




The Quality Edifice and Sterility Assurance of Parenterals

Nov 11-12, 2013 Mumbai



Connecting People, Science and Regulation

Sessions:



- 1. Investigations- The ABC of expectations**
- 2. Environmental Monitoring- Need for preventive controls & verification possibilities**
- 3. Understanding Risks for predictive controls**
4. Uncovering nuances of FDA's draft guidance on 'Circumstances that Constitute Delaying, Denying, Limiting, Or Refusing a Drug Inspection.
5. Manual Aseptic Processing- The Crossroads
6. Sterility Assurance Packages- Essentials and Expectations

Connecting People, Science and Regulation

Case 2



Environmental Monitoring- Need for preventive controls & verification possibilities

Vishal Sharma

Co-Founder
VIENNI TRAINING & CONSULTING LLP

Connecting People, Science and Regulation

Session: Environmental Monitoring - Need for preventive controls & verification possibilities



- Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

Connecting People, Science and Regulation

Session: Environmental Monitoring - Need for preventive controls & verification possibilities



- For example, there was **no scientific justification** for the sampling plans utilized **for environmental monitoring in areas** that your firm uses to manufacture terminally sterilized injectables. This included the **frequency and locations of viable airborne particulate** sampling activities, **the locations of non-viable airborne particulate** sampling activities, **the frequency and locations of non-product contact surface** monitoring, and the **evaluation of microorganisms found through environmental monitoring** activities.

Connecting People, Science and Regulation

Session: Environmental Monitoring - Need for preventive controls & verification possibilities



- Your environmental monitoring program was **insufficient to detect contamination of concern, including mold observed on the clean side of the air filters supplying air to the sterile filling areas.**
- In your response, you state that **you use a formal risk assessment to justify the type, extent, frequency, and location of sampling and test procedures.** also will create a procedure for periodic reassessment of that risk assessment to incorporate any relevant new or emerging information, and you will continue to conduct bioburden testing.

Connecting People, Science and Regulation

Session: Environmental Monitoring - Need for preventive controls & verification possibilities



- Although we acknowledge your use of formal risk assessments in implementing these revised environmental monitoring procedures and bioburden testing, your response is still deficient. In your response, you downplay the product quality and safety impacts posed by the mold observed on the clean side of HEPA filters supplying air to your sterile filling areas on the grounds that products made in these areas are terminally sterilized. Please note that sterile products should be protected from microbiological contamination during processing, even when terminally sterilized, in order to minimize sterilization challenge and byproducts of excessive bioburden.

Connecting People, Science and Regulation

Session: Environmental Monitoring - Need for preventive controls & verification possibilities



- What is the one thing, that strikes you, while reading this letter....
- "...establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures...."
- The word which rang a bell...

"Establish"

Connecting People, Science and Regulation

Next Logical question(s)...

- What is establish...
- How to establish...
- This brought another very disturbing question:
 - What should be the objective of EMP.



Connecting People, Science and Regulation



PDA Tech Report # 13, Fundamentals of an Environmental Monitoring Program

- "Environmental surveillance is a **tool utilized to evaluate the effect of controls** on the manufacturing environment."
- A comprehensive environmental control program should be supported by:
 - sound facility design and maintenance
 - Documentation systems
 - validated/qualified sanitization/disinfection procedures
 - reliable process controls,
 - good housekeeping practices
 - effective area access controls
 - effective training, certification/qualification and evaluation programs
 - quality assurance of materials and equipment.

Connecting People, Science and Regulation



So what has bird strike to do with EMP..



Let us understand; Why bird strikes happen?

This is blamed on four factors:

1. Large population of birds
2. There are also more flights, quieter engines
3. Many birds find airports to be attractive habitats
4. Greater awareness which has meant more rigorous reporting

So why does EMP excursion happens?

1. Because there is an enormous population of microorganisms outside clean rooms.
2. There are more batches & Larger batch sizes which are getting manufactured.
3. Many microorganisms find clean rooms to be attractive habitat.
4. Less awareness/ controls

Connecting People, Science and Regulation

Step 1



Understand Sociology of birds

- There is a department, which focus only on:
 - Identifying local birds, in and around airport.
 - Look at migrating birds
 - Migration routes
 - Behavioral patterns
 - Monitor plane behavior

Sociology of microbiology

- EM Department is expected to focus on:
 - Understanding of microorganisms present in cleanroom environment.
 - Detect changing trends in microbial count and types of micro-flora within cleanroom environments.
 - Routes of contamination
 - Production behavior?

