2015 PDA Aseptic Processing-Sterilization Conference | June 9-10, 2015 | Loews Coronado Bay Resort | San Diego, CA

Misinterpretation of the Aseptic Processing Guidance Document

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Misinterpretation in

Guideline and Regulations

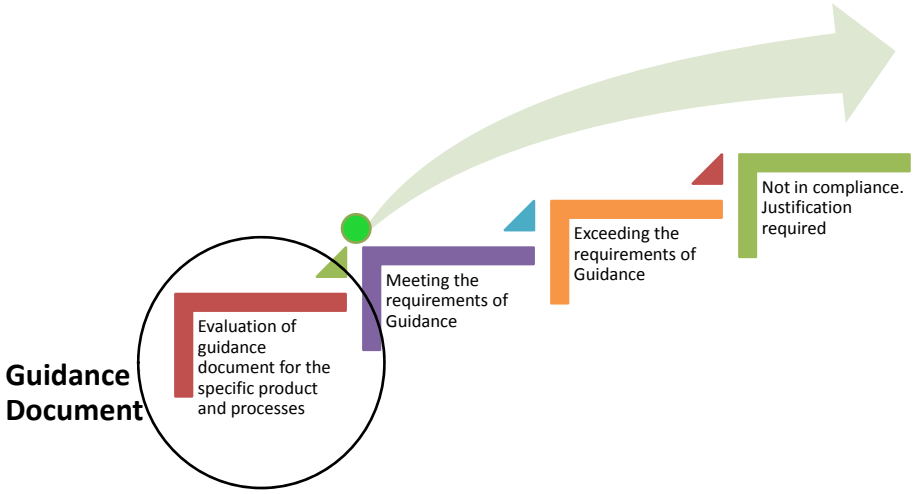
Guidance Document

- Guidance documents represent the Agency's **current thinking** on a particular subject. FDA's guidance documents do not establish **legally enforceable** responsibilities. It should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance's means that something is suggested or recommended, but not required. An **alternative approach may be used** if such approach satisfies the requirements of the applicable statute, regulations, or both.

Regulations (21 CFR art 210 and 211)

- The CGMP regulations for drugs contain **minimum requirements** for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. FDA can issue a warning letter or initiate other **regulatory actions** against a company that fails to comply with Current Good Manufacturing Practice regulations

Implementation of Guidance Document



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Misinterpretation in section

Validation of Aseptic Processing and Sterilization

In this presentation ……

Learn from examples, how

- Misinterpretation of guidance document leads to Non compliance
- Misinterpretation of guidance document leads to Overdoing!!

We will ……

- Review some observations by regulatory authorities (FDA, MHRA, KFDA) and correlating to misinterpretation of guidance document.
- Understanding the causes of misinterpretation
- Steps for avoiding misinterpretation.

Misinterpretation in section

Validation of Aseptic Processing and Sterilization

Guidance for Industry

Sterile Drug Products
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Current Good Manufacturing Practice

September 2004
Pharmaceutical CGMPs

Guidance

- Media fill studies should closely simulate aseptic manufacturing operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

Non Compliance

Simulation of bad practices justifying as worst case such as

- Personnel practices / Bad practices, Power failures during filling
- Disruption of unidirectional airflow over open containers/ closures without rejection of containers/ closures
- Pressure drops in cleanrooms and reduced air velocities
- Contacting of product contact surfaces with gloved hands
- Pinholes in gloves of RABS or isolator
- EM excursion (cleanroom/ personnel)
- Introduction of non properly sterilized or sanitized materials/ equipment into the cleanroom / isolator
- Transfer of item from Grade B to Grade A without sanitization

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- Size of the run

  A generally acceptable starting point for run size is in the range of 5,000 to 10,000 units.

Observation

The media fill is not representative of actual fill times. Breaks are extended during the media fills to lengthen the final run time of the media fill. These extended breaks are not representative of what takes place during actual production.

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Guidance

Frequency and Number of Runs

- All personnel who are authorized to enter the aseptic processing room during manufacturing, including technicians and maintenance personnel, should participate in a media fill at least once a year. Participation should be consistent with the nature of each operator's duties during routine production.

Observation

- There was no planning process to ensure that all individual aseptic filling and lyophilizer loading tasks were completed by operators during the annual media fill re-qualification programme. In was observed that all aseptic filling tasks had not been carried out by all operators during the annual media fill requalification.

  (Operators are not qualified for performing all interventions they perform in routine operations in a media fill at least once a year)

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Incubation and Examination of Media-Filled Units

- Incubation temperature should be suitable for recovery of bioburden and environmental isolates and should at no time be outside the range of 20-35° C. Incubation temperature should be maintained within +2.5° C of the target temperature.
- Incubation time should not be less than 14 days. If two temperatures are used for the incubation of the media filled units, the units should be incubated for at least 7 days at each temperature (starting with the lower temperature).

Observation

- Media fills are incubated at one temperature for 14-days duration (i.e. 22.5° C ±2.5° C or 32.5° C + 2.5°C) rather than at both temperature conditions.
- To incubate media-filled test units for 14 days @ 20-25° C followed by another 14 days @ 30-35° C.

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Media

- Use of anaerobic growth media (e.g., fluid thioglycollate medium) should be considered in special circumstances.

Non Compliance

- Anaerobic growth media is used for performing media fills alternatively to aerobic growth media every six months. Aerobic media fills are performed once a year.
- Anaerobic media fills were not performed even though routine environmental monitoring recovered an anaerobic organism.

