FDA Compliance Trends

Aseptic Practices and Environmental Monitoring

PDA Southern California Chapter
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A former FDA Investigator's "holistic" view of contamination control …

- Facility Design
  - Critical Utilities / Support Systems
    - Heating, Ventilation, Air Conditioning Systems (HVAC)
    - High Purity Water Systems (PW / WFI)
    - Compressed Gases (Nitrogen)
    - Pneumatic Air
    - CIP and SIP
- Personnel, Material, Product and Waste Flows
- Sterile Gowning / Aseptic Operator Behaviors
- Dedicated Equipment / EM Equipment
- Cleaning Procedures and EM Program / EM Trending
  - VHP
  - Sanitization and Disinfection
  - Material Wipe down
  - Disinfectant Efficacy Studies
- **Aseptic Processing**
  - Isolators
  - RABS
  - Primary Barriers
  - Open vs. Closed Processing
  - Aseptic Process Validation (Media Fills)
  - Smoke Studies

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- **ASEPTIC PROCESSING** - Aseptic processing presents a higher risk of microbial contamination of the product than terminal sterilization.
- In an aseptic filling process, the drug product, containers and closures are sterilized separately and then brought together under an extremely high quality environmental condition designed to reduce the possibility of a non-sterile unit.
- Aseptic processing involves more variables than terminal sterilization.
- *Any manual or mechanical manipulation* of the sterilized drug, containers, or closures prior to or during aseptic filling and assembly poses the risk of microbial contamination.

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- When conducting inspections of sterile drug manufacturers, it is important to cover systems and areas within systems that present the greatest risk of product contamination and/or require strict control of processing parameters.
- For example, if a firm has several aseptic processing lines, cover the line(s) that require the most manual manipulations in the Class 100 (ISO 5) areas.
- If the firm terminally sterilizes a number of products, review one that is sensitive to heat and requires a product specific (bioburden based) sterilization cycle.

Media fills must be “representative” of actual aseptic processing operations.

- Maximum duration of aseptic filling
- Frequency and type of aseptic interventions in Critical Grade A
- Maximum number of aseptic operators + support personnel in Grade A/B
- Manual “Open Door” Interventions
  - Set-up
  - Aseptic Filling
  - End of Production / Disassembly / Line Tear Downs
- Contamination Risks:
  - Proximity to sterile components (e.g., vials or stoppers) (direct risk to sterility assurance)
  - At or above the critical height of the aseptic filling line (indirect risk to the filling line)
  - At or below the critical height of the aseptic filling line

Know your aseptic processing area and aseptic filling line …

- There is an “Achilles heel” to every aseptic processing area; carefully evaluate your personnel, material, product and waste flows!
- Aseptic processes and aseptic practices should be designed to eliminate or minimize the *potential for impacting contamination and sterility assurance*.
- From an FDA inspection readiness perspective, it is important to “know and understand how you are managing your risks” vs. “simply ignoring your risks.”
- Maybe we’re not ignoring but “making *de minimis*” a potential contamination source or risk.
- Failure to have sufficient QA oversight during set up and aseptic filling operations

Classic Signs of Unwise Ignorance

- Our aseptic processes and aseptic practices are sound and defendable because we haven't had any media fill failures or sterility failures.
  - The odds that sterility testing on a limited sample size can detect a single non-sterile unit in a batch is "astronomical" in scale.
  - Media fill studies must be "representative" and "appropriately" challenge actual production conditions and situations.
  - Media fills have been used to "validate" bad aseptic practices or techniques
  - The aseptic filling line is **not** designed to facilitate proper aseptic practices.

