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Dockets Management Branch (HFA-305),
Food and Drug Administration,
Document : "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice, DRAFT GUIDANCE"
5630 Fishers Lane, rm. 1061
Rockville, MD 20852.

Docket No. 2003D-0382

To Whom may concern:
Please receive our comments and suggestions to the "Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice, DRAFT GUIDANCE"

This comments are respectfully submitted by: Franco A De Vecchi PE
VPCI inc.

The following constitutes my observations to the BUILDING and FACILITIES section of the document above mentioned.

Background.

I am and have been a consultant for the pharmaceutical industry in the field of aseptic processing design facilities for more than 35 years, have participated for more than 14 years as a presenter in the FDA courses for investigators, publish several book articles and paper on the field and trained more than 3000 industry professionals worldwide.

Comments to the reasoning for considering changes to the document:
"FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required."

As for the industry view :

The importance of FDA guidelines can not be overlooked. Although they are not intended to be regulations, many times are the only source of expert information for some industry and FDA personnel.
In this light it is important that the proposed document should be clear and when expressing technical issues they be supported by sound technical information not hearsay or empirical (rule of thumb) specifications.

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The document should provide direction in a clear and precise manner avoiding covering issues in superficial or limited way, or out of the full technical context. This can be a source of confusion and will defeat the intentions of the guideline preparers.
The purpose of this letter is to highlight a sample of the points that need further refinement in view of the presenter. It does not pretend to be a full analysis of the document nor constitute a critic of it.
One has to recognize the draft document has many valuable points and that some additional work is needed to make it more useful.

Comments and Suggestions.

Environmental requirements for Terminally Sterilized Products.

The first relevant comment on the environmental and facility design is in one of the first sentences of the document

- The document on line 73 states: "Terminal sterilization usually involves filling and sealing product containers under high-quality environmental conditions. Products are filled and sealed in this type of environment to minimize the microbial content of the in-process product and to help ensure that the subsequent sterilization process is successful. In most cases, the product, container, and closure have low bioburden, but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat or irradiation."
  Although this comment is buried in a section not pertaining "Buildings and Facilities" it can have a profound effect.
  - The first problem that needs to be solved is what are the parameters that define "high-quality environmental conditions" .
  - The second point is how to reconcile the differences for what is required for LVPs (Large Volume Parenterals)manufacturing environments and apparent requirements imposed by the guidance to SVPs (small Volume Parenterals).
  - The third point is why in Europe it is acceptable to have the same approach for LVP in SVP production environments (class C for filling).

Environmental Classifications for Aseptic Processing Environments.

- The document states on line 131

"Critical areas and support areas of the aseptic processing operation should be classified and supported by microbiological and particle data obtained during qualification studies"

- As it appears the guideline appears to endorse the ISO 14644-1. Is that the case???. If so - one has to consider that once this standard is adopted, one has to follow all the provisions stated within i.e. selection of the number of sampling points, sampling volume etc.. and the guideline should then indicate that the FDA contrary to what has happened in the past has decided to endorse or accept a non pharmaceutical international standard it.

In the Environmental Classifications table the subscript in table indicates:

Designations provide uniform particle concentration values for cleanrooms in multiple industries.

- An ISO 5 particle concentration is equal to Class 100 ??? and approximately equals EU Grade A. This is not totally correct as the new standard had to make some considerations to adapt a mix the old units in the Federal standard (metric (english /metric) to a metric base tabulation.

IT ALSO INDICATES:

- Values represent recommended levels (What PARTICLES ?)of environmental quality. This is not clear, the phrase should be revised.
- You may find it appropriate to establish alternate microbiological levels due to the nature of the operation.
- Includes a column with the reference to settling plates, as optional, nevertheless levels cross referenced to the area classification are provided.
- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

Comments :

- The ISO 146441-1 was not designed to be a pharmaceutical standard nor had any indications as the ones provided on line 142 "Air Classifications" where a non proven correlation between particle concentrations (non-viable) and viable concentrations is portrayed.
- The table proposes "Microbiological settling Plates Action Levels" as quantitative when they can only be considered qualitative at best. It is important that several studies indicated in the past and the agency refer to the idea that the use of settling plates is not been advisable for "unidirectional air flow devices". Although this is optional, we suggest this point be noted

On the other hand the document indicates the document states on the table: You may find it appropriate to establish alternate microbiological levels due to the nature of the operation.

