Avoiding Pitfalls in Disinfectant Qualification

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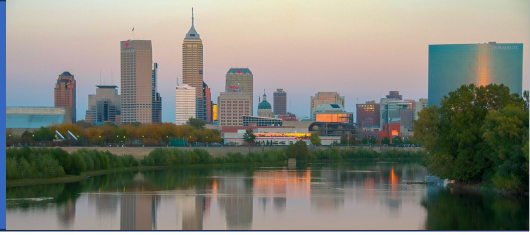
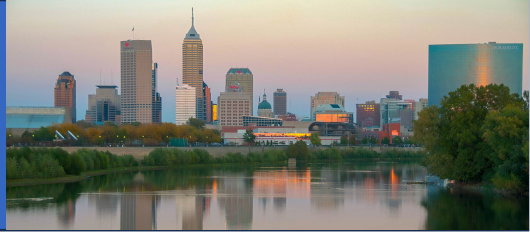


Topic Covered

- Regulations and Guidance on Disinfectant Qualification
- FDA 483's and Warning Letter
- Pitfalls Throughout the Disinfectant Qualification Process

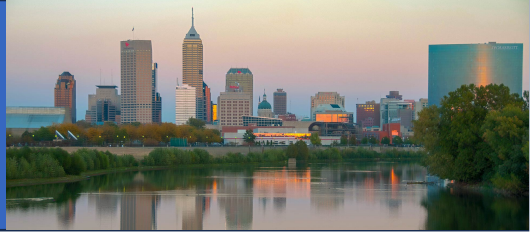


Regulations and Guidance on Disinfectant Qualification

FDA Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing, Current Good Manufacturing Practice (2004)
"The suitability, efficacy, and limitations of disinfecting agents and procedures should be assessed. The effectiveness of these disinfectants and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces." "Routinely used disinfectants should be effective against the normal microbial vegetative flora recovered from the facility."

Annex 1 – Manufacture of Sterile Medicinal Products (August 2022)
"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 on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions."

USP <1072> Disinfectants and Antiseptics
"The selection of suitable disinfectants and the verification of their effectiveness in surface challenge testing is critical in the development of a cleaning and sanitization program."



FDA 483's

OBSERVATION 4

Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room and equipment to produce aseptic conditions.

Specifically, classified area disinfecting procedures (SOP 201 Classified Area Cleaning) do not ensure contact times are accomplished, there is no contact time established for (b) (4) and there is nothing in the procedure determining how much area can be wiped with a single mop surface or hand wipe surface. For example, it was observed on 8/27/2020, as a regular practice, that the Operator used the same hand wipe surface to disinfect multiple production surfaces within the same ISO area.

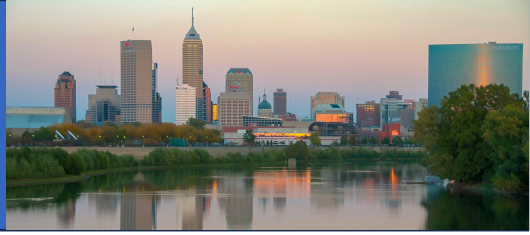
Source: https://www.fda.gov/media/143121/download

OBSERVATION 3

Disinfectant contact time (also known as "dwell time") and coverage of the item being disinfected were insufficient to achieve adequate levels of disinfection.

Specifically, during the daily cleaning of the clean room I observed on August 10, 2021, each of your disinfectants ((b) (4) wipes and spray and (b) (4) spray) used within the ISO 5 and ISO 7 environments had a less than (b) (4) wet contact time, despite the supplier's established (b) (4) minimum contact time needed for the disinfectant to achieve the necessary log reduction of microorganisms.