Appropriately Challenge Actual Production Conditions and Situations

- Proper aseptic practices must be supported by aseptic process validation (media fills) and smoke studies (airfl0w patterns)
  - List of **ALL** aseptic interventions (Personnel)
    - All Operations: Cleaning / Disinfection ➔ Set-Up ➔ Aseptic Filling ➔ Post-Production Activities ➔ Line Tear Downs ➔ Change Over
    - Planned vs. Unplanned (routine vs. non-routine)
  - Aseptic Operators / Sterile Gowned Qualified Personnel by Department
    - Primary vs. Secondary Operators

Sterile Gowning / Aseptic Practices

- **All** sterile gown components / elements must be “sterile” and disposable or “re-sterilized” prior to use including goggles.
- Sterile gowning procedures allow personnel to sit on a stool or bench “for safety reasons” while donning the sterile gown.
- Sterile gown comes in contact with equipment, materials or surfaces that have not been “sterilized” … “sterile must contact sterile” whenever possible.
- Failure to re-sterile gown whenever there is a possible “doubt” that the sterile gown has been potentially contaminated.
  - Isolators vs. RABS vs. Primary Barriers
  - Failure of other filling team members to notice possible contamination of the sterile gown or poor / less than “optimal” aseptic practices
- Failure to demonstrate or exhibit “slow and deliberate” movements in the critical Grade A **and** Grade B room background environment.

Sterile Gowning / Aseptic Practices

- Failure to spray sterile gloved hands prior to AND after exiting the Grade A critical zone
- Failure to spray sterile gloved hands or component bags / tray covers away from the aseptic filling line
- Lack of aseptic operator awareness with respect to the fact that personnel pose the “biggest” risk to contamination and sterility assurance
  - Speaking “over” a filling line / “excessive” handing items across the filling line during set up
  - Excessive talking / unnecessary talking in Grade A and Grade B
  - Touching “sanitized at best” surfaces unnecessarily (e.g., resting hands on HMI, leaning against the filling line, wall, table, tapping other sterile gowned operators on the shoulder or arm, adjusting face masks or goggles, etc.)
  - Not keeping “hands up and out” where they can be seen at ALL times
- Improper transfer of EM plates and changing of air sampling plates
- Sterile forceps/tools not kept on a sterile field or in sterile-filtered IPA

Environmental Monitoring

- Risk Assessments
  - Personnel, Material, Product and Waste Flows
  - Set Up
  - Critical Process Steps
  - Aseptic Interventions
- Scientific Rationale for EM Program
  - Site selection
    - Justification (Proximity)
    - Scientific rationale (Grid)
  - Frequency of monitoring
  - Timing of monitoring
    - Representative of entire time of aseptic filling
    - Interventions vs. EM monitoring “traceability” matrix

Environmental Monitoring

- EM Media
  - Failure to reconcile samples taken vs. samples incubated
  - Failure to growth promotion test and release every shipment or receipt of EM media prior to use
  - Improper sample techniques
    - Gloved fingers “rolled” impressions and palm
  - Failure to requalify incubators on at least an annual basis
  - Failure to sample at least one cubic meter of viable active air in Grade A and Grade B aseptic filling rooms

Environmental Monitoring

- Failure to statistically establish meaningful “alert” limits based on historical trend data
- Failure to address adverse EM trends especially for mold in adjacent classified support areas (e.g., formulation, component prep and equipment wash room).
- Failure to perform “extraordinary” investigative monitoring after repeated alert or action limit excursions
- Concluding that the excursion was due to laboratory contamination during sample handling without any initiating a formal production investigation
- Failure to conduct proper EM investigations based on the etiology or source of the isolate once identified to *genus* and *species*

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

Your firm failed to establish and follow appropriate written procedures that are **designed** to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

Poor Aseptic Processing Techniques

Our investigators observed poor aseptic processing techniques during the manufacture of **(redacted)** injection USP (aseptically filled for U.S. market) batch **(redacted)**, and **(redacted)** injection (aseptically filled for U.S. market) batch **(redacted)**. These poor techniques, which may compromise the sterility of injectable products, included the following.

a. Your operator placed a **(redacted)** cup on the floor of an ISO 7 area (Grade B) to collect water **(redacted)** from a **(redacted)** unit. As operators set up ISO 5 (Grade A) filling line, they used the cup contents to wet the mechanical assembly in the piston drive.
b. Operators crawled on the floor on their hands and knees under the filling line during routine aseptic filling operation activities.
c. An operator directed vials to the **(redacted)** with his hand located directly above open vials.

