Microbial Contamination and Control Conference

Developing a CCS for ATMP Cleanrooms

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Agenda

- Overview of CCS and ATMPs
- Requirements—Annex 1ATMP Guideline
- CCS Elements
- Challenges and Solutions

What are ATMPs?

Gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources;

Somatic-cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;

Tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue;

What is a Contamination Control Strategy?

"Contamination Control Strategy (CCS)—A planned set of processes and measures for the identification, assessment, control, and monitoring of contamination risks that include microorganisms, pyrogens/endotoxins, and foreign particles, derived from current product and process understanding, that assures process performance and product quality."

CCS Requirements in ATMP Guidance

- EudraLex—Volume 4—Good Manufacturing Practice (GMP) guidelines

9.36. The control strategy is multifaceted and should address all the potential risks, including therefore measures at the level of the facilities, equipment and personnel, controls on starting and raw materials, implementation of effective sterilisation and sanitisations procedures, and adequate monitoring systems. The totality of the measures applied should assure the absence of contamination of the products manufactured within the manufacturing site. Sole reliance should not be placed on any terminal process or finished product test.

CCS Requirements in Annex 1

"2.3 A Contamination Control Strategy (CCS) should be implemented across the facility to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. **The combined strategy of the CCS should establish robust assurance of contamination prevention**. The CCS should be **actively reviewed** and, where appropriate, **updated** and should **drive continual improvement** of the manufacturing and control methods. Its **effectiveness** should form **part of the periodic management review**. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood."

Annex I: Disinfectant Validation

"The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and should support the in-use expiry periods of prepared solutions."

Recent FDA 483

"Specifically, the disinfectant efficacy study, "Validation for Sterilization of ….. Surfaces," conducted 10 years ago is deficient in that:

a. The study was performed using only ….. No other typical USP growth promotion microorganisms, and especially no in-house isolates, were evaluated in this study.

b. The study included ….. No other surfaces present in the Cleanroom were evaluated.

c. There was no analysis to determine if the microbial population used consisted of spores and/or dividing vegetative microorganisms.

d. On multiple occasions, we observed ….. was used as disinfectant in the gowning room; however, it was not evaluated in this study.

e. The method of cleaning of the Cleanrooms is different than the method used in this validation study.

f. The firm has not conducted any other disinfectant efficacy study since this study 10 years ago".

GMP Trends September 15, 2021

Annex I: Pass Thru Decon

"For materials, equipment, components and ancillary items that are necessary for aseptic processing but cannot be sterilized, an effective and validated disinfection and transfer process should be in place. These items, once disinfected, should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring program."

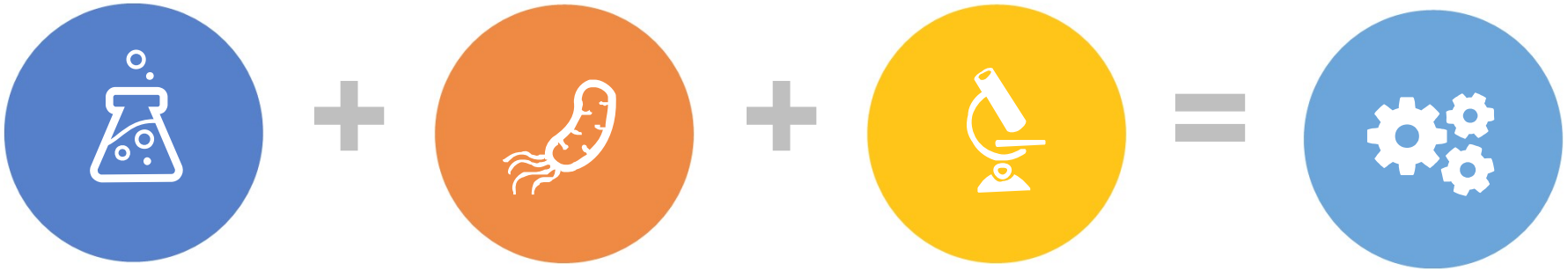
CCS-Eliminate or Minimize

- **Particulates** — Viable and Non-Viable
- **Microbial** — Spores, Fungi, Virus
- **Endotoxins** — Pyrogens

CCS-Largest Sources of Contamination

- **People** — Manufacturing, Cleaning
- **Raw Materials**
- **Process Materials** — Disposables, Filling, Supplies

Developing a CCS



Process Knowledge

Technical knowledge of operations including vulnerability profiles of the process, equipment, and materials.

