Avoiding Common Errors during Contamination Investigations

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Sterility Assurance Failure Investigations – Importance?

- Prevent 'bad' product from going out the door and entering the marketplace
- Regulatory Authorities [FDA, EMA, other A's] use the Quality of Failure Investigations performed as one **METRIC** by which they judge the capability of a facility to manufacture sterile products

Important Deficiency

Inadequate Investigations are consistently observed and cited during Regulatory Authority Inspections

FDA

MHRA
Medicines and Healthcare products Regulatory Agency
Safeguarding public health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Sterility Assurance Failures

- Sterility Test Failure [obvious] – this test is very insensitive; if you have a growth-positive test that should really grab your attention!
- Media Fill contamination event
- Multiple Environmental Monitoring [EM] Alert or Action Limit Excursions

Investigation Approaches

- Need to have a **'Common Sense'** approach, which is not very common
- Need to have a **'Patient-focused'** approach. The great majority of sterile products are given to patients who are already very ill. **"Don't add insult to injury"**
- Need to perform an **aggressive, effective investigation**; no easy task

Investigations – How to begin? / What to do first?

- Most people aren't very experienced in performing failure investigations
- Facilities are for the most part under an acceptable state of contamination control
- So, many people haven't seen a lot of Environmental Monitoring Excursions, Sterility Test or Media Fill Failures

Contamination Investigations – So, what's the plan?

- In many pharmaceutical companies there is no formal plan other than to follow a Chemistry test based OOS SOP and to form a cross-functional team to conduct the investigation
- There may be a checklist
- That's OK to help begin the investigation, but the list shouldn't be viewed as all inclusive

Check Lists – just a start

- Should be open ended so that one can think 'outside the box' and explore areas that have not already been identified or even thought about
- Some might include a decision tree to help get the investigation off on solid footing

Goals for the Investigation

- Determine the Source(s) of the microbial contamination
- Determine the **Root Cause** for the Contamination Event – how did the 'bug' [pathogenic microorganism not insect] get into the product or the highly controlled environment?

Goals for the Investigation

- One may **NOT** find the definitive Root Cause = Smoking Gun
- In my experience that **is** the typical case
- If you can find the definitive Root Cause 15-20% of the time you are doing good

Goals for the Investigation

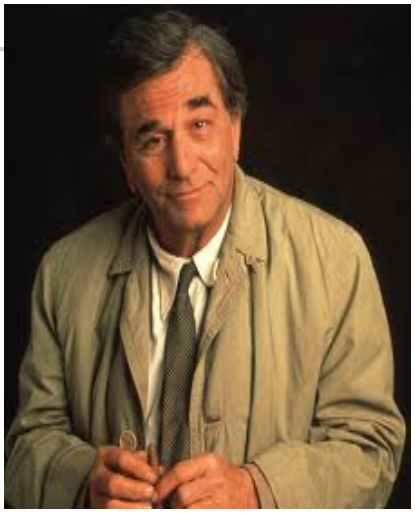
- A **'Probable Cause'** is the most common outcome of a contamination investigation
- One should be able to find this the majority of the time >60%
- An investigation result of **'Possible Causes'** means that you haven't worked hard or long enough yet

Goals for the Investigation

- Possible root causes result when a firm doesn't look hard enough for the source of the microbial contamination
- One must locate the source of the microbial contamination to have any real chance of finding the root cause

What is the best approach?

One needs to employ a methodical approach in sterility assurance failure investigations such as that taken by police detectives, e.g., Columbo



"WRONG Thinking"

- Definition – thought patterns that will prevent finding the source(s) of the particular microbial isolates and the root cause(s) for the contamination
- Most common example of wrong thinking is making assumptions based upon a little bit of information or knowledge

"WRONG Thinking"

- For example, information about the isolate from the contaminated media fill test unit is obtained 'on line' or from a Microbiology text book.
- The common source(s) listed are automatically assumed to be the same for the isolate from the pharmaceutical manufacturing facility

"WRONG Thinking"