Source: https://www.fda.gov/media/155499/download



FDA 483

OBSERVATION 14

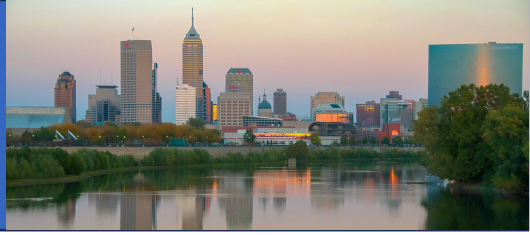
Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

Specifically,

A) The disinfectant efficacy study, entitled, "VALIDATION FOR STERILIZATION OF SURFACES BY (b) (4) (study (b) (4)) conducted in 2004 is deficient in that:

- The study was performed using only (b) (4) No other typical USP growth promotion microorganisms, and especially no in-house isolates were evaluated in this study.
- The study included (b) (4) no other surfaces present in the Cleanroom were evaluated.
- There was no analysis to determine if the microbial population used consisted of spores and/or dividing vegetative microorganisms.
- On multiple occasions we observed (b) (4) was used as disinfectant in the gowning room, however it was not evaluated in this study.
- The method of cleaning of the Cleanrooms ((b) (4)) is different than the method used ((b) (4)) in this validation study.
- The firm has not conducted any other disinfectant efficacy study since 2004.

Source: https:www.fdanews.com/altairepharma483.pdf



FDA Warning Letter

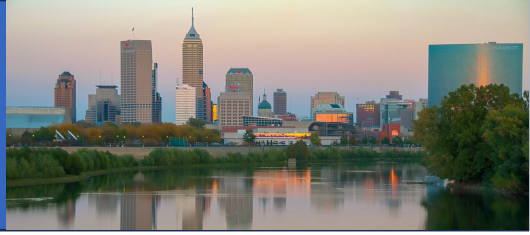
Disinfection Qualification

We observed that your firm did not adequately disinfect your RABS. For example, surfaces (b)(4) the RABS (b)(4) were not routinely disinfected, and your firm incompletely disinfected the bottom of the RABS (b)(4).

In addition, you have not sufficiently established the efficacy of disinfectants you use in aseptic processing cleanrooms. Your disinfectant study only challenged (b)(4) and(b)(4) manufacturing surfaces. You did not provide an adequate scientific rationale for not challenging other representative surfaces, such as glass windows, (b)(4),(b)(4), (b)(4), (b)(4), or other interior RABS surfaces.

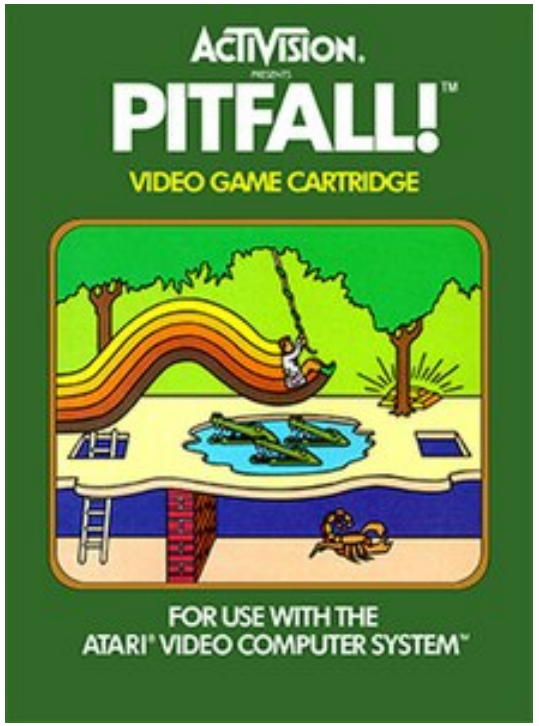
In response to this letter, provide data to support the efficacy of your disinfection procedures on additional representative surfaces.

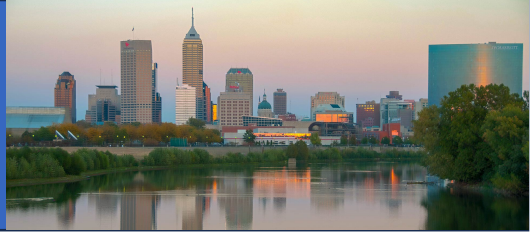
Source: https://www.gmp-navigator.com/mygmp/mikrobiologie-sterilherstellung-hygiene/warning-letters-sterilfertigung?file=files/eca/userFiles/mygmp-guidelines/16_11_16-cppharmaceuticals.PDF



What is a Pitfall?

