FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

Microbiology Contamination Control Considerations

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Question – What does design have to do with microbiology or what does microbiology have to do with design?

- "Since design is a human activity, it is also an imperfect one"
- "Everything designed has its limitations and its flaws"
- "This fact of design is what leads to constant change"
- "***Understanding how things fail – and might fail*** – provides insight into how to redesign them successfully."

❖Success Though Failure The Paradox of Design
Princeton University Press 2006
Henry Petroski, PhD.

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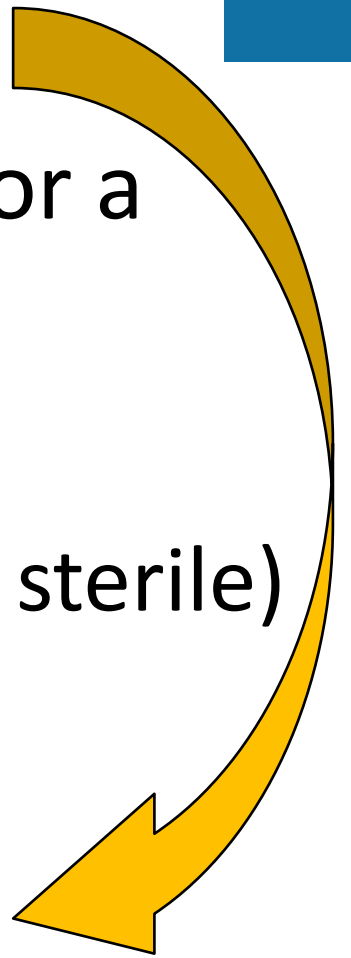
As a point of reference, I ask if you would pause for a moment and consider e.g.,

1. your pharmaceutical commodities (non-sterile or sterile)
2. your day-to-day normal / routine manufacturing operations
3. your facility and it's design
4. your material & personnel flow



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Regarding your Environmental Monitoring (EM) Program–

¿ Questions ?

1. What is the purpose of your EM Program?
2. What do you want the EM data to demonstrate?
3. Where do you monitor for the EM data and why?
4. What does the EM data tell you about your manufacturing operations / your facility?

WHAT IS THE POINT OF THE EM PROGRAM?

"In trying to determine the appropriate parameters of a complex program such as environmental monitoring, we first have to agree upon the scope and purpose of the program. The purpose of the *EM program is to document the state of control of the facility,* ***not*** to determine the quality of the finished product."

Scott Sutton, PhD.

The Environmental Monitoring Program In a GMP Environment –

Journal of GXP Compliance ~ Summer 2010 Volume 14 *Number* 3

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The Title 21 Code of Federal Regulations (CFR) 210 contains the following language i.e.,

"…this chapter contain the *minimum current good manufacturing practice* for the methods to be used in, and the facilities or control to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act offers the minimum…"

EU Annex-1 Manufacture of Sterile Products

regarding Contamination Control Strategy (CCS) –

"A ***planned set of controls*** *for microorganisms, endotoxin/pyrogen and particles*, derived from current product and process understanding that assures process performance and product quality.

The ***controls*** *can include parameters and attributes related to*

- active substance, excipient
- and drug product materials and components,
- facility and equipment operating conditions,
- in-process controls, finished product specifications,
- and the associated methods and frequency of monitoring and control."

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…can we agree there are any number of FDA Guidance Documents on a variety of subjects. There is a particular part of guidance documents that I continuously refer to i.e.,

> "This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. *You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations.* If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance."

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Here is some good news -

- the preceding three slides is all that I will be discussing about the Code of Federal Regulations, FDA Guidance and/or any other regulatory guidance

- …note for me…insert *Happy Dance*

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…so then, if we (FDA) agree that the following is true i.e.,

"*You can use an **alternative approach** if the approach satisfies the requirements of the applicable statutes and regulations.*"

I would encourage…

there are a number of different approaches & considerations that may be "***do-able***" with respect to the evaluations of microbiological excursions.

As an example, regarding a sterile commodity

1) Microbiological contamination was observed in media filled vials following an aseptic process simulation (APS, aka media fill).

2) As a point of reference, I ask you to refer back to your facility, manufacturing operations and aseptic filling process.

3) What do you currently perform if microbiological contamination occurs?