- That may **not** be the case at all
- For example, just because a bacterium is 'human borne' doesn't mean that was the source in any particular case
- When the scope of the investigation is too narrow, it gives new meaning to the term **'small minded'**
- Regulatory Authority inspectors make the same mistake and require unnecessary tasks [CAPA's] to be performed, without **any** proof that they contributed to the failure event

"WRONG Thinking"

- If you've seen a particular microorganism in your facility before, you think that you already 'know' where it came from
- That may be true
- But, it isn't necessarily the case
- The microbe may have remained undetected in a totally different area

"WRONG Thinking"

- Focusing the investigation on a really tight time frame around the date of the product or media fill that was contaminated
- The particular microbe may have been in the facility at low levels for a long time [years], but not detected because only microbes from Alert & Action level excursions are identified
- One may have to look at a years worth of data to figure out what is going on

"WRONG Thinking"

- Failure to conduct a thorough review of EM data for all classified areas, i.e., focusing only on the filling room in question
- Many facilities don't have a true 'Aseptic Core', so microbes may be closer to the filling line than is desirable to prevent product contamination

"WRONG Thinking"

- Assuming that the filling line and the clean room surrounding it are in an adequate state of control
- **"The FDA were happy with our data and said that we had a model filling operation"** – this actual statement represents a failure of management to admit that the manufacturing area could be responsible for the contamination seen in the sterility test

"WRONG Thinking"

- Failure to consider the possibility that the filling line was contaminated
- "It must be the Micro Lab's fault!"
- Assuming that the EM data used to make decisions during the investigation came from 'worst case' sample sites – that may **not** have been the case at all

"WRONG Thinking"

- Coming/jumping to conclusions about the contamination event without substantial information and data to support that
- Example, *Propionibacterium acnes* in Sterility Test failure
- "Must have come from the operators"

"The BIG Trap" – a Similar Circumstance

- You've seen it before at another facility with the 'same' microorganism
- So you assume that the source and/or root cause for the current contamination event is the same as the one that you saw before – **Wrong!**
- Easy trap to fall into
- I've been guilty of this myself

"The BIG Trap" – a Similar Circumstance

- So there is a failure to perform a thorough investigation, i.e., no depth and/or breadth
- CAPA's are performed based upon the previous knowledge instead of the results of a thorough investigation into current events
- Leads to additional contamination events, because the source of the microbe and/or the root cause were not identified and properly mitigated

Extraordinary [investigative] Environmental Monitoring

- Extra EM performed using swabs in 'nooks and crannies' to look for the source of the contaminating microbe
- "You'll never find anything!"
- "The facility has already been cleaned and sanitized 14 times since the product batch was filled"

Extraordinary [investigative] Environmental Monitoring

- Increased sampling frequency
- Sampling at sites that are hard to reach and may not be properly cleaned or sanitized [non-routine sample sites]
- Hundreds of samples may need to be taken; typically twenty (20) samples is viewed by regulatory authorities as just 'going through the motions'

Extraordinary / Investigative Environmental Monitoring

- "It is a waste of time, effort and resources!"
- Assumes that cleaning and sanitization was performed properly
  - Inside – Out [filling line]
  - Up and down
  - Cleanest areas to least clean

Extraordinary / Investigative Environmental Monitoring

- Assumes that disinfectants used were sterile
- Assumes that disinfectants were used at the proper dilution [concentration]
- Assumes that disinfectants have been properly qualified for the current use dilution [that a meaningful disinfectant efficacy study has been performed]

Extraordinary Environmental Monitoring

- Assumes that the contact time qualified in the microbiology laboratory is actually achievable in the clean room as well
- Disinfectants have to be **'wet'** to be effective
- Air flow in clean rooms can be substantial and the disinfectant can 'dry off' before the necessary contact time is achieved

Extraordinary Environmental Monitoring

- So, it may take more than one application to kill certain spore-forming microorganisms
- For example, a *Paenibacillus* species isolated from a sterility test required **two** applications of SporKlenz® to destroy its spores in a clean room setting