Identify the Hazards

Technical knowledge of microbial contamination considerations including microbial ingress, proliferation, and persistence.

QRM & Data Analytics

Inform the quality risk management and use data analytics.

Robust CCS

Evaluate and monitor through data analytics to provide a comprehensive assessment of the effectiveness of current controls and indicators of needed/desired improvements

ATMPs & Unique Challenges

- Potential risks to patients are different for each product, often requiring individualized CCS—challenge in multi-product facilities
- Increased risk of cross-contamination from lot to lot (single-product facility) and product to product (multi-product facility)
- Time constraints—product infused at-risk;

Engineering and Process Design Challenges

- Manufacturing is performed in ISO 7 or Grade B cleanrooms with open or aseptic connections
- Manual aseptic processes performed in BSCs, including manual filling operations

Engineering and Process Design Solutions

- Regular Cleaning, Disinfection, and Sporicidal application process
- Robust material flow and material transfer decontamination processes
- Implementation of barrier solutions

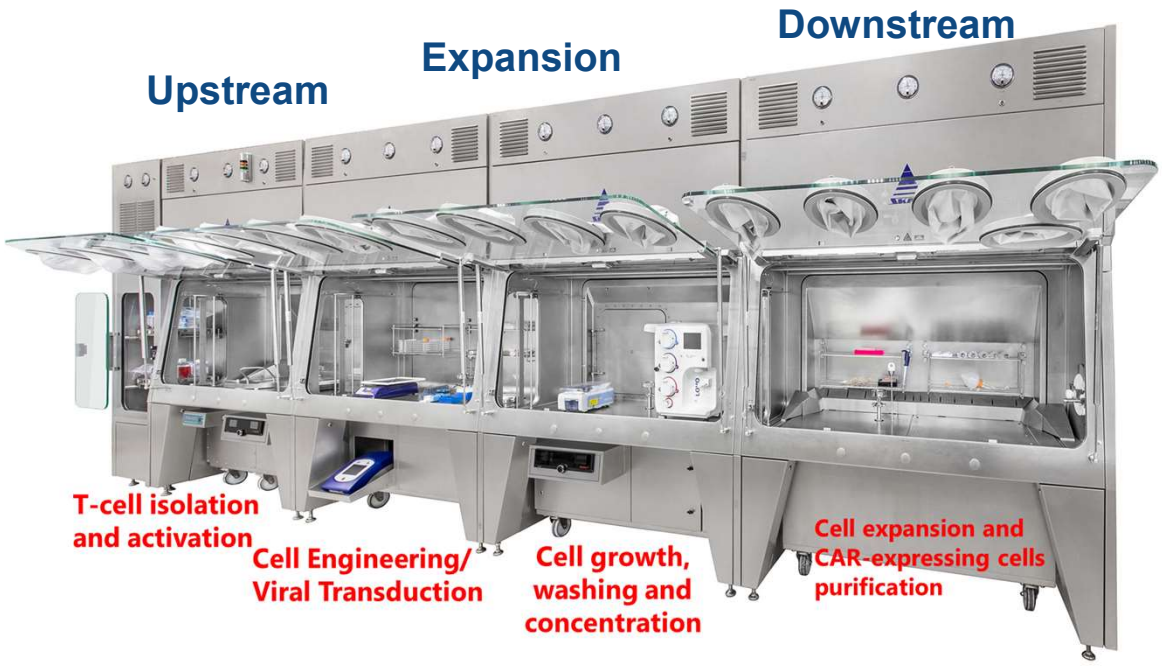
Engineering and Process Design Solutions

- Integrated VHP in ATMPs
  - Decontamination of multiple AHU zones/rooms
  - VHP is qualified as an automated building utility
  - Decontamination can be performed at-will—product change over, batch change over, in response to an event, after maintenance, etc.
  - Adjacent areas have the ability to continue to operate
  - Zones can be decontaminated sequentially