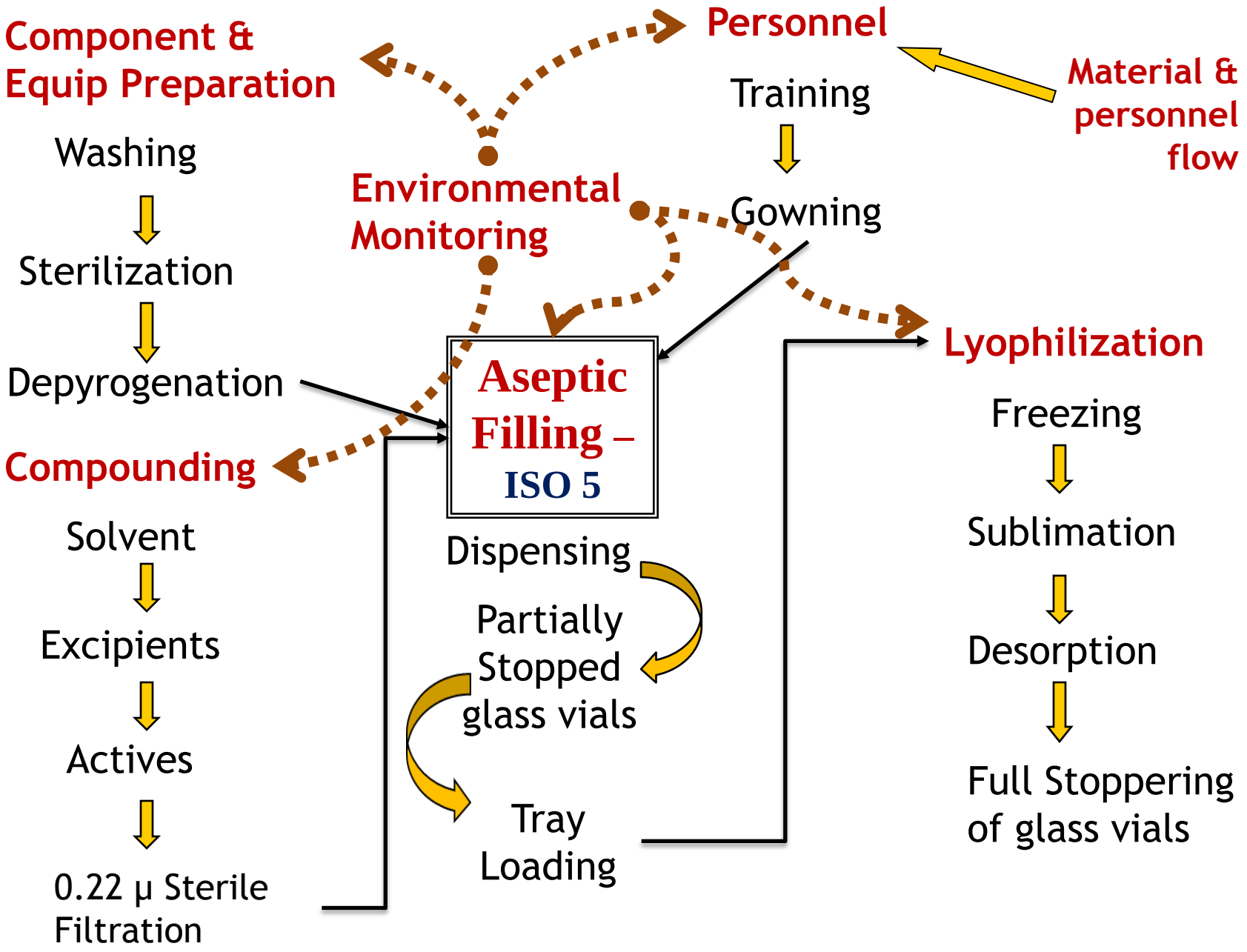
4) The Technical Council of Forensic Engineering (American Society of Civil Engineers) offers a definition i.e.,

*"Failure is an unacceptable difference between **expected** and **observed performance**"*

5) The fact that there is a vial or two with microbial growth does not suggest that the APS failed.

6) An evaluation will be performed to identify the root cause for the microbial contamination.

Convergence of well-planned orchestration of synchronized activities



Who is part of the team at the evaluation table and who is missing from the table?