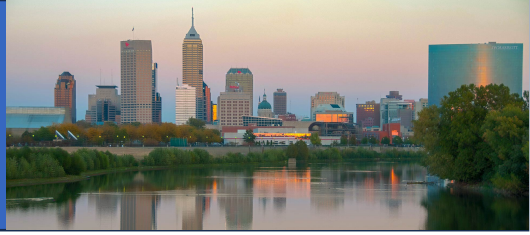
- a hidden or not easily recognized danger or difficulty



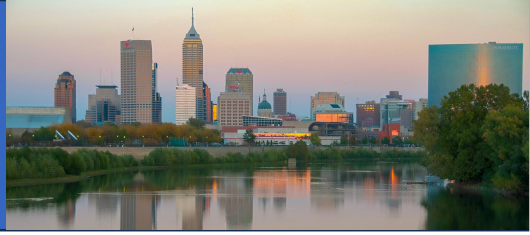


When can pitfalls occur?

- During Disinfectant Selection
- During DE Study Design
- When Performing the DE Study
- After the DE Study



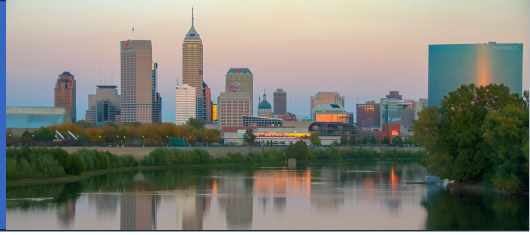
During Disinfectant Selection



Pitfall 1

Not Properly Qualifying Your Supplier(s)

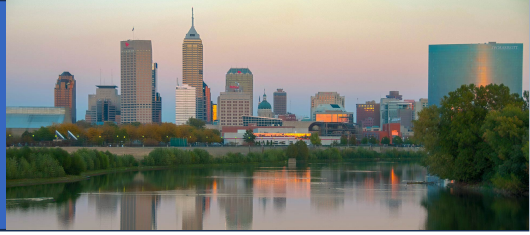
- Have a formal system for supplier evaluation and qualification.
  - Ensure that their manufacturing and quality operations meet your requirements.
  - Do they have a change notification system in place?
- Have a secondary supplier qualified.



Pitfall 2

Not Considering Safety/PPE

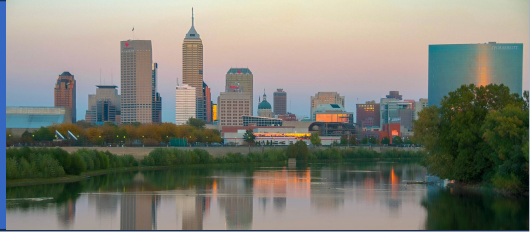
- Review the SDS's
- Review PPE requirements
  - Respirator Program?
- Storage? Disposal?
- Consult with your EHS department.
- Trial the product before spending resources to qualify it.



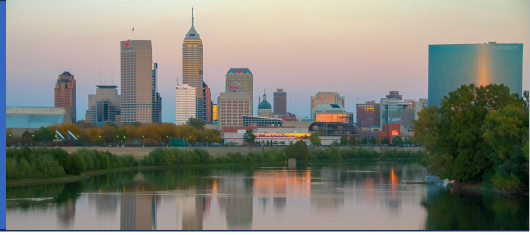
Pitfall 3

Not Considering Residues and Surface Compatibility

- All disinfectants beyond 70% IPA will leave a residue.
  - Corrosive?
  - Impact on your operations?
  - Impact on other chemicals?
  - Annex 1 compliance?
- Review the manufacturer's surface compatibility data vs your materials of construction and address gaps.
- Trial the product before spending resources to qualify it.



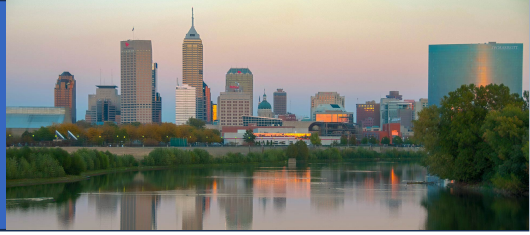
During DE Study Design



Pitfall 4

Not Testing EM Isolates

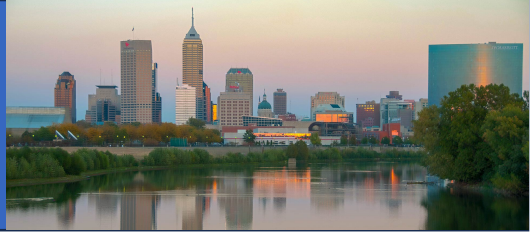
- The Disinfectant Efficacy (DE) Study should show that your disinfectant/sporicide rotation has a full spectrum of coverage.
  - Bactericidal
  - Fungicidal
  - Sporicidal
- Regulatory expectation is that EM isolates are included in the study.
- Rationale and justification for organism selection should be documented and included in your CCS.



