PDA 2019 Spring Seminar

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FDA Environmental Monitoring Observations

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FDA Observations

Agenda

- Warning Letters
- 483s
- Personal observations
- Attendee observations

Warning Letters #1

Cao Medical Equipment Co., Ltd.

Langfang, Hebei, China November 30, 2018

Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63).

Your facility is open to the outdoor environment where it is exposed to vermin, animal waste, and various contaminants.

You do not protect your products from the ingress and proliferation of objectionable microorganisms.

Warning Letters

Interpretation by FS

1. Describe controls already in place
2. Defend the products
3. Provide CAPAs
4. Provide CAPA effectiveness program
5. Keep the FDA informed

Warning Letters

Describe controls already in place

- EM program
- EM testing and results
- QA oversight

Warning Letters

Defend the products

- RM testing
- In process testing
- FP testing
- EM results during manufacturing
- Customer complaints/AEs
- Cleaning processes and reagents
- FARs/recalls

Warning Letters

CAPAs

- Construct barriers to outside
- Enhance housekeeping
- Enhance (rebuild) clean room suites
- Enhance EM program
- Enhance cleaning and sanitization
- Enhance Training
- Initiate monthly executive QA meetings

Warning Letters

CAPA Effectiveness

- Show reduction in microorganisms
- Show disinfection efficacy
- Show operational control over suites (DP, air flow, EM results)
- Create a plan if CAPAs are not effective

Warning Letters

Keep the FDA informed

- Monthly updates
- Protocol progress
- Final reports
- CAPA effectiveness
- FARs/Recalls?

Warning Letters #2

Genentech, Inc. San Diego CA November 29, 2018

(Human umbilical cord blood derived cellular products)

- **Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)]**
- **The manufacturing facility and gowning rooms are not classified with respect to air quality, so they are not controlled and maintained to ensure aseptic conditions**
- **There is no written procedure for gowning**

Warning Letters

- Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)].

  For example, your firm has not established an adequate system for environmental and personnel monitoring in the aseptic processing area where the products are manufactured.

Warning Letters

- Failure to have an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v)]. For example:
  - Your firm failed to validate your cleaning process
  - There is no data or rationale for the cleaning agents used or their rotation
  - The cleaning records do not include dilutions or contact times
  - Cleaning is not performed in between the manufacture of batches

Warning Letters

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Warning Letters

Current controls in place:

We have an established system for assuring the safety and quality of products that are manufactured.

- Operators are trained in gowning and aseptic practices and must pass skills testing prior to working in the area
- The sterile areas are cleaned daily
- Cleaning and disinfecting agents XXX and YYY were selected based on current industry practices

Warning Letters

Defense of Products

All finished products are tested for sterility and there have been zero sterility failures reported in the past two years. There have also been zero Adverse Events or customer complaints reported in the past two years. Therefore the products that have been manufactured meet the USP <71> sterility test requirements and do not pose a risk to patients.

However we acknowledge the observations and are drafting an overall compliance program (CP) to provide additional assurance that all of our systems support sustained safety and quality for our products.

Warning Letters

Summarize the main points of the CP:

- Six system evaluation
- Classification of rooms
- EM testing program including personal monitoring
- Gowning program
- Cleaning disinfection program
- Frequencies of testing and cleaning
- Other areas that are deficient

Warning Letters

Immediate Actions

- Enhanced EM testing
- Enhanced gowning training
- Complete product review from past 2 years
- Potential manufacturing hold or FAR
- Continuous FDA updates

Warning Letters

Long Term Actions – Future Corrections

- Classification of areas
- Monitoring
- Gowning
- Cleaning
- Provide CAPAs
- Provide CAPA effectiveness program
- Keep the FDA informed

Warning Letters #3

StemGenex Biologic Laboratories, LLC

San Diego, CA October 31, 2018

Adipose tissue for regenerative purposes; stromal vascular fraction (SVF) is the product cited.

Your SOP STEM-LAB-011: Gowning, does not specify that manufacturing personnel should wear appropriate sterile gowns or other garments, including: sterile overalls, surgical masks, disposable shoe covers and bouffant caps.

Warning Letters

Routine personnel monitoring and qualification is not performed for individuals involved in the aseptic manufacturing process for your SVF product.

Failure to have a system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)]. Specifically, your firm has not established a system for monitoring environmental conditions in the aseptic processing area where the SVF product is manufactured.

Warning Letters

Specifically, your SVF product does not meet the minimal manipulation criterion set forth in 21 CFR 1271.10(a)(1) as defined for structural tissue, such as adipose tissue, in 21 CFR 1271.3(f)(1). Your product does not meet this criterion because your processing alters the original relevant characteristics of the adipose tissue relating to its utility for reconstruction, repair, or replacement.