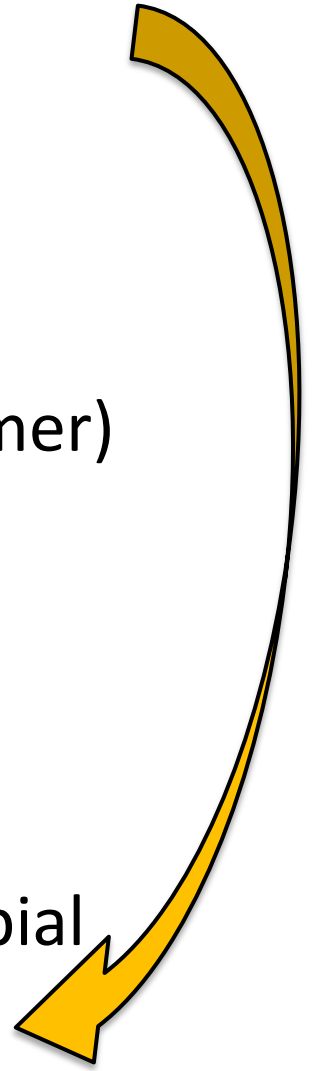
1. What is the microbiological contaminate & has the same genus & species been recovered via the EM Program?

For example;

- gram-positive cocci (common skin microbes)
- gram-negative rod (water borne contaminate)
- gram-positive rod (soil borne spore former and/or non-spore former)
- Mold contaminate

***¿Question** (and here's the **rub !**)*

Mindful of all the good controls that are in place, how did the microbial contaminate get to ***location-X**…?!?!*



2. What does your evaluation consist of and *why*?

For example, aside from reviewing the batch manufacturing records (BMR paper and/or electronic);

a. Is there real-time observation of the aseptic filling process and if so, what is observed and by whom?
b. If there is video recording(s) of the aseptic filling process, are the videos reviewed, by whom and *why*?
c. *Note* - due to the location of the video camera, the viewing angle may present limitations with observing the aseptic manual operations e.g., you may see a top-down view of the operators with operator's torso blocking the view.
d. The video camera may not be positioned to observe the aseptic manual operations e.g., at the working height of the aseptic process and of the operators' arms & hands.

2. cont. -What does your evaluation consist of and *why*?

For example;

a. The BMR will document the individual(s) who perform the aseptic manual operations, however, is it possible to identify the aseptic manual intervention(s) in relationship to the glass vials that were observed with microbial growth?

b. What does the airflow visualization studies document e.g., could air eddies / air turbulence be an aerial transmitter of the microbial contamination? e.g., being mindful that Isolator decontamination is not a sterilization process.

3. Who is part of the team at the evaluation table and who is missing from the table?

As an example;

c) Do you perform a *Gemba* walk of your facility / operations?
   1. *why* do you perform the walk? and,
   2. *what* does the walk provide?

d) Is the *Gemba* walk performed by a team of diverse disciplines e.g., Microbiology, QA, Production, Engineer & Maintenance or ***NOT***?

Consider your manufacturing operations for a moment -

- Imagine observing the same operations repeatedly, over and over, and over again; and,
- Overtime…is it possible to become "snow blind"?

- "It is very difficult for an organization to see the truth about itself.

  Those inside a box can seldom see what is happening within it.

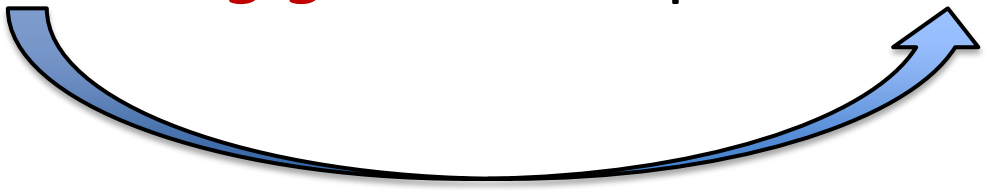
  It usually takes someone looking from the outside in to produce useful evaluations."

➢ Management *f*-Laws *how organizations <u>really</u> work* Triarchy Press, 2007- Russell L. Ackoff

4. Keep your facility / operations in mind – as an example of the root cause(s) that created the Deepwater Horizon Accident

Regarding Oil Inquiry, Panel Sees *No Single Smoking Gun* (8/27/10)

- More than four months after the Deepwater Horizon oil rig explosion, there appears to be ***no single smoking gun*** that implicates ***one person or company*** in the disaster.



