Environmental Monitoring Fundamentals

West Coast Chapter PDA

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Biography
Barry A. Friedman, Ph.D.

Barry A. Friedman, Ph.D., is a consultant in the Regulatory Compliance, Biotechnology and Aseptic Processing arena. He previously was the Director, Quality Control, with Cambrex Bio Science Baltimore, a contract manufacturer of GMP bulk biopharmaceuticals and prior to that was the Laboratory Director for a contract Aseptic Fill 'n Finish manufacturer.

Dr. Friedman has over 30 years of industrial experience in various aspects of biopharmaceuticals and medical devices to include quality control, sterility assurance, validation of microbiological methods and fermentation technology. His associations have included Cambrex Bio Science Baltimore, Chesapeake Biological Laboratories, W.R. Grace, Sigma Chemical, Sherwood Medical and Becton Dickinson. He is a member of AAMI, ASM and PDA. He received his Ph.D. from The Ohio State University and served as a Captain in the U.S. Army. He is the past President of the Capital Area Chapter, PDA and the 2009 PDA recipient of the James Agalloco award for teaching excellence.

Goals and Objectives

- Assuring your understanding of the fundamentals of a Environmental Monitoring Program
- Identifying key elements of an Environmental Monitoring Program
- Understanding how the regulations impact your CGMP facilities' "Controlled" and "Classified" environment
- Consideration required for the Design and Operation of a "Controlled" and "Classified" Environment

Goals and Objectives (con't)

- Understanding why a documented Plan needs to be in place prior to the initiation of environmental monitoring
- Learn how having a Plan in place reduces testing through Risk Assessment

SECTION I

Regulatory Requirements Within A GMP Environment

The Regulatory Requirements

- The production of various products may dictate a controlled and classified environment from ISO CLASS 5 (Class 100) to ISO CLASS 8 (Class 100,000) or Grade A through Grade D (European)
- Typically, a medical device facility requires no higher classification than ISO CLASS 7 (Class 10,000)
- A pharmaceutical or biopharmaceutical facility will require a variety of classes from ISO CLASS 5 through ISO CLASS 8

The Regulatory Requirements CLEAN AREA CLASSIFICATIONS

Clean Area Classification (0.5 um particles/f^3)	ISO Designation Class	≧0.5um particles/ m^3	Microbiological active air action levels (cfu/m^3)	Microbiological settling plates action levels (90mm diam., cfu/4 hrs.)	
100	5	**3,520**	≤1	≤1	
1000	6	**35,200**	7	3	
10,000	7	**352,000**	10	5	
100,000	8	**3,520,000**	100	50	

The Regulatory Requirements

- Filtered air requirements are critical to maintaining a successful environment
  - Air entering a classified environment must be pre-filtered, filtered and humidified prior to entering this environment
  - Air turnover rates per hour for an ISO 5 environment should be 100 – 200; ISO 7, 40 -80; ISO 8, 20 -40
  - Temperature ranges of 19-22^{o}C and humidity levels of 30-60% are desirable

The Regulatory Requirements

- The number of particulates remaining in the air following filtration becomes especially important if one is attempting to meet European requirements (see Annex 1, revised) in today's regulatory environment
  - FDA regulates airborne non-viable particulates at only the 0.5 micron level
  - EMA regulates airborne non-viable particulates at both the 0.5 and 5.0 micron level
  - One may pass a room at the 5.0 micron level and, yet, fail at 0.5 micron

The Regulatory Requirements

- Cleanroom is composed of non-shedding, smooth surface, washable floors, walls and ceilings
- Viewing windows abut the walls and contain no ledges
- Lighting is housed in “tear-drop” enclosures (typically ISO CLASS 5 and 6)
- The ISO CLASS 5 rooms are often constructed to be “explosion-proof”

SECTION II

Key Consideration In The Development An Environmental Monitoring Plan

Key Considerations

- Key considerations in the development of an Environmental Monitoring Plan include:
  - Purified Water and Water for Injection
  - Airborne viable particulate and non-viable particulate
  - Gowning
  - Cleaning/Sanitization/Disinfection
  - Identification of Microorganisms
  - Planned and Unplanned Facility Shutdowns
  - Equipment DQ/IQ/OQ/PQ
  - Data Capture, Analysis and Storage