- This phrase can be the source of many potential misunderstandings and differences of opinion. If that is the case, the guideline should indicate that the "levels" listed on the table are recommended.
- The last statement under the table indicates: samples from (collected?) in Class 100 (ISO 5) environments should normally yield no microbiological contaminants. We think this phrase is broad and leaves too much for interpretation. We agree it should not yield airborne microbial contaminants, as for surfaces it may be different as it will depend where in the ISO 5 environment the sample is collected and what method was used.

As a general information changes to all the family of standards that preceded ISO 14644-1 were motivated by:

- Needs of other industries (electronic industry which needed the inclusion of class 10 and lower),

- Those industries (electronic) use the documents as a referee in contract negotiations and not typically with government regulators involved in public heath or safety.
- The changes in particle concentration measuring technologies, certainly not microbial airborne measurements. As the particle counters improved it was easier to measure effectively smaller particles and this helped in the development of lower level classifications.
- The influence and participation of the pharmaceutical industry and regulators (FDA) in the development of the ISO standard has been very limited.
- If the standard is endorsed by FDA, it needs to be clearly defined as the industry will have to adhere to the changes and evolution of it. By the extensive use of the "class" terminology one could imply that the Federal Standard 209 (b, e ...) was also endorsed

Nevertheless particle concentrations are not the element of consideration in designing an environment with microbial contamination control requirements used for aseptic processing.

Thus **we suggest using classification based on the risk of exposure of a sterile product and components to the environment** thorough the various phases of manufacturing.

In short, using the Risk Assessment concept currently strongly suggested by the agency

We suggest Environmental Classifications based on Risk Assessment.

In this venue why not classify pharmaceutical environments used for the production of parenteral (Aseptically or terminally sterilized) products based on the level of risk represented by exposing the sterile product, containers or closures to the environments in the various phases of the process.

- **High microbial contamination risk**, defined alternatively as : Class A or primary environments : those environments where the sterile products, containers, stoppers etc are directly exposed to the environment;
- **Medium microbial contamination risk**, defined alternatively as :Class B or ancillary : areas with potential entrainment of microbial contaminants to enter the Class A environments. In general, environments located in the perimeter of Class A and used for the storage of non-exposed sterilized components or background for aseptic processing manufacturing equipment;
- **Low microbial contamination risk**,, defined alternatively as :Class C, secondary: those environments dedicated for formulation and preparation of components where levels of particulate and bioburden are to be controlled to reduce presence of microorganisms that could impact (endotoxin) the finished product quality attributes.
- **Negligible microbial contamination risk** , defined alternatively as :Class D, : those environments used for general pharmaceutical operations where there is no risk of microbial contamination

This classification is based on applying the basic principles of risk management:

- GRAVITY of the event, effect on the product.
- PROBABILITIY to occur in view of the methods and technology employed.
- PREDICTABILITY, ability to foresee or prevent adverse environmental conditions in time to prevent the event from occurring.

Environmental Classifications

Using the risk classification approach can make the language in the document more consistent eliminating the mix and matches when referring to the classifications. The document currently employs a variety of terms to indicate the same:

- Critical areas
- ISO 14644-1 classes
- Fed Std 209E particle concentration classifications(class100,1000, etc)

This is done in a very inconsistent fashion (If the risk classification is not adopted, we suggest using only one of these terms to avoid confusion).

Lastly the use of the "risk based classification" will favor, at least in part, the harmonization with the European Classification, this also outlines the activities to be carried out within a specific risk class.