Pitfall 5

Not Setting Appropriate Acceptance Criteria

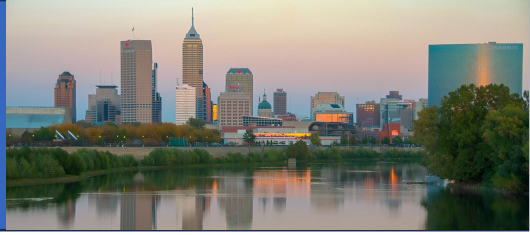
- USP <1072>
  - 3 log reduction of vegetative organisms
  - 2 log reduction of bacterial spores
- PDA Technical Report 70
  - At least a 1 log reduction
- What is a log reduction…?



Pitfall 6

Not Choosing Realistic Starting Enumerations

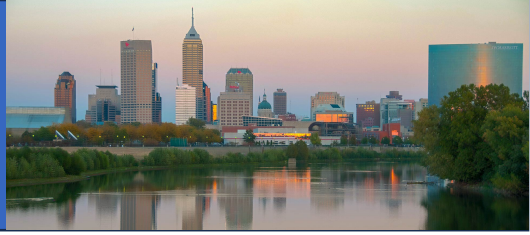
Log Reduction	CFUs killed from 10^4 Starting Inoculate	CFUs killed from 10^5 Starting Inoculate	CFUs killed from 10^6 Starting Inoculate
1 Log	9,000	90,000	900,000
2 Log	9,900	99,000	990,000
3 Log	9,990	99,900	999,000
4 Log	10,000	99,990	999,900
5 Log		100,000	999,990
6 Log			1,000,000



Pitfall 7

Not Choosing Test Surfaces Based on Risk

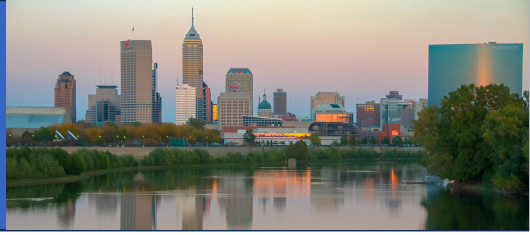
- Porosity
- Roughness/Texture
- Proximity to critical operations
- High touch points
- Have a rationale and justification in your CCS for your choices



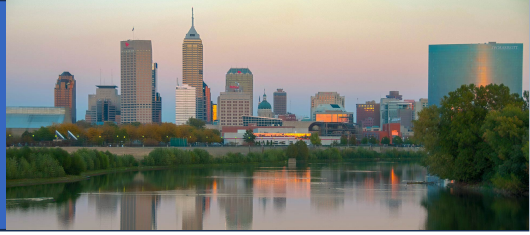
Pitfall 8

Not Assessing Disinfectant Dry Times in Your Facility

- Humidity
- Air flow
- Temperature
- Horizontal vs Vertical Surfaces
- Aqueous based products vs IPA
- Wiping (multiple passes)
- Mopping (multiple passes)



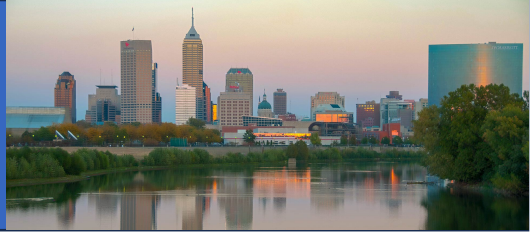
When Performing the DE Study



Pitfall 9

Trying to Incorporate Application Methods in Your DE Study

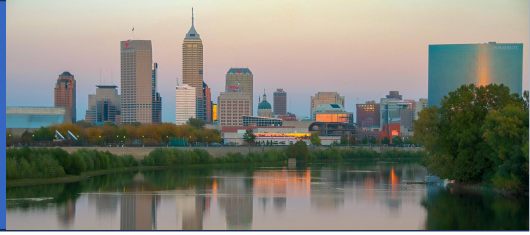
- The DE Study is designed to test the chemical vs organism on a surface while minimizing physical action.
- Any physical action (wiping, squeegeeing, coarse spray) will result in inflated log reductions.
- This is not representative of the chemical efficacy.