Key Considerations in a Classified Environment

Facility Design

- Facility design and a review of the flow of components, product and personnel will help to reduce the potential for the contamination of low bioburden components
- Issues normally associated with facility design are ease of cleaning, adequate space for segregation of components, and proper balancing of the air within the facility to assure needed pressure differentials are maintained between adjoining areas
- Management of change is critical to assure that there is agreement and awareness of design features to avoid deviations when tested

Water Considerations

- In-house water requirements may be:
  - Tap Water considerations only (capsules, tablets, liquids)
  - Purified water (as above)
  - Water for Injection (injectables)
- Each of these types of water has varying test requirements and frequencies
- FDA and EMA may allow differing methods to obtain Water for Injection

Frequency of Sampling During and Following the Qualification of the USP PW/WFI and Clean Steam Systems

SYSTEM	LOCATION	INITIAL 2 WEEKS	WEEKS 3 AND 4	ROUTINE MONITORING
R/O Unit	Exit from R/O	Mon thru Fri	Mon thru Fri	Mon, Wed, Fri
USP PW/WFI	**Leaving Storage Tank**	Mon thru Fri	Mon thru Fri	Mon, Wed, Fri
USP PW/WFI	Room Ports	Mon thru Fri	Mon, Wed, Fri	Once per Week
USP PW/WFI	**Returning to Storage Tank**	Mon thru Fri	Mon thru Fri	Mon, Wed, Fri
Clean Steam	**Leaving Clean Steam Unit**	Mon, Wed, Fri	Mon, Wed, Fri	Monthly/ Quarterly
Clean Steam	Autoclave	Mon, Wed, Fri	Once per Week	Monthly/ Quarterly

Validation Sampling Schedule

	Sample Point	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
First 30 days	Feed SP-1	*	*	*	*	*	*	*
	Return SP-9	*	*	*	*	*	*	*
	POU SP-2	*	*	*	*	*	*	*
	POU SP-3	*	*	*	*	*	*	*
	POU SP-4	*	*	*	*	*	*	*
	POU SP-5	*	*	*	*	*	*	*
	POU SP-6	*	*	*	*	*	*	*
	POU SP-7	*	*	*	*	*	*	*
Next 150 days	Feed SP-1	*	*	*	*	*	*	*
	Return SP-9	*	*	*	*	*	*	*
	POU SP-2	*			*		*	
	POU SP-3		*			*		*
	POU SP-4	*		*			*	
	POU SP-5		*		*			*
	POU SP-6	*		*		*		
	POU SP-7		*		*		*	
Next 6 Months Monthly Testing	Feed SP-1	*	*	*	*	*	*	*
	Return SP-9	*	*	*	*	*	*	*
	POU SP-2	*						*
	POU SP-3		*					
	POU SP-4			*				
	POU SP-5				*			
	POU SP-6					*		
	POU SP-7						*	

Airborne Viable Particulates

- Airborne viable particulates may consist of bacteria, yeast and mold
- Requirements vary with the ISO CLASS – being more stringent with ISO CLASS 5 and least stringent with ISO CLASS 8
- The number of microorganisms will vary with:
  - Number of HEPA filters within the room
  - Air turnovers per hour
  - Number of personnel in room (NOTE: Personnel are the greatest source of contamination)
  - Activity occurring in room, e.g., fermentations, purifications

Airborne Non-Viable Particulates

- Airborne non-viable particulates may consist of dirt, dust, fibers, equipment “junk”, flakes of skin, etc
- Requirements vary with the ISO CLASS – being more stringent with ISO CLASS 5 and least stringent with ISO CLASS 8
- The number of non-viable particulates will vary with:
  - Number of HEPA filters within the room
  - Air turnovers per hour
  - Number of personnel in room (NOTE: Personnel are the greatest source of contamination)
  - Activity occurring in room, e.g., fermentations, purifications, liquid droplets from autoclaves

Airborne Viable and Non-Viable Particulates

- Selected factors such as temperature, humidity, duration of personnel in classified areas may adversely impact the environment
  - Increased room air temperatures cause perspiration and additional airborne microorganisms as the gowning degrades
  - Low humidity can cause more flaking of skin
  - The flakes coming from the skin will often contain microorganism
  - Typically, these will be Gram positive cocci
  - Extended stays in a classified environment will adversely impact the number of airborne viable and non-viable particulates