- Instead, ***several missteps and oversights by the crew*** are being explored by federal investigators as possible triggers of the emergency.

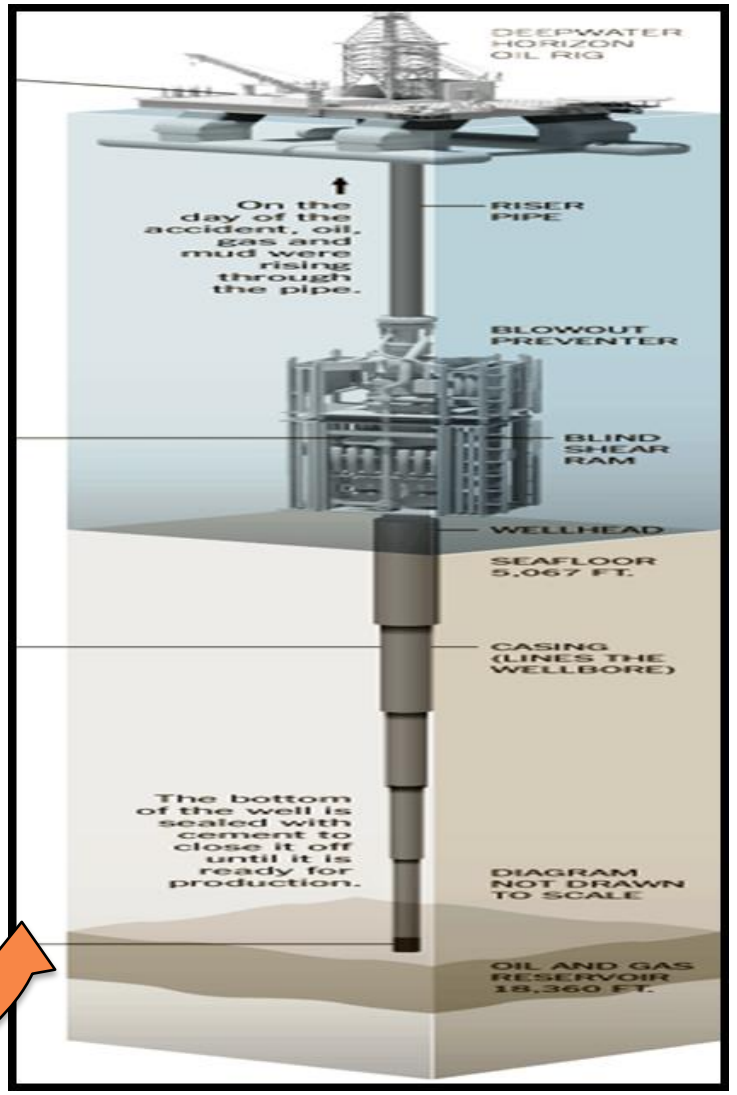
4. As an example of the root cause(s) that created the Deepwater Horizon Accident

Investigation Report Executive Summary – 9/8/10

"The team did not identify any single action or inaction that caused this accident.

- Rather, a ***complex and interlinked series of***
  1. ***mechanical failures,***
  2. ***human judgments,***
  3. ***engineering design,***
  4. ***operational implementation***
  5. ***and team interfaces came together to allow the initiation and escalation of the accident***.

- Multiple companies, **work teams and circumstances were involved over time.**"



Microbiological Investigations – A few points to ponder

- "The most successful improvements ultimately are those that focus on the limitations – on the failures"

- "Success is not simply the absence of failure: it also masks ***potential modes*** of failure."