Pitfall 10

Not Including Multiple Contact Times in Your DE Study

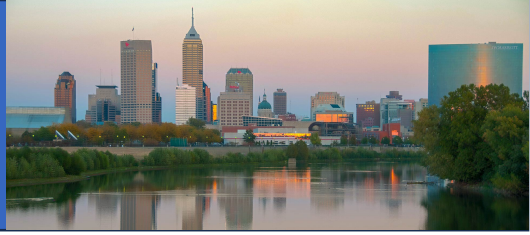
- Encompass the contact times found from your facility assessment.
- All surfaces and chemicals do not dry at the same rate.
- Vertical surfaces will dry faster than horizontal surfaces.
- Aqueous based products – 3, 5 and 10 minutes
- Alcohol based products – 30, 60, 90 seconds



Pitfall 11

Not Accounting for Variability in the DE Study

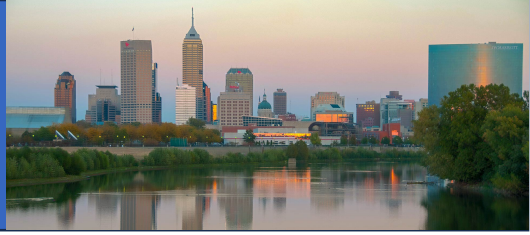
- There is inherent variability when performing a DE Study.
  - Working with living organisms
  - Lot of manual manipulations
  - A single data point is not enough
  - Consider duplicate or triplicate testing to mitigate variability.



Pitfall 12

Not Including Negative Controls in the DE Study

- Negative Control
  - Verifies that appropriate aseptic technique was used during the execution of the DE Study.
  - Verifies that the coupons were properly sterilized.
  - The methods used in the study should be followed with the exception that no inoculum should be used.
  - No CFUs should be recovered from the negative control.



Pitfall 13

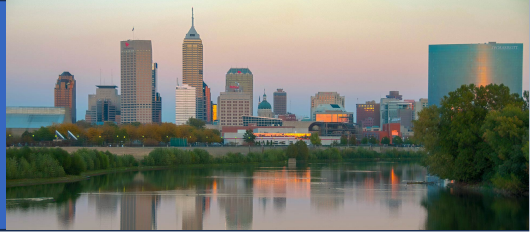
Not Including Neutralization Confirmation in the DE Study

- Neutralization Confirmation
  - Validate that the neutralizing agent does not prevent the growth of the test organisms.
  - Validate that the neutralizing agent can neutralize the disinfectant.

Table 5.2.1-1 Commonly Used Neutralization Agents

Antimicrobial Chemical Agent	Neutralizing Agent
Alcohols	Dilution or polysorbate 80
Sodium hypochlorite	Sodium thiosulfate
Quaternary ammonium compounds	Polysorbate 80 and lecithin
Phenolic compounds	Dilution or polysorbate 80 and lecithin
Hydrogen Peroxide/Peracetic Acid and Hydrogen Peroxide	Catalase

Source: PDA Technical Report 70 – Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities"

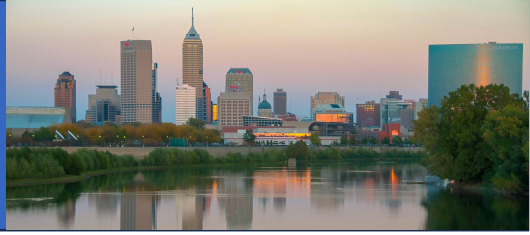


Pitfall 14

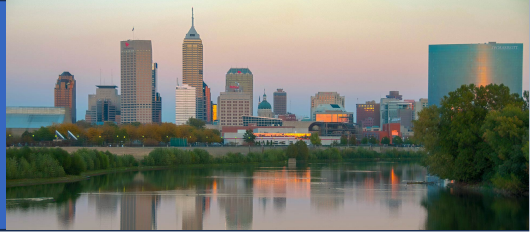
Improper Sporulation of Spore-Forming Organisms