Observation can be KEY to Solving a Contamination Event

- A Safety Shower and Eye Wash Station
- Dead Legs!!
- Source of Gram-negative bacteria
- Can be a problem if near aseptic manufacturing process

Wrong Thinking – other examples

- Assumes that the sterility test samples were **not** contaminated externally during selection, handling and transport to the micro lab; so little or no decontamination required
- Assumes that triple bags of gamma – irradiated RODAC plates were properly decontaminated when transferred into the Aseptic Processing Area

Wrong Thinking – other examples

- Mold was transferred from a laboratory refrigerator to the aseptic core because of failure to properly decontaminate the outside of the bag containing RODAC plates
- Lab technician was trying to be efficient and labeled plates in the lab on the bench top, contaminated them with mold which was then transferred to the manufacturing areas – one would assume that there in 'no chance' of this type of thing happening

Wrong Assumptions

- Assume that gamma-irradiated 'bunny suits' were properly decontaminated when transferred into the Grade B gowning room
- The bags containing the gowning materials could have a **HUGE** bioload which may have not been eliminated altogether

Wrong Assumptions

- Assume that the 70% Isopropyl Alcohol [IPA] was suitable for material transfer decontamination at the interface of controlled and classified areas
- However, 70% IPA is **not** sporicidal
- Materials were not properly decontaminated – molds or *Bacillus* survived

Wrong Assumptions

- Assumption that all materials used in the Sterility Test were in fact sterile
- Case example – DMSO was used in a sterility test and thought to be sterile
- Used to dissolve the product so that it could be filtered through a membrane

Wrong Assumptions

- DMSO is bactericidal and readily kills vegetative cells
- But, it may **not** destroy bacterial spores
- *Bacillus* species was isolated from the sterility test canister
- Represents a false-positive sterility test

Wrong Assumptions

- In this particular case the manufacturing area was assumed to be at fault for the contamination
- Four (4) rooms of equipment [sterile 'closed system'] were dismantled and sampled for viable microbes
- >1,000 samples were taken!

Wrong Assumptions

- **NO** Bacillus species were found at all
- When the sterility testing methodology was thoroughly examined it was discovered that the DMSO had **never** been sterilized, let alone by a qualified cycle

Wrong Assumptions

- Assumption that the 'Qualified VHP Cycle' will decontaminate 100% of the microbes existing on the outside of sterility test samples and testing materials
- This assumption ignores points of contact or mated surfaces

Wrong Assumptions

- Assumption that VHP was able to penetrate the Sterility Test isolator load
- Assumption that the loading pattern was the same as that originally qualified
- Or, that as long as you 'can see space' between the items in the load that the VHP will penetrate/flow everywhere it needs to go

Wrong Assumptions

- Assumption that **wiping** sterility test samples with a sporicide will be effective
- However, the necessary contact time may **not** be achieved to destroy all of the bacterial or fungal spores present on the exterior surfaces of sterility test samples

Wrong Assumptions

- Assumption that interviews with aseptic fill line operators ≥ two (2) weeks after a batch was filled will fail to yield **any** meaningful information
- In my experience operators often remember 'Oh Dear' events that could have contributed to the microbial contamination seen, but were **not** recorded in the batch record

Wrong Assumptions

- If you ask the operators, they are just as likely to remember something important that could have caused a batch contamination as not
- I've seen operator interviews glean extremely important information that lead to discovery of the root cause for a microbial contamination event.

Wrong Assumptions

- Assume that the disinfectant efficacy results for compendial and 'in-house' isolates can be extrapolated to any adventitious 'bugs' that are brought into the manufacturing facility
- Increased frequency of isolation of any particular microorganism may be indicative of inadequate contact time or use of the wrong type of disinfectant

Conclusions

- Keep an open mind when conducting microbial contamination event investigations
- What you find will probably surprise or amaze you
- If you make assumptions you can go down the 'wrong rabbit hole' and fail to have any chance of finding the root cause for the Microbial Contamination Event observed

Conclusions

- Extraordinary/Investigative sampling and an Open Mind are the two most valuable tools that you have at your disposal when you are faced with performing an investigation for a sterility assurance failure event