Using the same designations will avoid unnecessary conflicts when working in international trade.

Sampling Locations

- The document states line 172:
- "Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations would be of appropriate particle quality when it has a per-cubic-meter particle count of no more than 3520 in a size range of 0.5 micron and larger when counted at representative locations normally not more than 1 foot away from the work site"

The word "appropriate" indicates this is a prescription. The use of that level of particle count concentration in the Pharma industry originated from the ability to measure particle concentrations with a light scattering photometer and the assumption that 0.5 particles were close to bacterial size.

Today one has to question this value, as the air supplied from HEPA filters and before enter in contact with any surfaces has typically 0 (zero) particles of 0.5 microns (either by liter or cubic feet of air).

Concentrations of non-viable airborne particles in the proximity of sterile products, containers or closures does not necessarily represent the microbiological quality of the incoming air. i.e.. if one measures the particle concentrations inside of a stopper bowl, he will find a particle count way higher that the stipulated amount. These are not necessarily microbial contaminants, but particles released by the friction of the stoppers among themselves and the surfaces of the bowl.

As for the sampling location (1 foot above the filling point) we consider that this statement does not correspond to a full risk assessment approach and may not be conducive to obtaining a real profile of the microbial contamination profile of the line.

This prescription to test a specific location is not in line with the referenced ISO standard or any other standard's for the site selection of sampling points.
Today one can argue that : The filling point may be the point of highest risk on a filling line (needles penetrate into a sterile container, displace the air, thus penetration of outside air is impossible). While probably the areas of heavy manipulation such as stopper loading could be more risky.
It is our view that airborne particle concentrations should be measured at the point of HEPA filtered air delivery and they should be zero particles of 0.5 micron and larger per cubic meter or cubic feet.
We consider that microbial samples are to be taken at selected locations in a constant fashion using remotely operated samplers, currently available in the market. This will permit the monitoring of the environment continuously during two or three hours without individuals interfering with sampling during operations. (Process Analytical Technology PAT)
"Unidirectional Airflow Devices" can only guarantee the quality of the air until it contacts a surface. After that the particle count is the result of the particles swiped away from equipment surfaces (not necessarily a microbial contaminant) and those originally delivered by the air filter.
Additionally it has to be recognized that air is a compressible fluid and when it contacts surfaces, its velocity may change. Once air contacts surfaces, they may induce a greater or lesser degree of turbulence depending on whether or not they are aerodynamic.
Thus, to verify the quality of the air delivered by a Unidirectional Air Flow Device, one has to measure particle concentrations before the air encounters an obstacle.
Prescribing in a general way where to sample or indirectly pointing out what a critical area is can render poor results for evaluating the overall contamination profile of an aseptic line.
On the other hand measuring of non viable particles should not be the prime concern. Is the measuring of microbial contamination the issue?. The use of particle counters at the filling point is only a "patch" for deficient microbial airborne sampling methods and devices. We suggest the guideline motivate users to seek better ways to asses the airborne microbial contamination levels using techniques consistent with the degree of development of the analytical technologies available for the industry.
We suggest the application of the methodology proposed by the Hazard Analysis Critical Control Point HACCP which is more in line with risk assessment approach. We suggest this method be used in more of the current guidelines for microbial monitoring.
Based on the HACCP approach we suggest that:

- Critical Control Points on every phase of the process.
- Defining the method used for risk management (SOP and equipment).
- Defining the method for monitoring the levels of microbial contamination (frequency and location).
- Defining the approach to verify effectiveness of the overall microbial contamination control program.

All of this as part of a "Comprehensive Environmental Control Program".

Particle Counter Probe Direction.

The document on line 181 states :

"Measurements to confirm air cleanliness in aseptic processing zones should be taken with the particle counting probe oriented in the direction of oncoming airflow and at specified sites..."