Monitoring of Airborne Viable and Non-Viable Particulates

- Airborne viable monitors usually include some form of positive or negative pressure, either vacuum or centrifugation, that allows the microorganisms to collide with the medium
- The media may be purchased as a strip or plate, depending upon the equipment, and may be unique to the equipment or universal and capable of being used with a variety of airborne viable monitors
- The media may be aseptically filled and bagged for usage or aseptically filled, bagged and then gamma irradiated prior to usage
- Gamma irradiation eliminates media false positives

Monitoring of Airborne Viable and Non-Viable Particulates

- Airborne viable monitors may also be portable or stationary
- Portable instruments are self-contained and move with the technician from room to room
- The stationary unit contains a number of remote heads onto which the plated media is added
- The remote heads are located within critical areas within the cleanroom and permit finite quantities of air to be pulled through each head before the unit automatically shuts off

Monitoring of Airborne Viable and Non-Viable Particulates

- Unfortunately, these data files could be manipulated, and, with the advent of 21 CFR Part 11, this method of collection was not looked upon favorably by the FDA
- Now, companies that manufacture these units have developed technologies that eliminate the possibility that the data, once downloaded, can be manipulated within the computer. Data may also be saved on a CD ROM that does not permit alteration once all of the information has been collected

SECTION III

Cleaning, Sanitization and Disinfection

Cleaning, Sanitization and Disinfection

- Cleaning, sanitization and disinfection of all classified environments is a key consideration in the plan's development
  - Surfaces to include ceilings, walls and floors must be cleaned and meet the microbial requirements for the classified area
  - Simultaneously, the chemicals used should not degrade the facilities
  - Both the FDA and the EMA require that facilities test the acceptability of the chemicals on coupons
  - They also require that "in-house" microorganisms can be killed when placed on a coupon, dried and then have the specific sanitizer/disinfectant added

Equipment Requirements for Cleaning, Sanitization and Disinfection

- Sanitization, disinfection and cleaning materials are regulated by the EPA, not the FDA
- All materials must have a C of A
  - Bleach purchased from the local grocery store is not acceptable
- Mops and mop covers should be sterile for classified area
- Vacuum cleaners within classified areas should possess HVAC filters
- Water used in ISO CLASS 5 – 7 areas should be Water for Injection, not Purified Water

SECTION IV

Sampling Locations, Methodologies and Frequencies

Critical Sampling Locations, Appropriate Sampling Methodologies and Frequencies

- Development of an Environmental Monitoring Plan requires the areas described above to be carefully planned and executed utilizing a Gantt chart or an Excel spreadsheet to determine manpower requirements, duration of testing, disposable supplies, refrigeration and incubation equipment, paperwork management, etc
- This Plan must be developed as a protocol that includes objective, scope, all above items as well as Acceptance Criteria for each tested area or utility

Critical Sampling Locations

- Airborne and surface sampling is a defined process that is based upon ISO 14644-1/2
  - Measurements of each classified room are obtained in square meters and samples are based on the square root of the area.
  - Thus, a room of 10X10 meters or 100 square meters would require ten samples once the room was established
  - However, during the room's qualification, testing of airborne non-viable particulates would occur at one square meter intervals

Critical Sampling Locations

- Airborne and surface sampling is a defined process that is based upon ISO 14644-1/2 (con't)
  - Because equipment often interferes with sampling, allowances must be made for equipment that might relocation of a sampling location

Critical Sampling Locations (con't)

- While sampling locations within an ISO 7/8 environmental follow ISO 14644-1/2 very closely, exceptions exist for ISO CLASS 5
  - Within ISO CLASS 5 environments (filling suites, hoods, lyophilization areas) critical areas require additional sampling
  - Within a filling suite, three additional areas warrant consideration to include the empty bottle "racking" area, the filling area and the stoppering area

Critical Sampling Locations (con't)

- While sampling locations within an ISO 7/8 environmental follow ISO 14644-1/2 very closely, exceptions exist for ISO CLASS 5
  - These areas are considered extremely critical because of their exposure to the room
  - Both airborne viable and non-viable particulates should be collected on an on-going basis while the process is on-going

Continuous vs. Non-Continuous Monitoring

- USP <1116> has been an advocate of continuous monitoring for ISO Class 5 cleanrooms since its inception
- It, however, does not recommend the continuous monitoring of either ISO Class 7 or 8 where a greater airborne particulate level is permitted
- The EMA with the revision to Annex 1 is now recommending continuous monitoring of both its viable and non-viable air for its Grade A and B areas