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

d. During set up, an operator moved un-bagged sterilized tools from the ISO 7 to the ISO 5 area, which he placed in the filling area near the stoppering equipment.
e. During **(redacted)** unloading in the ISO 7 area, an operator dropped a sterilized lid from a **(redacted)** container onto the floor, which he then picked up and placed it back on the container.
f. Before performing aseptic filling activities in the filling room during aseptic setup, operators wore goggles on their foreheads and exposed skin.
g. Operators opened **(redacted)** barrier **(redacted)** to adjust or remove vials from the line with bare hands, instead of wearing Restricted Access Barrier Systems (RABS) **(redacted)**.
h. Operators carried unprotected sterilized RABS **(redacted)** from the **(redacted)** ISO 5 area, to the ISO 7 area, and then to the mobile Laminar Air Flow (LAF) ISO 5 area.

Your procedure BRD/GEN/011/08, *Behavior and Aseptic Practices in Classified Areas,* restricts operators from touching the floor or leaning over opened vials. The above examples show that your operators engaged in these practices.

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

Facility Design

Your facility design may represent an additional contamination risk to the products you manufacture. For example, we observed an employee crawling under filling equipment to get to the area where he performed other critical operations. Collecting **(redacted)** water from the bottom of the filling machine to lubricate equipment, as mentioned above, **also raises concerns about the design and qualification of your equipment**.

Your response is inadequate because it is limited to a review of video recordings reviewed by FDA and referenced on the FDA Form 483. Your response does not **include an evaluation of all available videos to identify all batches that could be affected by poor aseptic practices and associated risks**.

In response to this letter, list the batches manufactured from November 2014 to the end of the inspection. Include your **independent third party's evaluation of these recordings, and their findings**. Also include a detailed action plan describing the revisions made to your procedures, the content of employee training, and how video recordings are evaluated and by whom.

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

Unreliable Environmental and Personnel Monitoring

… Our investigators observed dried media plates you used for surface and personnel monitoring in the **(redacted)** facility incubators. We documented that 36 of **(redacted)** plates inside the Plant **(redacted)** incubator showed signs of dryness and desiccation.

Your response indicated that you initiated a study to assess the signs of desiccation in **(redacted)** plates. You committed to switch to outsourcing **(b)(4)** and **(redacted)** plate supplies. However, your use of dried **(redacted)** plates in prior testing was not scientifically sound, and compromised your results.

In response to this letter, indicate steps you have taken to determine whether products made under these conditions meet limits. Also explain how you will improve laboratory controls to prevent use of unsuitable media in the future.

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

Unreliable Environmental and Personnel Monitoring

Your EM data for the filling areas did not specify the sampling location of the RABS **(redacted)** used during filling and **(redacted)** operations. SOP QCD/MIC/034-10 *Procedure of Surface Monitoring by Swab does not require sampling from predetermined **(redacted)** locations identified as critical risk points of your filling and **(redacted)** operations*. Instead, the procedure permits individual operators to determine the location to be sampled. Additionally, you only collected a **(redacted)** swab sample from **(redacted)**, and failed to sample other **(redacted)** used in daily aseptic operations.

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

According to your response, it was difficult to accurately locate plates corresponding to specific operators, because the plates were not uniquely identified. You indicated that operators were trained in aseptic practices; **practices we observed were "deviations" that you "considered serious lapses by the facility management."** Furthermore, **you acknowledged serious gaps "especially with respect to the suspected data integrity and falsification" in data generated in your environmental monitoring program**.

Your response is inadequate. *Despite your claim that your operators were appropriately trained, video recordings of your manufacturing operations clearly showed that your employees were not following proper aseptic techniques.*

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

EM records for active air monitoring of the aseptic filling area reported samples as being collected when they were not actually collected, and some records documented purported EM results of zero colony forming units (CFU) even when the samples for which those results were reported were not actually collected.

