24

Training Delivery

Step 1 - SOPs, Read and Understand **(Reading – 10%)**

Step 2 - Classroom – trainer delivering content **(Audiovisual – 20%)**

Step 3 - Watch someone perform gowning **(Demonstrate – 30%)**

Step 4 - Q&A regarding previous content **(Discuss – 50%)**

Step 5 - Students perform gowning outside of cleanroom **(Practice – 75%)**

Step 6 - Qualification / evidence of successful performance

- During the qualification process, two students are put through at a time, often resulting in students having the opportunity to coach / teach each other, which provides a potential 90%+ chance of knowledge retention!

Project Outcome

Total trainees: 112

No show: 10

DQ'd: 9

Trained and tested: 93

Successfully qualified: 91

Success Rate first time:

98%

Final Thoughts

Training is an effective way to **reduce contamination risk** within your facility

Teaching "**why**" is equally critical to the "**how**". Understanding the importance of a task is the first step in ownership.

Increased ownership and agency ultimately lead to increased "Right First Time" execution.

AZZUR GROUP

Thank you!

Shelley Preslar
President & COO, Azzur Training Center
shelley.preslar@azzur.com
(919)-534-6997