Continuous vs. Non-Continuous Monitoring

- The inclusion of periodic hourly contact plate monitoring (continuous) of the hands and forearms during fills also provides insight should contamination occur
- Soybean Casein Digest Media is the recommended choice for this monitoring

Continuous vs. Non-Continuous Monitoring

- The rationale for continuous monitoring includes the knowledge that should a contamination of a vial occur during its filling, the continuous monitoring (airborne or surface) of the fill (ISO CLASS 5/6) may assist in determining whether the contaminant arose from an airborne source
- Often the first response that is observed consists of a rapid change in the airborne non-viable particulates. The individual monitoring the environment should watch all airborne non-viable monitors to assure that none of the sites drift from anticipated levels

Continuous vs. Non-Continuous Monitoring

- If these data collaborate the data obtained from the positive obtained during a sterility test of the product, then the evidence will suggest that a true failure has occurred

SECTION V

Identification of Microorganisms

Identification of Microorganisms - General

- During the development of the Environmental Plan, microorganisms must be considered as a key element to control
- ISO CLASS 5 controlled environments should be absent of microorganisms, while ISO CLASS 7/8 will be expected to have finite numbers
- As the facility is being commissioned, tentative Acceptance Criteria should be developed based upon regulatory requirements, historical data or a combination of both
- The Plan should consider these criteria to control these microorganisms as well as to isolate and identify them

Preparation of a Facility for Microbial Control

- The Gantt Chart should provide a provision for cleaning and disinfecting the facility prior to obtaining the “basic” data
- All rooms should have construction debris removed prior to initiating and cleaning. This should include any corrugated that may be present
- No equipment should be present at this time if at all possible

Preparation of a Facility for Microbial Control (con't)

- The entire facility must be "broom cleaned".
- Vacuum cleaners without HVAC capabilities are preferable
- Mopping with tap water should then follow
- Do not use detergents unless absolutely necessary since this will add an immediate Total Organic Carbon load to the floors
- Walls and ceilings require cleaning; a sponge mop with a cover should be used for these purposes
- Do not wet mop over any HEPA filters

Preparation of a Facility for Microbial Control (con't)

- Several mopping applications may be required to remove the dust from the floors, walls and ceilings
- Because microorganisms will be present within the facility, some organizations desire to obtain a baseline of the typical microorganisms found within the site
- Others may decide to directly use a sterilant to remove as many microorganisms as possible
- Two applications of the sterilant on sequential days will reduce the level of surface microorganisms to zero in ISO CLASS 5/6 environments
- The HEPA filters should be in use for at least several days prior to the initiation of the use of sterilant

Types of Microorganisms Isolated

- Gram positive bacteria will be the most commonly isolated microorganisms within a new facility
- Yeast and mold will be present from the presence of the various construction materials, corrugated and lack of a controlled or classified environment
- Gram negative bacteria should not be present within the facility unless there is a “water” issue
- Once the facility is “buttoned up”, the number of environmental microorganisms should rapidly diminish from the air and “people” microorganisms will be the most frequently observed

Types of Microorganisms Isolated (con't)

- These microorganisms will consist of Gram positive bacteria to include:
  - *Staphylococcus sp.* (*epidermidis, aureus*)
  - *Kocuria*
  - *Micrococcus*
  - *Corynebacteria*
- Environmental Gram positive bacteria primarily will consist of *Bacillus* and will all be spore-forming
- Anaerobic microorganisms should be minimal – *Clostridium* and *Propionibactium acnes* may be present
- Yeast will be less frequent; molds to include *Aspergillus* and *Penicllium* will be more frequent

Identification Methods

- Historically, phenotypic methods were most commonly used to identify the microorganisms present
- These methods were then miniaturized or replaced by methods that measure fatty acids (FAME) and had an enhanced rate of identification
- In today's environment, the above testing has been greatly replaced by genotypic testing that analyses the initial 500 base pairs (Applied BioSystems) of the genome.
  - The cost for DNA Sequencing is available from reputable vendors for less than $130 per assay and results are available in several days

Top 15 Bacterial Isolates Accugenix, Inc (2010)

