Aseptic Drug Manufacturing Inspections

By Investigator Russell Glapion

Disclaimer

- Aseptic essentials in 20 minutes.
- All examples used in this presentation are from first-hand experiences.
- The names of the firms or personnel have not been identified.

Private Sector Pharmaceutical Experience

- As a first line Supervisor at a large pharmaceutical company and the Operations Manager at a small pharmaceutical company from 1991 to 1995, I had knowledge of three FDA inspections, with operational responsibilities for two of them.

- The outcomes from those inspections helped shape my approach to work as an FDA Investigator. I have learned from those experiences and trained other FDA Investigators.

1st FDA Inspection – As a Supervisor

- Post FDA inspection lesson learned was to fear the FDA.
- Being summoned to our firm's Regulatory Affairs Office to correct batch record errors was akin to being sent to the Principal's Office.
- I got chewed out for mistakes and even for signing records in blue ink, because I was told the FDA wanted all records signed in black ink. (FYI - not a real FDA requirement.)

2ND FDA Inspection – New Operations Mgr.

- I learned to fear my boss and to resent the FDA.

- I observed the CEO ball up and throw a FDA 483 in the face of the QA manager, while screaming at her, “I pay you not to get these (expletive) things”. (The QA Manager and CEO were personal friends and I was the new person.)

3rd FDA Inspection – Operations Manager

Upon FDAs departure the General Manager said to me '*They did not know (expletive). I could fool them all day. Go back to work*.'

The company cultures that I was exposed to taught me that FDA inspections were a game to be won by whatever means necessary.

When I became an FDA Investigator, I learned, worked, and trained others to not be 'fooled all day'.

Industry Challenges

- Designing it.
- Building it.
- Maintaining it.
- Controlling it.
    - SOPs
    - Training
    - Supervision

‘This is hard.’

(A firm’s QA Manger.)

FDA Inspections

- It is not the FDA Investigator's job to know everything.
- It is our job to verify that you understand your processes and have created procedures that document with a high degree of integrity that your processes are understood and in control.
- The FDA rarely tells a firm something that they do not already know. Firms do tend to re-prioritize resources based on FDA 483s and other findings.

FDA Inspections

- We only write FDA 483 observations when you do not have adequate answers to significant deficiencies.
- If it is not documented, it did not happen.
- Approximately 40%+ of all my inspections result in FDA 483's.
- Approximately 95% + of my inspections find deficiencies, which are captured either as FDA 483 Observations or as General Discussions with Management points.

FDA Inspections

- We start noting things from when we first arrive at your firm. We tend to drive around it if we can.

- Are your people outside in lab coats, smocks, and hair nets on their cell phones or smoking a cigarette?
- Are warehouse doors left open when there are no delivery trucks?

Do you project a lack of confidence in your day-to-day QA controls?

- Are we kept waiting in the lobby or the conference room for an extended period of time?
- Are our document requests always delayed?
- Do you attempt to steer the FDA Investigator towards or away from certain areas?
- *Mr. Philips please report to the accounting department.*

  (THE FDA IS HERE!)
- Is your firm having trouble finding the documents? Are you re-reviewing them? Are you intentionally trying to run out the inspection clock?
- Why?

FDA Inspections

- We do not “tour” we “inspect.”
- Management is not exempt from its own procedures.
- e.g. *If you make your production employees change shoes to enter the restroom, why are there no shoes for the managers*? *Does that mean they never use the restroom or that they never enter production?*

Do not underestimate the importance of just watching your cleanroom operations.

- ISO-5 cell culture incubation dilution steps.

- Frequent ISO-5 hood hand/arm entries by a second person increased processing speed by about 10 minutes, but each entry increased the risk to batch.

‘Only the Canadians have ever come in here before.’

When you watch – you learn.

- Operators allowing the sleeves of the sterile gown to touch the floor during the gowning process.

- Operators handling non-sterile items and reaching back into the ISO-5 area without changing their gloves or even re-sanitizing them.

- Operators improperly/incompletely sanitizing ISO-5 hoods.

You get what you inspect, not what you expect.

- Operators proceeding with aseptic operations after spilling or contaminating the ISO-5 hood or other sterilized equipment.

- Excessive cleanroom equipment that obstructs the flow of HEPA filtered air or cleanroom exhaust.

- Operators spraying alcohol on their hands or a contact surface just before taking an environmental monitor sample.

Poor Design/Inadequate Capital Investment

- *'We did not really want to build it that way. We did not have the capital to build it the way we originally recommended.'*

Firm's engineers on cleanroom stoppering operations "validated" outside the ISO7 area.

Poor Design/Inadequate Capital Investment

- Wiping down the stainless-steel batch tank.
- Rolling it through the gowning room.
- Wiping it down again in the ISO-7 area.
- Wiping it down again in the ISO-5 area.
- Making the aseptic connection to the filling line in the ISO-5 area.

Poor Design/Inadequate Capital Investment

- Rolling a cart with bags of autoclaved stoppers from the ISO-5 autoclave unload area, through the ISO 7 area, spraying the bags with alcohol, moving them to the ISO 5 filling area.

- *How did you validate that*?

Present a team that actually knows the process and the design controls.

- You lose credibility when your team misspeaks.

e.g. 'No, you could not have seen an empty vial, we have a sensor to detect empty vials.'

I watched a few extra minutes before confirming another empty unit. The engineers later confirmed that there was no empty unit senor on the fill line (it was on the labeling line).

Media Fills and Environmental Monitoring

Did you design robust challenges to your aseptic processes or did you create limited challenges unlikely to detect potential problems?

e.g. *The RODAC contact plate samples taken above cleanroom doors but not on surfaces routinely touched by operators*.

- Media fill interventions that simulate actual operations and worse case conditions.

How is it we always happen to be there for events that have never happened before?

Media Fills

- You should be inspecting and determining that all media filled units are properly sealed and not cracked before placing into the incubator. That is your chance to reject suspect units. We expect incubated units to be read and the results accepted.

- Who have you designated in writing to makes the call if there is growth? This is not a best out of three, or five opinion. e.g. *17 people do not approve a media fill*.

What does FDA think, it was quality by accident?

- It was always quality by design, but we have inspected numerous firms that have tried to use work arounds, “creative” validations, and complex procedures to compensate for poor design.

When “we” get it wrong – they lose.

Thank you for your attention.