- Sterile 70% IPA DE Study from a 3rd party lab…

		S. aureus		*P. aeruginosa*		*B. subtilis*		*C. albicans*		*A. brasiliensis*		*Cladosporium sp*		*M. luteus*	
		Rep A	Rep B	Rep A	Rep B	Rep A	Rep B	Rep A	Rep B	Rep A	Rep B	Rep A	Rep B	Rep A	Rep B
Stainless Steel	Initial (log cfu)	5.13	5.17	5.27	5.75	5.04	5.10	4.98	5.10	5.45	5.48	4.73	4.52	4.61	4.80
	10 minutes (log cfu)	<1	<1	<1	<1	<1	<1	<1	<1	1.30	1.0	<1	<1	<1	<1
	Ave. Log Reduction	>4		>4		>4		>4		4.32		>3		>3	
Plexiglass	Initial (log cfu)	5.34	5.40	4.34	4.45	4.99	5.18	3.84	4.71	5.56	5.38	4.76	5.25	N/A	4.68
	10 minutes (log cfu)	<1	<1	<1	<1	1.00	<1	<1	<1	<1	<1	<1	<1	<1	<1
	Ave. Log Reduction	>4		>3		4.09		>3		>4		>4		>3	
Glass	Initial (log cfu)	5.32	5.21	5.84	5.83	5.12	5.12	5.03	5.07	5.46	5.45	4.71	5.00	4.77	4.63
	10 minutes (log cfu)	<1	<1	<1	<1	<1	<1	<1	<1	1.00	2.08	<1	<1	<1	<1
	Ave. Reduction	>4		>4		>4		>4		3.92		>3		>3	
Gloves	Initial (log cfu)	5.27	5.37	5.79	5.73	5.21	5.21	5.53	5.91	5.59	5.53	4.95	4.99	4.96	4.92
	10 minutes (log cfu)	<1	<1	<1	<1	<1	<1	<1	<1	1.78	<1	<1	<1	<1	<1
	Ave. Reduction	>4		>4		>4		>4		4.17		>3		>3	



After the DE Study

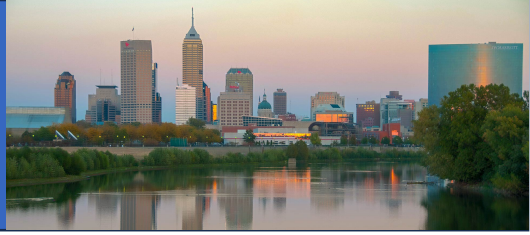


Pitfall 15

Not Performing an In-Situ Study

PDA Technical Report 70

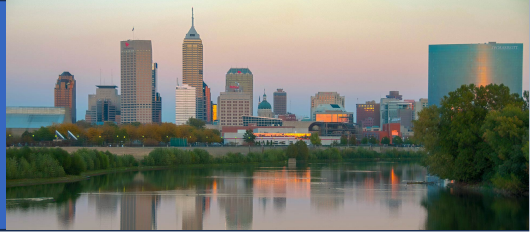
"The true test of the effectiveness of a cleaning and disinfection program is the monitoring data collected from the manufacturing area. Evaluation of the in-situ data being generated from a robust environmental monitoring program will verify that the program is capable of attaining and maintaining a level of cleanliness that minimizes the probability of contamination of the manufacturing process by the environment."



Pitfall 16

Not Making Disinfectant Preparation Simple and Repeatable

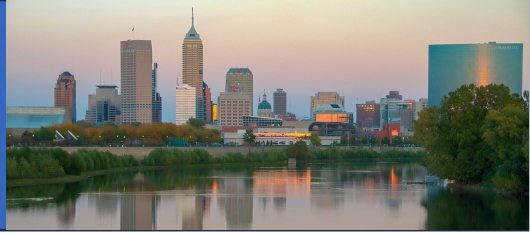
- Concentrate
- Pre-measured Unit Dose
- RTU



Pitfall 17

Not Periodically Reviewing Your DE Study

- Review your EM data vs your DE Study.
  - New isolates that were not included in the original study?
  - New materials in the facility?
  - Do you need to retest?
- Document this review.