RANK	GENUS/SPECIES	PERCENT
1	Micrococcus luteus	9.6%
2	Staphylococcus epidermidis	8.7%
3	Staphylococcus hominis	5.6%
4	Bacillus cereus/thuringiensis	4.3%
5	Corynebacterium tuberculostearicum	2.9%
6	Staphylococcus capitis	2.8%
7	Bacillus pumilus	2.7%
8	Staphyloccus warneri	2.5%
9	Bacillus amyloliquefaciens/subtilis	2.4%
10	Staphyloccus haemolyticus	2.2%
11	Ralstonia pickettii	1.7%
12	Paenibacillus glucanolyticus	1.5%
13	Bacillus megaterium	1.5%
14	Propionibacterium acnes	1.0%
15	Bacillus licheniformis	0.9%

SECTION VI

Planned and Unplanned Shutdown of Facilities

Planned and Unplanned Shutdown of Facilities

- Cleanrooms may be shutdown during planned and unplanned activities.
- A Plan should be in place to manage both the removal of the cleanroom from as well as its return to activity.
- Planned activities may include shutdowns for maintenance, extended holidays, non-use of or renovation of an area.
- Unplanned activities may include equipment malfunctions, utility outages, other utility problems, fire drills, etc. and may last from a few seconds to weeks
- The Plan should minimize a “what do we do” attitude and permit a well thought out series of activities

Planned and Unplanned Shutdown of Facilities

- If an ISO Class 5 cleanroom used for aseptic filling were to have an unplanned malfunction, many of today's cleanrooms would maintain positive pressure with back-up HEPA filtered air and permit the orderly closure of all remaining vials as well as the bulk active pharmaceutical ingredient – even though the temperature and humidity of the room would likely degrade.
- All monitoring equipment would remain active if sufficient auxiliary power were present. If such power were not available, then the plates sitting within the airborne viable sampling units as well as any passive monitoring plates would be closed and removed from the room along with the personnel

Planned and Unplanned Shutdown of Facilities

- Planned shutdowns will differ markedly from unplanned shutdowns in that the cessation of activities is not usually a part of this type of shutdown
- The length of the shutdown and the activity within the room often determine the requirements to resume activity. If a room has had extensive renovations, it is likely for the room(s) to be broom cleaned, cleaned with warm water, and water containing a detergent or a diluted quaternary ammonium compound (if absolutely required) prior to using a sterilant to kill spore formers that may be present

Planned and Unplanned Shutdown of Facilities (con't)

- Materials that are used most frequently include bleach, hydrogen peroxide or a combination of hydrogen peroxide/peracetic acid. Following the use of one of these materials, the room is monitored to include ceilings, walls, floors and bench surfaces
- Airborne viable microorganisms are also included in the sampling. However, the greatest source of contamination, following the resumption of the HVAC system, is often found on the floors. Often a second application of a sterilant is required to assure the removal of all spore formers

Planned and Unplanned Shutdown of Facilities (con't)

- Following either a planned or unplanned shutdown and the follow-up cleanup, a Plan should be in place to determine the frequency of airborne viable and surface monitoring. The Plan should also include a provision for additional disinfection applications and monitoring if the initial bioburden is not removed by the application of the sterilant. Management and other impacted departments should be kept informed of the progress in the return of the cleanrooms to occupancy

Planned and Unplanned Shutdown of Facilities (con't)

- If the planned shutdown will be for a short duration (usually less than 24 hours), and the activities can be defined, the requirement for disinfectants may be more limiting and may not require a sporicide as part of the cleaning process. An analysis of the activities will assist in determining how extensive a cleanup, if any, may be required. Some facilities use time intervals of <1 hour, <4 hours, <24 hours and set boundaries around each time

SECTION VII

Data Capture, Analysis and Storage

Data Capture, Analysis and Storage

- Data capture, analysis and storage must be considered very early in the development of the Environmental Plan
- Decisions must be made to use manual methods to include Excel and Access or an automated system such as NovaTek
- An automated system provides not only pre-developed reports, but also Alerts that are sent by e-mail within 24 hours of the Alert being recorded
- Regardless of the system, during the initial facility start-up, large quantities of data must be obtained and analyzed as noted above

Data Capture, Analysis and Storage

- These data need to be stored and retrieved to determine if the facility is meeting the Acceptance Criteria established throughout the Environmental Plan
- Once the facility has been commissioned, reports must be prepared at a pre-determined frequency, e.g., monthly, quarterly, annual, for both internal and regulatory reviews
- Both the FDA and EMA expect raw data to be available as “hard” copy if it has not been stored electronically