Warning Letters

Interpretation by FS

This company has issues well beyond EM, for example not having a Biologics License Application (BLA).

The response needs to address this requirement first, more likely to modify claims.

Warning Letters

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Warning Letters

Defend the products

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Warning Letters

- Gowning
- Personal Monitoring
- EM program

Warning Letters

Defend the current gowning process. For example operators DO wear sterile overalls, surgical masks, disposable shoe covers and bouffant caps.

This is not documented and the SOP will be revised to include proper documentation, including pictures and instructions.

Warning Letters

Defend the current personal monitoring program:

- **Fingertip samples are taken at the end of each operation**
- **Summarize the data (e.g. 0 CFU per operator during a 2 year period)**
- **CAPA to write/edit SOP that defines specific procedures for personal monitoring**

Warning Letters

Defend the current EM program:

- EM is conducted (settling plates, air samples, NVP) during operations although it is not formalized in a procedure
- Results are recorded
- Summarize results from the past 2 years
- CAPA to write/edit SOP that defines specific procedures for EM

Warning Letters

Incorporate the current data from gowning, personal monitoring and EM to support the microbiological safety of the SVP product.

Many startup companies fail to establish GMP compliance or proper licensing prior to manufacturing and are issued 483s and Warning Letters. They are subject to seizure, loss of revenue and possible loss of the company.

Warning Letters #4

Globus Medical Audubon, PA October 30, 2018

Our review of Validation Report as well as the prior validation reports for the ViaCell process, found that all of the environmental and personnel monitoring results showed no growth for every sample tested.

We note having no positive results for any environmental monitoring samples is highly unusual, especially when your sterility failure rates were so high.

Warning Letters

Globus Medical Audubon, PA October 30, 2018

We strongly suggest that you review your environmental monitoring program to ensure that it is capable of detecting microorganisms in your environment and on your personnel.

Warning Letters

Interpretation by FS

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Warning Letters

The company did not have a validated process for manufacturing and had multiple sterility failures during a 7 month period.

Therefore there is a major discrepancy.

Warning Letters

It will be difficult to defend the products

- **RM testing**
- **In process testing**
- **FP testing**
- **EM results during manufacturing**
- **Customer complaints/AEs**
- **Cleaning processes and reagents**
- **FARs/recalls – most likely solution**

Warning Letters

Defense of the EM program

- Describe the program in detail. Air, settling, surface, NVP, personal monitoring, smoke studies.
- Provide data to show the efficacy of organism recovery (e.g. GP data and organisms used)
- Show that USP <1116> requirements are met
- Provide frequency of EM

Warning Letters

CAPAs for the EM program

- Use microorganisms isolated from sterility tests or manufacturing for GP of media
- Assess the frequency of EM and increase the frequency if necessary
- Assess the sampling sites and increase the number if necessary
- Repeat smoke studies if necessary
- Modify SOPs based on results of new data

Warning Letters #5

Custom Rx, LLC Wichita, KS October 18, 2018

Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas (21 CFR 211.42(c)(10)(iv)).

Warning Letters

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Warning Letters

Defend the products

- RM testing
- In process testing
- FP testing
- EM results during manufacturing
- Customer complaints/AEs
- Cleaning processes and reagents
- FARs/recalls

Warning Letters

Defense of the EM program

- Describe the program in detail. Air, settling, surface, NVP, personal monitoring, smoke studies
- Provide data to show the efficacy of organism recovery (e.g. GP data and organisms used)
- Show that USP <797> requirements are met
- Provide frequency of EM

Warning Letters

CAPAs for the EM program

- Assess the frequency of EM and increase the frequency if necessary
- Assess the sampling sites and increase the number if necessary
- Repeat smoke studies if necessary
- Modify SOPs based on results of new data

483s #1

Abbott's Compounding Pharmacy, Inc. Berkeley CA
January 8, 2016

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

- **Non-viable particular counts, viable air and surface monitoring are not performed at the frequency cited in SOP 3.030, "Environmental monitoring of the clean Room facility".**

- **Personnel monitoring of operators gloves are not sampled daily upon completion of sterile compounding. Instead, they are performed according to SOP 3.030".**

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483s

Interpretation by FS

There are two problems:

1) Not following SOPS and 2) Inadequate EM

- **Describe the SOP and its EM requirements**
- **Describe the frequency of EM and how it differs from the SOP**
- **Conduct a risk assessment to determine the risk to products**
- **Raise a CAPA to align the EM with the SOP**

483s

- Conduct a risk assessment of not monitoring gloves at the end of operations. Include EM data, FP testing, customer complaints and AEs
- Cite the USP <797> requirement for gloves
- Raise a CAPA to conduct monitoring at the end of each operation and to include this requirement in the SOP