Pitfall 18

Overreliance on Disinfectants

- No amount of disinfection can make up for poor contamination control practices.

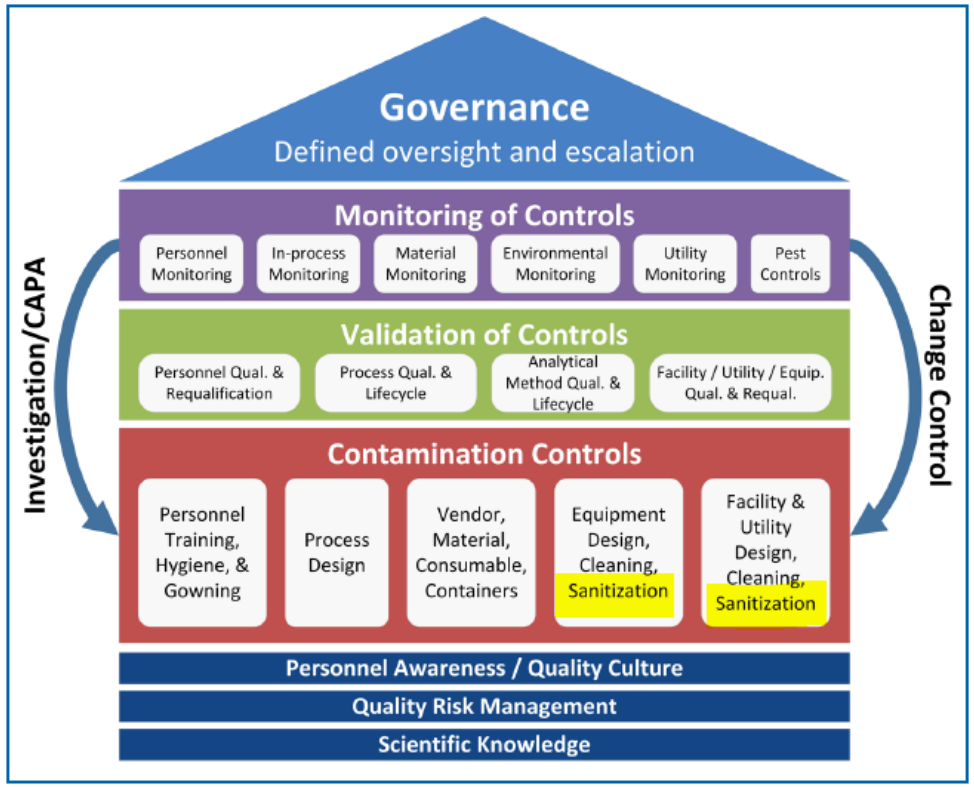
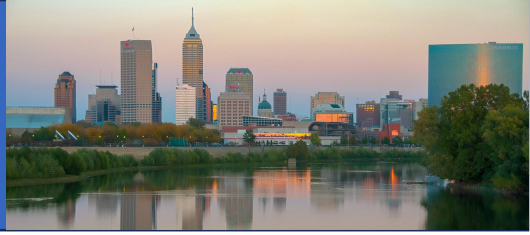


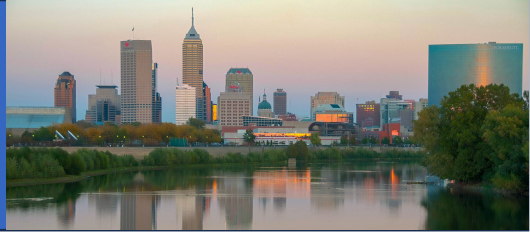
Figure 3.0-1 Elements of a Contamination Control Strategy (courtesy of Sanofi)

Source: PDA Technical Report 90 – "Contamination Control Strategy Development In Pharmaceutical Manufacturing"



Conclusion

- This is not an encompassing list of all the “pitfalls” that can occur with disinfectant qualification
- There are many facets of disinfectant qualification that should be considered.
- A well mapped out disinfectant qualification strategy can save you a lot of headaches in the future.



Thank you!

Questions?