Contemporaneous video recordings that FDA reviewed during the inspection showed that such EM samples had not been collected, even though your laboratory records reported results for those samples. **Our investigators observed your firm's practice of falsifying EM results for samples that were not collected** for multiple drugs, ….

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

During the inspection, your microbiologist confirmed that these EM samples were never collected. Additionally, two microbiologists informed the investigator that media plates were labeled and submitted for incubation as though they had been exposed to the environment. However, these media plates were never actually exposed to the environment. **Your microbiologist indicated that this practice was routine and due to "work pressure."**

Because the EM results for samples were falsely reported as having been collected and/or as having produced no CFU growth, you lack assurance that the injectable drugs your firm produced in this area were sterile at the end of the aseptic filling process.

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In your response, **you stated "there have been serious gaps in the management, oversight and execution of the environmental monitoring program, especially with respect to the suspected data integrity and falsification of data concerns."** Your response also indicated that you revised procedures, provided training, and reviewed documents from March 2013 to January 2015. **Your investigation confirmed that EM samples were not collected and "the data was fraudulent."** You acknowledged these problems in your response and took some corrective actions. However, your response is inadequate because **you have not demonstrated** how you can ensure that EM records generated before the inspection were reliable and accurate, or **how the falsification of some of your reported EM data may have affected the quality of your products.**

Emcure Pharmaceuticals Ltd. Warning Letter (WL-320-16-08 March 3, 2016)

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm's compliance with CGMP, **FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer.** In addition, your failure to correct these violations may result in **FDA continuing to refuse admission of articles** manufactured at Emcure Pharmaceuticals Limited, Plot No. P-1, IT BT Park Phase II, MIDC, Hinjwadi, Pune 411 057, Maharashtra, India, into the United States. Under Section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3), articles may be refused admission **because manufacturing methods and controls do not appear to conform to CGMP** within the meaning of Section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

Teva Pharmaceutical Works Pvt. Ltd. Warning Letter (WL-320-17-01 Oct. 13, 2016)

Poor Aseptic Behavior

During the inspection, our investigators o*bserved poor aseptic processing techniques that had been previously* ***videotaped*** at your facility. For example, video from September 8 and 9, 2015, showed the following during the set-up and filling of the sterile injectable drug **(redacted)**:

- an operator passing a pen directly over the stopper bowl to another operator.
- an operator sitting on the clean room floor during set-up of the filling line and not changing the gown after standing up.
- operators leaning against the cleanroom walls.
- an operator leaving the RABS **(redacted)** open for extended periods of time during filling line set-up, even when he was not working in the immediate area.

CP Pharmaceuticals Ltd. Warning Letter (WL-320-11-002 October 29, 2010)

There is no documentary evidence of in-situ air pattern analysis (e.g., smoke studies) conducted at critical areas to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. Your firm failed to demonstrate that the appropriate design and controls are in place to **prevent turbulence and stagnant air in the critical area**. It is essential that you evaluate airflow patterns for turbulence that can act as a channel for air contamination. **The studies should be well documented with written conclusions, and should include an evaluation of the impact of aseptic manipulations (e.g., interventions) and the equipment design.**

CP Pharmaceuticals Ltd.

Warning Letter (WL-320-11-002 October 29, 2010)

The inspection documented **mold contamination** in the class 100 production room and poor conditions of a wall in the freeze dryer room, even though maintenance is conducted on the freeze dryer every **(redacted)** months. An incident report, initiated in November 2009, **identifies holes in the ceiling and visible light coming from the roof near the ventilation system, bubbling of the vinyl and disintegration of the wall under vinyl in the freeze dryer room**, **visible black mold on the wall, a poor drain system for the freeze dryer steam venting system, and a soft (spongy) wall**.