(True anaerobic conditions cannot be attained in the vast majority of conventional aseptic filling operations. Anaerobic conditions (oxygen levels NMT 0.2%) can only be attained in isolator systems with a total inert gas environment.)

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Container size

- Largest container size with lowest speed and smallest container size with highest speed.

Non Compliance

- Standard practice is to bracket the vial sizes. Smallest and largest
- Vials having other challenges and requiring added human intervention should also be considered other than the smallest and largest.
- Size alone should not dictate the simulation design.

Misinterpretation in section

Buildings and Facilities

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Guidance

- Qualification studies: Air Quality in As Built, Static and dynamic conditions
- Dynamic conditions (i.e., with personnel present, equipment in place, and operations on going)

Non Compliance

- During qualification of HVAC system dynamic conditions did not include routine activity. Site included only personnel movement in the aseptic core as Dynamic condition.
- Surface monitoring's were not done as part of qualification studies.

PDA: Points to consider-Aseptic processing (Definition of At Rest, As Built, In operation, Static and Dynamic)

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- Microbial Action Levels defined in Table 1- Air Classifications
- Table 1- Air Classifications d- The additional use of settling plates is optional.

Non Compliance

- Action levels are not defined based on trends
- Microbiological monitoring is not performed throughout the Set-up and filling activity.

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- Particulate: Regular monitoring should be performed during each production shift.
- Videotape or other recording mechanisms have been found to be useful aides in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes.

Non Compliance

- The NVP monitoring frequency for the Grade A is once during operational condition at 6 locations. There is no data to demonstrate the particulate counts during Line setup activity and interventions.
- No smoke studies has been performed at site since the initial smoke studies at the time of inception.

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- Velocities of unidirectional air should be measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area. A velocity of 0.45 meters/second (90 feet per minute) has generally been established, with a range of plus or minus 20 percent around the setpoint.

Non Compliance

- This criteria is considered for the working level.

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- The Agency recommends that pressure differentials between cleanrooms be monitored continuously throughout each shift and frequently recorded.
- HEPA Filter: A single probe reading equivalent to 0.01 % of the upstream challenge would be considered as indicative of a significant leak and calls for replacement of the HEPA filter or, when appropriate, repair in a limited area.

Non Compliance

- Air pressure differential are not monitored between the Grade A interior of the filling & stoppering equipment and the Grade B room.
- Site does not have HEPA filters repair criteria.
  - Decision tree of when to repair?
  - How much repair is allowed (%)?
  - Which HEPA filters are allowed for repair?

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- It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters)

Non Compliance

- There is no acceptance criteria for velocity of adjacent filters.

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- Carefully designed curtains and rigid plastic shields are among the barriers that can be used in appropriate locations to achieve segregation of the aseptic processing line.
- Both personnel and material flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment.

Non Compliance

- Personnel entering the Grade A work areas. No barrier systems are available
- There was an increased man movement during the entire filling process. The aseptic filling line was breached for personnel movement on the other site of the filling line.

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Personnel Training, Qualification & Monitoring

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Guidance

- A vigilant and responsive personnel monitoring program should be established. Monitoring should be accomplished by obtaining surface samples of each operator's gloves on a daily basis, or in association with each lot.
- Monitoring should be accomplished by obtaining surface samples of each operator's gloves on a daily basis, or in association with each lot. This sampling should be accompanied by an appropriate sampling frequency for other strategically selected locations of the gown

Non Compliance

- Personnel monitoring is not conducted every time an individual exits the Class A/B clean room areas .
- “Employees reported as ‘sweating’ during set up operations for the filling line were only monitored on their gloves; no gown surfaces were monitored”

Misinterpretation in section

Personnel Training, Qualification & Monitoring

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Guidance

- Monitoring critical and immediately surrounding clean areas as well as personnel should include routine identification of microorganisms to the species (or, where appropriate, genus) level. At minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in these ancillary (ISO 8) environments at frequent intervals

Observation

- "Identification of environmental microbial isolates which do not meet or exceed the firm's action or alert levels are only identified on a monthly basis. This identification frequency does not enable the firm to have a sufficient understanding of the normal microbial flora that could be present in the firm's production area"

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- If stoppered vials exit an aseptic processing zone or room prior to capping, appropriate assurances should be in place to safeguard the product, such as local protection until completion of the crimping step. Use of devices for on-line detection of improperly seated stoppers can provide additional assurance.

Non Compliance

- There is no Raised Stopper detection for the vials that exit the aseptic processing area.

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Guidance

- **Monitoring :** The location, frequency and duration of environmental monitoring should be based on scientific analysis and risk based analysis.

Non Compliance

- The risk assessment and rationale for EM monitoring was based on physical location and personnel flows rather than a programme of intensive monitoring at numerous locations to determine where contamination was found.

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Causes of Misinterpretation

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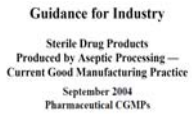
- Considering that the guidance addresses all aspects of aseptic processing.
- Site specific product / process specific challenges is not taken into considerations
- “Guidance does not say that…!”
- “Show me the guidance document where it states that….!”

Avoiding Misinterpretation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- Evaluation of guidance document to specific processes, systems and products.
- Compliance to CFR.
- Understanding “Why”?
- PDA Guidance documents

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Thank you PDA