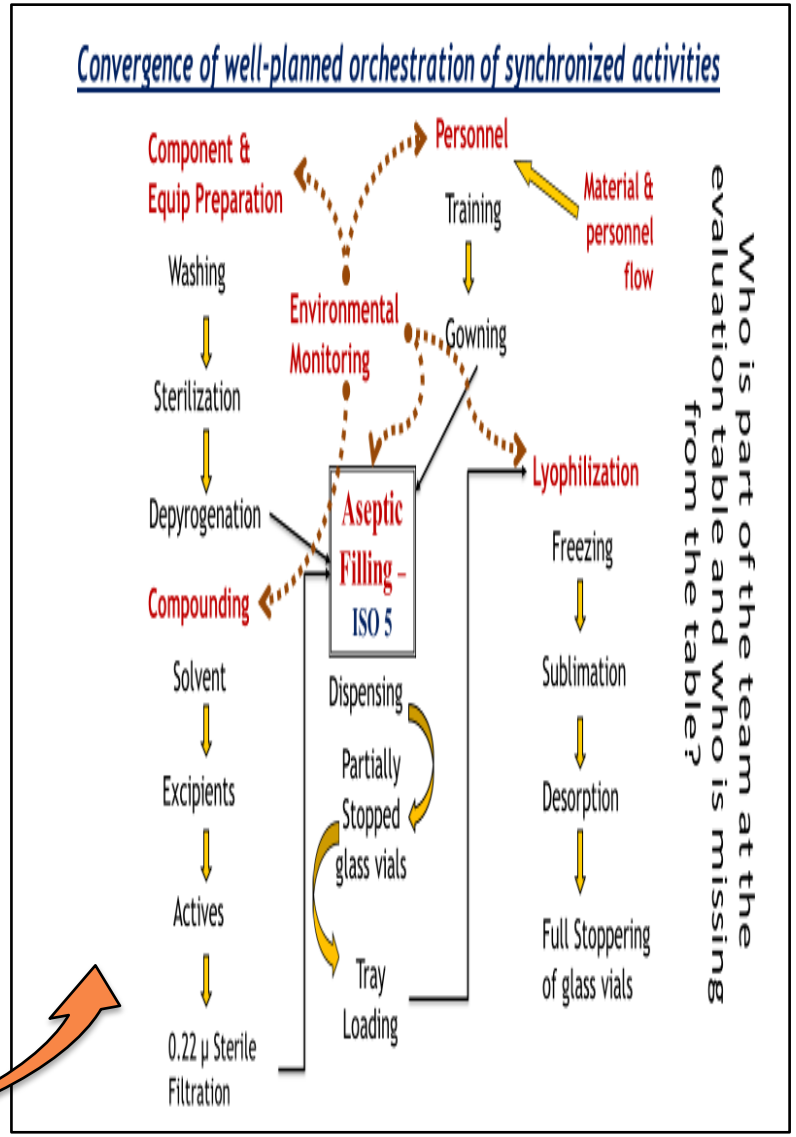
- "The *more complicated the design problem, naturally the more difficult the solution* and hence the *more likely that some details and features* ***may be overlooked***, only to have their absence come to the fore after the thing is manufactured or build and put to the test of use."

❖ Success Though Failure The Paradox of Design
Princeton University Press 2006
Henry Petroski, PhD.

4. Mindful of your facility / operations, what is/are the root cause(s) that created the contamination?

Similar to the Deepwater Horizon explosion – your ***team*** did not identify any single action or inaction that caused this accident.

- Rather, a ***complex and interlinked series of***
  1. ***mechanical failures, (e.g., deviations, non-conformances)***
  2. ***human judgments, (e.g., operators' errors)***
  3. ***engineering design, (e.g., aseptic filling area, manufacturing support utilities)***
  4. ***operational implementation, (e.g., SOPs, CAPAs)***
  5. ***and team interfaces, came together to allow the initiation and escalation of the accident***. ***(e.g., where is the Quality Unit?)***
- Multiple companies ***(e.g., suppliers)***, work teams ***(e.g., company departments)*** and circumstances were involved over time."



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Aside from the less than positive comments regarding an aseptic process simulation failure, I would offer there are some learning opportunities e.g.,

1) In the process of performing an evaluation(s) you may identify some gaps that created the microbial contamination;

✓-This is a ***positive opportunity to address & correct*** whatever gaps that were revealed during an APS.

2) What better time to address the causality of a microbial contamination than during the APS;

X **-** as opposed to having gaps that may have occurred during routine aseptic operations, which may result in having adulterated commodities out in the marketplace.

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I appreciated the language in the guidance documents regarding *"alternative approach"* for a number reasons e.g.,

1. The guidance is ***NOT*** prescriptive; rather
2. The language provides an opportunity to engage in considerations that best meet the needs for your unique manufacturing operations;
3. It fosters an opportunity for the industry to consider new innovations, refinements and engage in continuous improvements; and lastly,
4. As a Regulator, and to my good fortune, "*your approaches*" continue to offer opportunities to listen & learn of new considerations, developments and innovations in this field of play.

Microbiological Contamination Control Considerations

Dhanyavad !!!

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