CP Pharmaceuticals Ltd. Warning Letter (WL-320-11-002 October 29, 2010)

Operators involved in the filling operations for the sterile drug products manufactured at your facility do not practice adequate aseptic techniques to prevent product contamination. The environmental monitoring performed at the end of the production run consist of **sampling the chest and the hand** most frequently used (right or left) of the employee's gown. Also, this procedure is performed by the gowned operator and **is not monitored by a second qualified person (e.g., supervisor; quality unit personnel) to ensure the proper techniques are being applied**. This practice is unacceptable. We expect that all operators who conduct operations within aseptic processing areas be properly trained and monitored to ensure that proper techniques are utilized during all operations, including aseptic filling operations and personnel sampling.

CP Pharmaceuticals Ltd. Warning Letter (WL-320-11-002 October 29, 2010)

Your firm failed to adequately address the increased adverse trends observed in the environmental monitoring trends for the period of August 2009 to May 2010; and, therefore, did not recognize that the environment did not appear to be under control.

Your firm did not establish a schedule for the cleaning with an agent designed to kill spores, although mold continued to be found in the class 10,000 area.

Our investigators observed that the mold contamination had not been eliminated at the time of the inspection in July 2010, almost a year after the initial discovery.

Mylan Warning Letter

(WL-320-15-14 August 6, 2015)

On February 6, 2015, our investigator observed **(redacted)** environmental monitoring plates previously incubated at **(redacted)** C being used for surface and personnel monitoring. Three of **(redacted)** plates showed signs of desiccation. Media was shrinking away from the edge of microbial plates.

On February 13, 2015, our investigator observed signs of drying on three of **(redacted)** plates used for water samples and four of **(redacted)** plates used for bioburden.

These observations indicate that your **media's growth promotion potential may be compromised**. In your response to this letter, inform us if you will be discontinuing this practice of pre-incubating plates.

Mylan Warning Letter
(WL-320-15-14 August 6, 2015)

You **do not have a scientific rationale for the environmental monitoring sampling locations** in aseptic filling Suites **(redacted)**. You **did not include factors such as smoke study findings, number and location of operators, and historical microbial data in your assessment of hazardous points**.

For example, we found that **settling plates are not appropriately placed in critical areas**. Your *smoke study* showed that during set-up and filling, air flows toward the front (when the **(b)(4)** is open) or back of the RABS. However, two relevant sampling points were recently eliminated. As a result, these **points of increased risk are not monitored**.

Mylan Warning Letter
(WL-320-15-14 August 6, 2015)

During our inspection, we noted that you have **no justification for two different action levels for finger dab results**. While you have **an ISO 5 action level** of **(redacted)** CFU **for set-up personnel**, you use **an ISO 6 action level** of **(redacted)** CFU for operators who **do not routinely participate in aseptic processing operations** using the RABS.

However, the inspection found that these "ISO 6 operators" made ISO 5 interventions, including within the **(redacted)** laminar airflow hood (LAF) and the RABS. *Notably, when >**(redacted)** CFU was recovered from an "ISO 6 operator" who had accessed the RABS during an intervention, your firm did not consider the result to be outside the action limit*.

Movements in the cleanroom

- Excessive body movements
- Talking and gesters
- Personnel are a contamination “risk”
  - Sitting without moving – 100,000 skin cells
  - Moving hands, arms, head – 500,000
  - Active hand/arm movement, Fast turning of the head -1.1MM
  - Standing up from a sitting position or vice versa – 2.5MM
  - A person walking can generate – 5MM
  - Rapid movement, climbing stairs, etc. – 110MM

Improving cleanroom behaviour

- Understanding why we need to control our behaviour
  - Impact to patients / Sterility assurance
- Knowing how to behave correctly
  - Ongoing training
- Observation of behavior
  - Production and QA oversight, if you video tape, review video footage, constant observation and awareness of each other's practices
- Ongoing monitoring of your personnel and facility
  - Recognizing adverse trends (pro-active vs. reactive)
- Discipline becomes part of your everyday routine and behaviors

Good aseptic practice should be like riding a bicycle

Quality is what **<u>you do</u>**
when no one else is watching

Contact Information

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Thanks For Your Attention