Engineering and Process Design Solutions

Engineering and Process Design Solutions

Some steps are performed outside and some inside the isolator such as thawing the starting material or cell expansion on a rocker bioreactor outside – cell culture mixing and transferring oxygen



Engineering and Process Design Solutions

Closed, robotic isolator

- Reduces human intervention
- Robots for EM

Equipment Challenges

- Process equipment is unable to be sterilized, difficult to clean, and/or possesses a favorable environment for microbial growth—not designed for cleanrooms

Equipment Challenges: Case Study

- Viable air mold recoveries
- Not recovered from surface monitoring
- Mold recoveries increased with activity and personnel
- Video footage review determined aseptic practices were being followed
- Material was either sterilized or disinfected with sporicidal agent
- Process area removed from service pending investigation
- Plenum of the incubator was reservoir for mold
- Source was identified as insulation from mechanical panel of incubator- “closed” system

Equipment Solutions

- Equipment should be evaluated by a risk assessment and should take into consideration its use in manufacturing
- Develop a routine cleaning and disinfection process; process should consider the principles of clean in and clean out, batch to batch change over, and product change over
- Consider including equipment sample sites into the Environmental Monitoring program
- Evaluate new technologies and alternative equipment

Pass Thru & Material Transfer Challenges

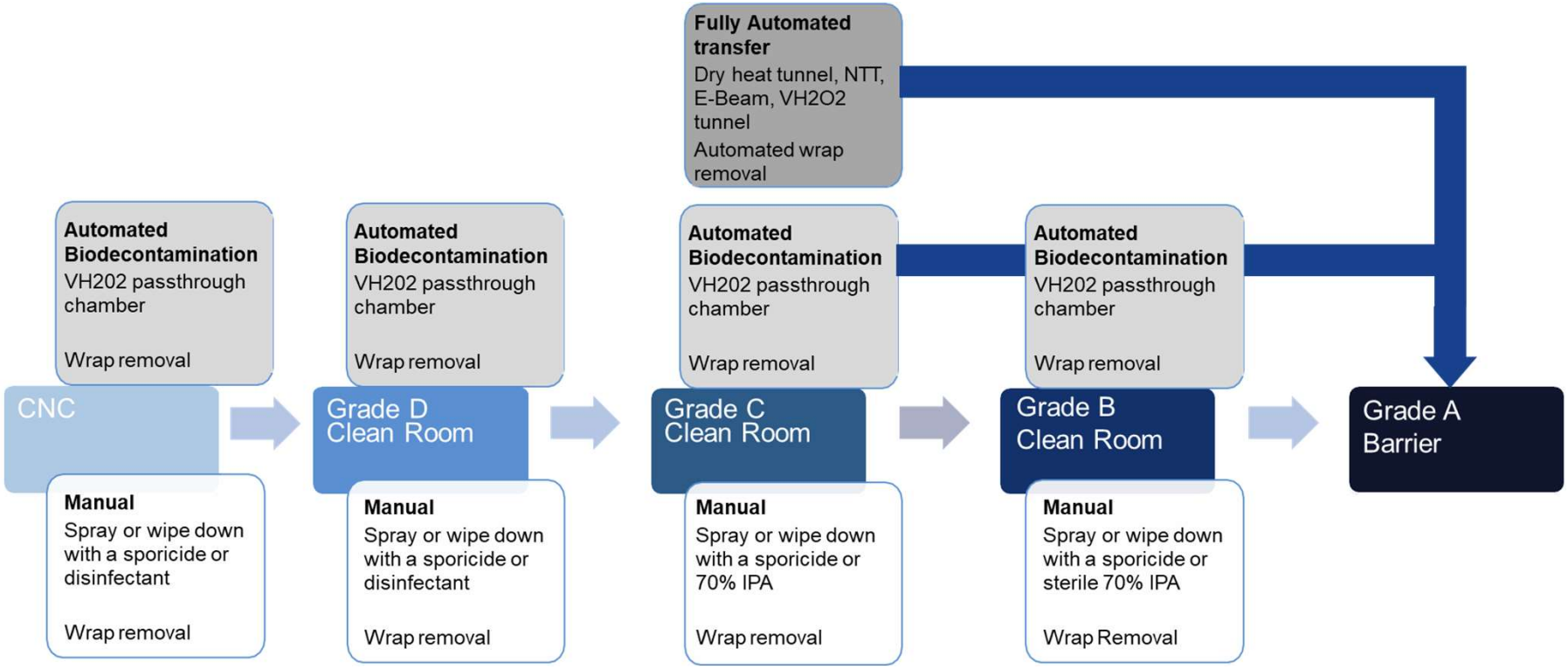
- Raw materials—use of non-sterile components; must be kept cold or frozen until used; primary or secondary packaging consists of cardboard or unable to be disinfected/withstand established dwell time
- Large volume of materials flowing in and out of the process
- Pass thru decon