This may be inaccurate as with the use of iso-kinetic probes and the vacuum of the particle counters a sample taken with the probe located horizontally may be valid. (Smoke studies demonstrate this fact) and the probe will cause less turbulence to the critical areas.

It our view that the user of the particle counter should document and validate the appropriateness of the selection of the positioning of the sampler probe.

Area pressurization

On line 236 the document states: C. Clean Area Separation (pressurization)

"... Rooms of higher air cleanliness should have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. For example, a positive pressure differential of at least 12.5 Pascal (Pa)5 should be maintained at the interface between classified and unclassified areas."

We must note that the value suggested was selected as rule of thumb in the past and was based on the ability to read the manometers that was available at the time.

The first part of the sentence (using "for example") is not clear. Is this a prescription or a suggestion. If this is the expected alarm trigger value, the actual gradient value should be higher.

We consider that attaining the proper environmental segregation should be a responsibility of the system designers as this closely related to the type of process, regular pharmaceutical production with no bio-hazard considerations, production of potentially bio-hazard substance, type and nature of the architectural components and the HVAC system etc.. for the guideline to list all of this considerations will be a very complex task.

We suggest the first part of the sentence be included without giving specific values out of the general context of HVAC design, operation, monitoring and room management practices and forcing the designers to consider all the elements required to provide proper segregation of the manufacturing environment as to provide support for an adequate aseptic process..

Air Changes per Hour.

The document states line 247:

"An adequate air change rate should be established for a cleanroom. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour would be typically acceptable. For areas of higher air cleanliness, significantly higher air change rates will provide an increased level of air purification."

The overall concept of air changes was developed to indicate the dilution (elimination) ratio of contaminants in a controlled environment.
The value stated is a rule of thumb not always applicable as you may require more or less changes as a function of the selected HVAC air filtration chain, the quality and quantity of the fresh air make-up, the particle generation within the environment etc..
The following represents a simple Mathematical model of a Cleanroom, useful to express the changes per hour concept:

$$C= S/Q+ (1-x)(1-Np) (1-Nf) Coa$$

C= Expected Cleanliness Level
S = Contamination generated in the room (concentration at a particle size)
X = Recirculation ratio
Q = Total air flow (mt3 per hour)
Np = Pre-filter efficiency (% of penetration at a specified particle size)
Nf = Final filter efficiency (same as above)
Coa = particle contamination from outside air (concentration at a particle size same as filters)
One has also to understand that there are systems that have no recirculation due to mostly safety considerations. In those cases we have " total air replacement" and serial filtration of the supplied air.
We suggest the document indicate: "Room Air Changes (changes per hour) are calculated with the scope of diluting or eliminating non-viable contaminants present in a controlled environment. This effect is obtained by re-circulating the air through pre-filters (low efficiency) or HEPA air filters (high efficiency). In some cases where recirculation is not allowed or desired (for safety reasons) the total air of the room is filtered through air filters of various efficiencies installed in series and eventually discharged to the atmosphere. The actual number of changes are dependant on the level of generated internal contamination as well as the ones provided as part of the make-up or fresh air"

<u>HEPA filter Integrity Testing</u>
The document goes into great detail explaining the principles for the testing of HEPA filter integrity without giving the full story for some key aspects of the test i.e.. scanning velocity which is critical for the success of the test.
Line 2888 states High-Efficiency Particulate Air (HEPA) An essential element in ensuring aseptic conditions is the maintenance of HEPA filter integrity. Leak testing should be performed at installation to detect integrity breaches around the sealing gaskets, through the frames, or through various points on the filter media. Thereafter, leak tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility.
A [1] The same broad principles can be applied to ULPA filters
This statement is OK.
The document indicates: "this testing is usually done only on a semi-annual basis." It is important to conduct periodic monitoring of filter attributes such as

uniformity of velocity across the filter (and relative to adjacent filters) to determine the optimum time for filter testing, certainly a pro-active approach is to be considered but also one should remember that CHALLENGING the filters represents an additional risk for the environment.