483s #2

Boothwyn Pharmacy LLC Kennett Square PA
June 16, 2017

- **EM of t he ISO 5 area is not performed each day that sterile drug products are produced.**
- **EM sampling on equipment which are touched and/or handled during sterile drug production is not performed**
- **The temperature of the incubator used to Incubate medial fills, environmental monitoring surface samples, and samples is not monitored.**

483s #2 (continued)

Boothwyn Pharmacy LLC Kennett Square PA

- **Test procedures relative to appropriate laboratory testing for EM are not followed. Specifically, plates used to perform EM were not incubated at the correct temperature.**
- **Sample results are not documented for evaluation of overall control of the drug production environment.**
- **No justification was provided for EM limits**

Interpretation by FS

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483s

Interpretation by FS

- Provide an overview of the EM program including type of monitoring, frequency, sites and smoke studies
- Conduct a risk assessment of the current program to include trends, excursions, AEs, complaints to determine product impact
- Describe how the current limits were derived

483s

- Raise CAPAs to enhance the EM program by increasing frequencies, sites, personal monitoring and repeating smoke studies if necessary
- Assess the current limits and change them based on the data that have been collected. Reassess the limits at the end of one year
- Modify SOPs to reflect the changes that are made
- Assess CAPA effectiveness over time

483s #3

Hieber' s Pharmacy Pittsburg PA February 17, 2017

- Depyrogenation of glass vials is conducted in a room that lacks environmental controls
- No environmental monitoring is performed during production in the glovebox isolator or in the sterile Compounding Room
- Non-sterile gowning articles are worn by the technician during cleaning of the glovebox isolator.
- An operator cleaned the inside of the ISO 5 area with exposed skin around their neck and face.

483s #3 (continued)

Hieber' s Pharmacy Pittsburg PA February 17, 2017

Warning Letter issued December 5, 2017

- **An operator cleaned the inside of the ISO 5 area with exposed skin around their neck and face**
- **No other mention of EM**

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483s

- Conduct a risk assessment for the glovebox and depyrogenation room to determine product impact. The assessment should include use of non-sterile garments and exposed skin.

- Since no EM was done, use data from AEs, complaints and sterility/endotoxin testing to defend the low risk.

483s

- Raise CAPAs to conduct EM in the glovebox and depyrogenation room
- Raise a CAPA to use only sterile garments during cleaning of the glovebox
- Raise a CAPA to enhance the gowning training (no exposed skin)
- Determine CAPA effectiveness
- Update the FDA

Personal Experiences #1

The investigator observed the Grade A operator passing the operator's gloved hand over an uncovered settling plate in the process of removing the lid and placing the settling plate on the designated plate stand.

The Grade A operator's gloved hand appeared wet with IPA when the operator removed the settle plate and passed the operator's gloved hand over the uncovered settling plate.

Personal Experiences

The investigator observed the Grade A operator consistently standing with hands down near the operator's sides, rather than held in front of the body at waist height to maintain exposure of the Grade A operators gloved hands to first air, for 31 minutes 13 seconds.

Personal Experiences

Your written EM Procedure states "Position lid facing down onto fixed or portable settle plate stands with the wipe in place to protect the inside of the lid from contamination."

The investigator observed the Grade A operator in the filling line area did not place the inverted settle plate lid on a wipe on the settle plate stand.

Personal Experiences

You do not have an effective quality system to ensure FIP (Finger Impression Plate) samples are properly collected from operators working in aseptic processing areas and to correct poor/incorrect FIP sampling techniques.

Testers review FIP's taken from operators in aseptic processing areas to look for microbial growth. Testers do not document the number or quality of finger impressions taken from each hand on an FIP.

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Personal Experiences

Resolution:

- Conduct a risk assessment by reviewing BRs, other EM data, AEs, complaints to determine the effect of excess IPA, position of hands, placement of lids and FIP
- Conduct GP on plates exposed to excess IPA
- Determine product impact
- Raise CAPAs to correct the observations

Personal Experiences

Resolution:

- Raise a CAPA to correct excess IPA
- Raise a CAPA to correctly position lids
- Raise a CAPA to correctly obtain FIP
- Raise a CAPA to design a system to support the proper positioning of hands

OR

Draft a report defending the practice of holding the hands below the waist for limited times based on smoke studies and EM data.

Personal Experiences #2

You stored 153 environmental monitoring plates inside a double plastic bag and you also store some environmental monitoring plates in a double plastic bag inside a closed plastic container inside your incubators.

You do not have incubator qualification data to support the aforementioned practices of stacking and bagging plates inside the incubator.