Pass Thru and Material Transfer Challenges

- Efficacy
- Wet Contact Time
- Full Coverage
- Delegated Tasks
- Complex Surfaces
- Technique Dependent
- Disinfectant and Sporicidal Wipes

Pass Thru and Material Transfer Challenges

Materials Transfer in ATMP



Pass Thru & Material Transfer Solutions

- Contamination control starts at receipt of incoming items at the door
  - Remove cardboard; implement a deboxing zone for cardboard packaged materials
  - Perform a wipe down of materials upon receipt to remove extraneous contamination from shipping
  - Implement a material kitting process, when possible
  - Materials that cannot withstand the dwell time during material transfer process, must be evaluated by a risk assessment and approved in the procedure as an exception

Pass Thru & Material Transfer Solutions

Automated transfer of IV Bags.
Design to meet throughput
ISO 9 to ISO 7
6-log BI
Cycle time ~70 min

ATMP Surface Selection

- **Risk-Based Decisions**
- **Group like materials and select representative based upon risk score**
  - Large surface area (% of the area)
  - Challenge to cleaning/disinfection
    - Surface roughness, surface hardness, porosity, chemical compatibility, etc.
  - Criticality/risk to product
    - Proximity to any open intervention, has operator contact, etc.

ATMP Substrates for Coupon Testing

- Cleanroom disinfectant qualifications – representative materials
  - Stainless steel (316, 304)
  - Glass
  - Polycarbonate
  - Various plastics and elastomers
  - Lexan curtains
  - Trespa panels and Kingspan panels
  - Kydex and uPVC
  - Bodycote aluminum wall
  - Epoxy-coated flooring
  - Polymeric flooring
  - MMA Flooring
  - Vinyl Flooring
  - Terrazo Flooring
  - Acyrlic and Grout
  - Saniflex
  - Paints (Epoxy and Water Based) & Sealants
  - Gaskets (EPDM, Teflon)
  - Rubber or Nitrile gloves