The use of challenge aerosols (such as the old DOP and Emery 3000) are not the only ways used for assessing the integrity of filters, outside air is also used as a challenge.

Also the use of particle counters and special particle generators are used (mostly in Europe) for this test.

In view of it we suggest reference to the following documents that were developed by HEPA filter experts under the auspices of the Institute of Environmental Science and Technology they provided a comprehensive and detail procedures as how to go about for the HEPA filter testing, which by the way is somewhat different than that of the ULPA filters:

IEST-RP-CC001.3: HEPA and ULPA Filters
IEST-RP-CC007.1:Testing ULPA Filters; IEST-RD-CC011.2:A
IEST-RP-CC021.1:Testing HEPA and ULPA Filter Media;
IEST-RP-CC034.1: HEPA and ULPA Filter Leak Tests

On line 337 the document states: "Airflow velocities are measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area. Regular velocity monitoring can provide useful data on the clean area in which aseptic processing is performed. HEPA filters should be replaced when no uniformity of air velocity across an area of the filter is detected or airflow patterns may be adversely affected."

It must be noted that Air flow uniformity is not an attribute of the filters but for "Unidirectional Air Flow Devices" (attributes of the filters are flow rate , efficiency and pressure drop).

The document mixes the concepts.....Variations in velocity generally increase the possibility of contamination

<u>It is not variations in velocity but turbulence that increases the probability for cross contamination</u>

It continues ....., as these changes (e.g., velocity reduction) can have an effect on unidirectional airflow.

The statement is not totally correct. Air is to be measured before the air encounters any obstacle as it will be unidirectional until there is interference of a non-aerodynamically shaped surface with a viscosity different than that of the air

.

We suggest to refer to the Air flow uniformity testing procedures for unidirectional air flow devices are clearly described in the IEST :

IEST-RP-CC002.2: Unidirectional Flow Clean-Air Devices; recommended practices.

The use of this guideline concepts will eliminate confusion and ambiguities.

<u>Clean Room Testing</u>

Under the same direction we suggest the preparers of the guideline either incorporate or reference the concepts listed for Cleanroom testing indicated in the following documents:

- IEST-RP-CC006.2: Testing Cleanrooms;
- IEST-RD-CC011.2:A Glossary of Terms and Definitions Relating to Contamination Control

Environmental Monitoring

The document indicates:

"Evaluating the quality of air and surfaces in the cleanroom environment should start with a well-defined written program and scientifically sound methods....Locations posing the most microbiological risk to the product are a critical part of the program....."

As indicated we suggest the HACCP approach which is systematic and well known , it is comprehensive and covers the full and appropriate logic of an environmental control program for clear determination of the Points at RISK (CCP) to the evaluation of the effectiveness (trending) of the selected program

Conclusion

The effort made by the FDA in the review of this critical guideline is commendable. There are many valuable points that will help the industry understand FDA's position.

We suggest a recommendation in the guideline to structure a: "Comprehensive Environmental Control Program" be provided

That includes as minimum:

- Cleanroom and facilities design program.
- Personnel contamination control program
- Cleaning and disinfection program
- Environmental monitoring program
- Aseptic processing equipment and devices selection program

In order to make this document useful we ask the FDA to consider and evaluate the points mentioned above.

Finally we suggest that references provided in the guideline they be more specific for the facilities design, construction and operation than the ones cited in the document . Here are some suggestions.

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National Environment Balancing Bureau "Procedural Standards for Certified Testing of Cleanrooms" 8575 Grovemont Circle, Rockville, Maryland 20877.

Validation of Pharmaceutical Processes /Sterile Products 2nd. Edition Marcel Dekker NY.

Pharmaceutical Dosage Forms/ Parenteral Medications volume 2 / Marcel Dekker NY.

ISO 14698-1 and 2
"Cleanroom and Associated Controlled Environments – Biocontamination Control-"

We are open to collaborate with the agency at your request,
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