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Personal Experiences

Resolution:

Perform a study to evaluate the growth promoting properties of environmental monitoring plates when incubated in a double plastic bag within a closed container.

Use the data to defend and continue to use the current practice

Personal Experiences

Resolution:

If the data do not support the current practice conduct a risk assessment to determine product impact and raise CAPAs to modify the storage of EM plates.

Personal Experiences #3

You do not always appropriately place settle plates for environmental monitoring during testing activities. As an example, one settle plate is placed in the far-right back corner of the LAF.

No testing activities occur in the far-right back corner of the LAF and no settle plates are placed near the actual testing activities in the LAF.

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Personal Experiences

Resolution:

Write and execute a Protocol to determine the optimal locations for Environmental plates. The Protocol will include Smoke studies to support the rationale for setting up equipment and consumable locations during testing.

If the study shows that placement of plates is incorrect a risk assessment will be conducted to determine product impact and CAPAs will be raised to change the locations for Environmental plates.

Personal Experiences #4

At each active air sampling location the sample size of 1 m^3 of air takes approximately 5-6 minutes to collect, and is collected once per shift. As indicated by firm's management, a typical commercial batch may take approximately from 5 to 6 hours to fill.

There is no rationale to justify how one sample collected per location during a 5-6 minute time interval may provide significant and/or adequate information in order to assess the quality of the air circulating in the monitored areas within the filling line enclosure and throughout the filling process of a batch.

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Personal Experiences

Resolution:

1. **Defend the current practice:**

- **Aseptic Processing Guidance: *We recommend that such devices be used during each production shift* (No mention of time)**
- **WHO: *For Grade A, volumetric sampling, settle plates, and finger dabs must be performed during each shift of operations* (No mention of time)**
- **Settling plates provide long term sampling of the entire process**
- **Conduct a risk assessment to determine the differences between one, two, three sampling time points. Include EM trends, HVAC validation, finished product results, AEs and customer complaints.**

Personal Experiences

Resolution:

2. **Raise a CAPA to modify the process based upon the risk assessment, if warranted**

Personal Experiences #5

Your firm's qualification for the Scan 1200 Automatic Colony Counter is inadequate. Specifically, the manufacturer of the counter performed OQ and PQ by using a standard plate with 45 artificial colonies.

Your firm performed PQ by using eleven plates. Among the eleven plates, eight plates had no colonies and three plates had 22, 23, 36 colonies on each plate, respectively. Your firm performed re-qualification using ten plates, which had colonies ranging from zero (0) to fourteen (14).

Personal Experiences

All of the plates that were used in your firm's PQ and re-qualification were settling plates from routine environment monitoring and all the colonies were classified as routine bacteria in the facility.

No experiments were performed to verify that the counter is suitable to count colonies with various microorganisms and morphologies, from plates with bigger range of number of colonies on each plate, and on different types of plates (55 mm RODAC and 90 mm plates from active air sampling).

Interpretation by FS

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Personal Experiences

Resolution:

- **Draft and execute a Protocol to show equivalency between manual and automated counting.**
- **Utilize USP <1227> to compare the methods**
- **Defend the current practice with the results of the Protocol**
- **If the results do not show equivalency conduct a risk assessment that includes finished product testing results, AEs and customer complaints.**

Personal Experiences #6

Active air samples for injections/filling area monitoring were not performed from February 09 to March 01

Settling plates in the filling line were placed below the vials rotary table blocking the airflow into the settling plate

Environmental monitoring samples are not documented at the time of performance with the date of sampling, time, sampling locations, performed by and incubation in/out date and time

TSA strips culture media used for active air sampling are not challenged for growth promotion to assure suitability for use

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Personal Experiences

Resolution:

1. Provide an overview of the EM program including types of monitoring, time, placement of sampling devices, incubation, training, etc.
2. Provide an overview of microbiological QC including growth promotion and acceptance of media
3. Explain (via investigation) the differences between the programs in place and the activities that were conducted
4. Conduct a risk assessment to show product impact
5. Raise CAPAs to correct the deficiencies

Attendee Experiences

What happened to you?

SUMMARY

1. Describe controls already in place
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SUMMARY

Describe controls already in place

- EM program
- EM testing and results
- QA oversight

SUMMARY

Defend the products

- RM testing
- In process testing
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- Cleaning processes and reagents
- FAR/recall

SUMMARY

CAPAs

- Enhance EM program
- Enhance Training
- Initiate monthly executive QA meetings
- CAPA Effectiveness

SUMMARY

Keep the FDA informed

Questions?

Thank you

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References

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3. FDA Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice 2004

4. WHO Environmental Monitoring of Clean Rooms in Vaccine Manufacturing Facilities 2012

5. USP <1227> Validation of Microbial Recovery From Pharmacopeial Articles