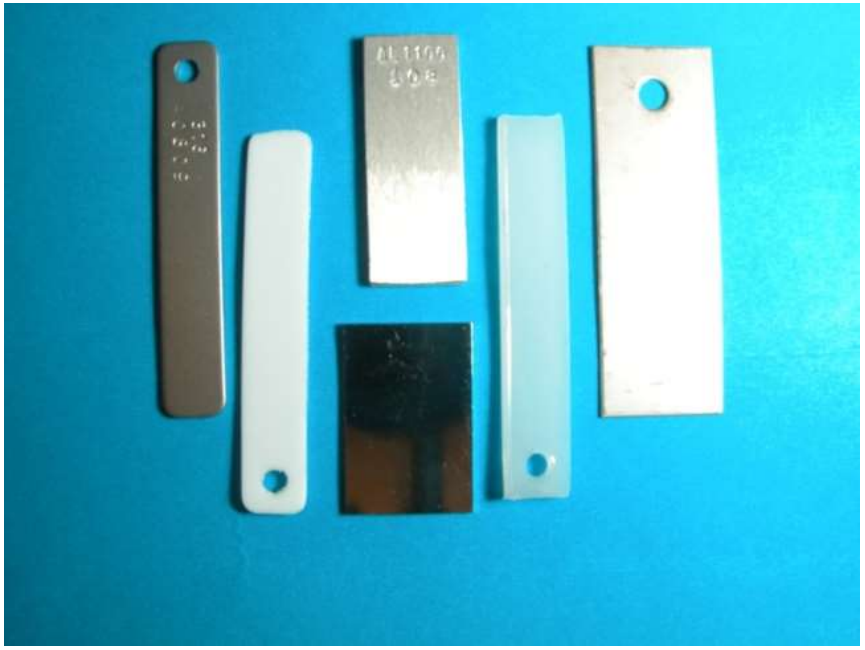


Table 1: Risk parameters and classification of substrates

Risk Parameter	Risk Classification		
	Low (1)	Medium (3)	High (5)
Relative surface roughness	Low surface roughness	Intermediate surface roughness	High surface roughness
Touch point	No contact	Occasional operator contact	High frequency of operator contact
Percentage surface area of substrate in item / cleanroom	Small percentage (<25%)	Intermediate percentage (<25% to 75%)	Large percentage (>75%)
Proximity to critical process	Not in close-proximity	NA	In close-proximity

Table 2: Risk assessment

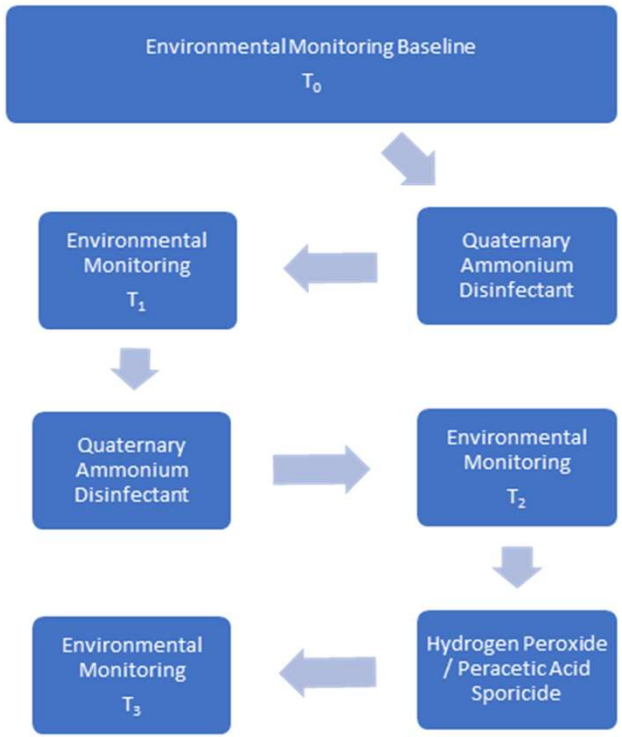
Description			Risk Assessment				
Category	Area	Substrate	Surface Rough-ness	Touch-point	% surface area	Proximity to critical area	Total
Cleanroom	Floor	Terrazzo tiles	3	5	3	1	45
	Wall	Powder coated galvanized steel sheet	3	3	5	1	45
	Ceiling	Powder coated galvanized steel sheet	3	1	3	1	9
	Windows	Glass	3	3	3	1	27
	Sealant	Silicone	3	1	1	1	3
Furniture	Tables, chairs, trolleys, shelves	Stainless steel 304L	3	5	5	1	75
	Caster wheels of trolleys	Polyurethane	5	5	1	1	25

Common Causes of Failures in Coupon Studies

- General Causes of failures
  - Improper dilution of concentrated disinfectant
  - Generating data that is not useful
    - Using AOAC test methods for coupon studies
  - Ineffective chemistries
    - Testing alcohol or disinfectants without sporicidal claims against bacterial endospores
  - Contact time too short
    - Inadequate wet contact with inoculum