Connecting People, Science and Regulation

Step 2



Effectiveness of pyrotechnics

- Flash or Bang...
- Birds get accustomed to the noise or light and do not fly away.

Effectiveness of routine cleaning & Sanitization

- Sanitizer and/or Disinfectant
- Microbes get resistant to cleaning and disinfection regimen.
- Cleaning & disinfection are manual process, how is effectiveness monitored?
- Hand sanitization and personal hygiene are very personal!

Connecting People, Science and Regulation

Step 3



Effectiveness of Bird distress signals

- Speaker mounted cars which emit sounds of different species of birds in distress.

Effectiveness of manual intervention

- CCTV, why do we have it in our areas?

Connecting People, Science and Regulation

Step 4



Effectiveness of eliminating vegetation

- Weeds and grass provide rich habitat to insects, which are source of food for birds.

Effectiveness of air curtains

- Any disruption of airflow, provides ample chances of microorganisms to enter product stream.
- What is the use of smoke studies?

Connecting People, Science and Regulation

Step 5



Effectiveness of border collie

- Since 1999, when dogs were first used, there has been a 17% drop in bird strikes. While the egrets, herons and moorhens can get used to pyrotechnics, they never adapt to the presence of a natural predator.

Effectiveness of line clearance

- Consistency in material movement in hatches!
- Role of supervisor/ IPQA?

Connecting People, Science and Regulation

Step 6



Durability of aircraft windscreens and engines

- **A chicken gun** is used to test the durability of aircraft windscreens and engines. A thawed chicken is fired out of the gun using compressed air, in an effort to simulate the impact of a bird hitting the plane in flight.

Effective design of Process Simulation runs

- Challenging manufacturing operations through media fills is a known method.
- Challenging paraphernalia is real fun.

Connecting People, Science and Regulation

Step 7



Lights on aircraft

- The idea is to manipulate the characteristics of the light by varying the pulse rates and wavelengths in the electromagnetic spectrum and tune these changes to specific bird species.
- The lights would provide an earlier warning so the birds can detect and avoid the aircraft.

Rapid Microbiology

- Identify areas where we need early warning signals.
- Is there something which can be done to salvage the situation.

Connecting People, Science and Regulation



Step 8

Use of detecting radar

- Bird detecting radars are small and mobile, and technology has come on in the last 10 years

EMP Trends

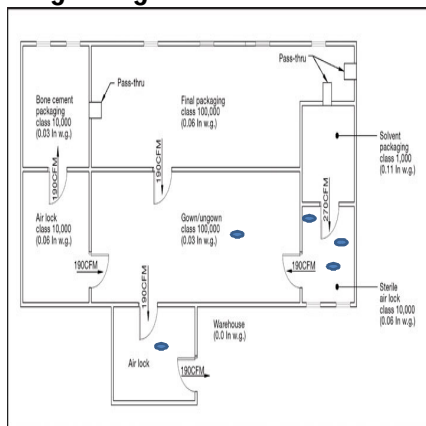
- Do we read them?
- Are they functioning as radar to us?
- How many times they have predicted potential EM excursion?
- How precise are they in their prophecies?

Connecting People, Science and Regulation

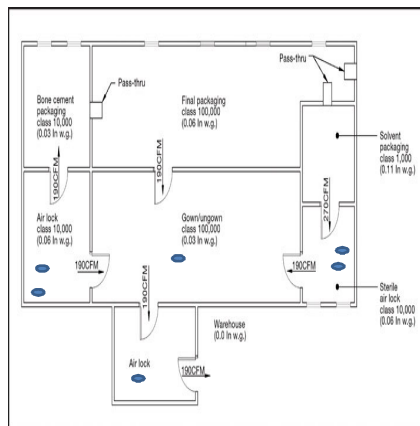


EMP Trends

Beginning of the month



End of the month



Connecting People, Science and Regulation



To conclude

- Have we established fair amount of controls, that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures, for EMP?
- If yes, do we have breathing space below our radar?

Connecting People, Science and Regulation