General
Neutralization
Inoculum
Surfaces
Recovery

In Situ Disinfectant Field Trial Testing

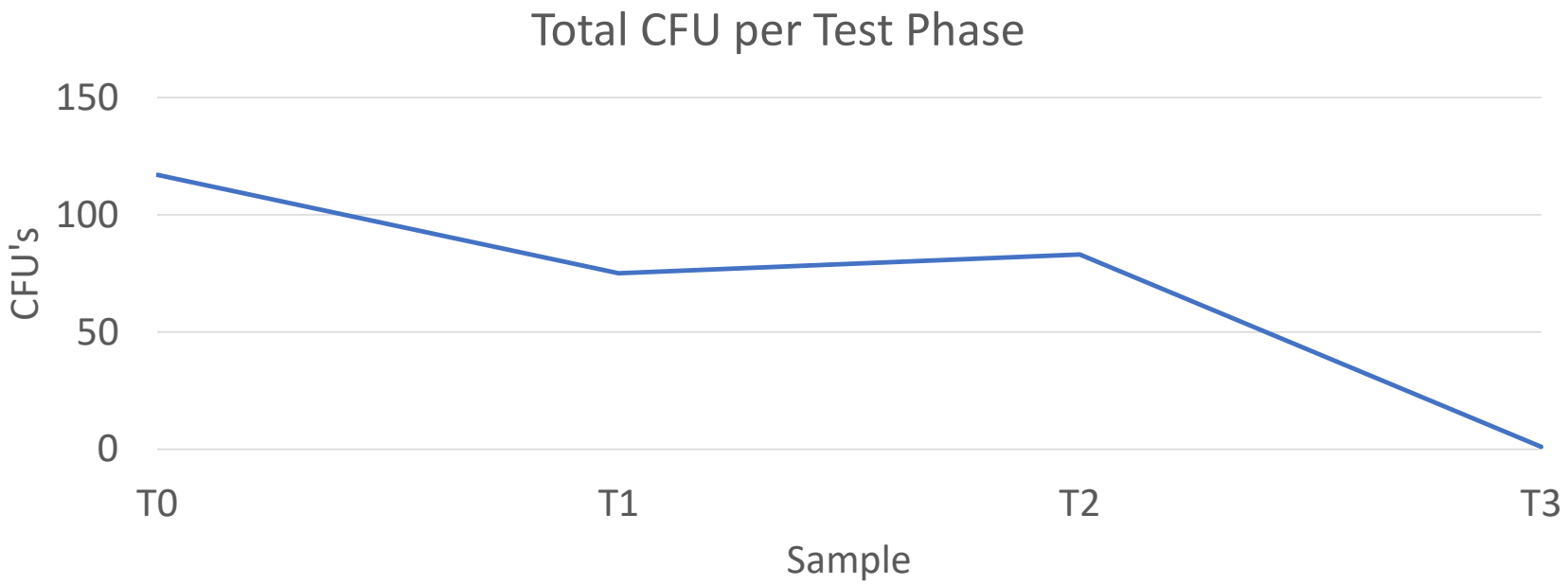


- Use actual cleaning procedure SOPs (update prior to Validation study)
- "Worst case" conditions
  - Higher microbial load
- Compare environmental data before and after procedures
- Should include data from more than one cleaning event

In Situ Testing

Summary: Sample Collection and Test Results													
Room	ISO Class	Samples				CFU count				CFU/Plate			
		T_0	T_1	T_2	T_3	T_0	T_1	T_2	T_3	T_0	T_1	T_2	T_3
B107 Clean Corridor	8	16	16	16	16	10	8	10	0	0.63	0.50	0.63	0.00
B120 Prep Room	8	12	12	12	12	9	5	6	0	0.75	0.42	0.50	0.00
B123 Material Entrance	7	5	5	5	5	0	0	0	0	0.00	0.00	0.00	0.00
B125 Aseptic Gowning	7	6	6	6	6	4	3	0	0	0.67	0.50	0.00	0.00
B124 Compounding Room	7	16	16	16	16	15	7	5	0	0.94	0.44	0.31	0.00
B118 Pass Through	7	6	6	6	6	4	2	3	0	0.67	0.33	0.50	0.00
B116 Filling Suite	7	19	19	19	19	24	30	21	1	1.26	1.58	1.11	0.05
B116 Laminar Flow Hood	5	3	3	3	3	2	0	0	0	0.67	0.00	0.00	0.00
B116 Behind Curtain	5	10	10	10	10	10	2	0	0	1.00	0.20	0.00	0.00
B116 Fill Machine	5	14	14	14	14	29	3	0	0	2.07	0.21	0.00	0.00
B116 Isolator Finger Tips	5	13	13	13	13	4	0	0	0	0.31	0.00	0.00	0.00
B114 Material Exit	7	6	6	6	6	0	0	0	0	0.00	0.00	0.00	0.00
B113 Personnel Exit	7	6	6	6	6	6	15	37	0	1.00	2.50	6.17	0.00
Overall	NA	132	132	132	132	117	75	83	1	0.89	0.57	0.62	0.01

In Situ Testing



Thank You for Attending

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Questions?