Data Capture, Analysis and Storage (con't)

- A system for Deviations and CAPAs must also be in place
- Metrics that track critical issues to include Alert and Action Levels as well as specification limits should be present
- The Environmental Plan should also have a provision for decreasing the frequency of testing based on the attainment of certain predetermined airborne viable and non-viable levels as well as surface counts
  - This provision should be placed within the Plan at it initiation
  - Attempting to have this provision added after obtaining a year of results often leads to inactivity and prolongs intensive data capture when it is not necessarily required

SECTION VIII

Recent Warning Letters

Formatech Inc. Warning Letter 2/10/11

1. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. §211.192]. For example,

- a) Your firm has routinely failed to thoroughly investigate and identify root causes when environmental monitoring data exceeds the action limit.
- In your response, your firm states that you have hired a consultant to assess the environmental data and subsequently, repaired the facility.

Formatech Inc. Warning Letter 2/10/11 (con't)

- Your response, however, is inadequate because your firm failed to investigate adequacy of your disinfectant procedures, frequencies, and preparation as part of your investigation for environmental samples that exceeded action levels in the critical and supporting clean areas. For example, your firm's disinfection program included insufficient use of sporicidal agents. It is essential that environmental control is continually maintained throughout your aseptic processing facility.

Formatech Inc. Warning Letter 2/10/11 (con't)

- Your risk assessment for microbial and particulate contamination of products produced at your facility failed to properly evaluate excursions associated with the filling room area adjacent to the lyophilizer in which vials are manually transferred from the filling line to the lyophilizer. Furthermore, your assessment did not provide a plan of action to effectively investigate future environmental excursions.

Iso-Tex Diagnostics, Inc Warning Letter 12/3/10

2. Your firm has not established appropriate written procedures for validation of all aseptic and sterilization processes designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. §211.113(b)]. For example,

- c. Your firm's Standard Operating Procedure (SOP) 3004 entitled, "Sanitization of an Environmentally Controlled Area," does not describe the sanitization of the plastic totes used to transport supplies from the uncontrolled areas to the **(b)(4)** environment.

Iso-Tex Diagnostics, Inc Warning Letter 12/3/10

- In addition, your SOPs do not require the use of sterile or sterile filtered bleach and water for sanitization of your controlled areas.

3. Your firm does not have adequate control systems to prevent contamination of your floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable [21 C.F.R. § 211.42(c)(10)(i)].

Dakota Labs Warning Letter 3/17/11

- Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications, whether or not the batch has already been distributed, as per 21 CFR 211.192. For example,
- a. You failed to investigate environmental monitoring data recorded in your aseptic processing suite, which failed to meet your established limits.
- Your response states that you have revised your environmental monitoring form to allow space for explanation when needed; however, your response is not adequate.

Dakota Labs Warning Letter 3/17/11 (con't)

- 4. Your firm does not have an adequate system for monitoring environmental conditions in aseptic processing areas, as per 21 CFR 211.42(c)(10)(iv)]. For example,
  a. Your firm does not have written procedures for environmental monitoring during aseptic processing, including sampling frequency, sampling locations, or procedures for alert and action levels.

Dakota Labs Warning Letter 3/17/11 (con't)

- In your response, you state that you have revised your environmental monitoring form to include a place for explanations and that you are developing an environmental monitoring procedure. You also state that your acceptance criteria currently listed on your worksheets is your action limit. You are required to ensure all sampling locations, sampling frequency, and alert and action levels are justified by a scientific rationale. We request you provide your alert levels. If these levels have not already been established, provide the timeframe within which they will be established.

Sanofi Aventis Deutschland GmbH Warning Letter 2/11/11

- 2. Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during aseptic processing. [21 C.F.R. § 211.42(c)]. For example,
- b) Your environmental monitoring program does not give assurance that environmental contaminants are reliably detected. Your practice of collecting samples from the gloves of operators, from left and right hands on alternate days is unacceptable. In addition, your SOP fails to include instructions for the location and duration of samples collected in the critical aseptic processing areas.

Background Resources

- www.pda.org
- www.fda.gov
- www.usp.org
- Freedom of Information reading room- www.fda.gov/ora/frequent/default.htm
- Warning Letters page- www.fda.gov/foi/warning.htm

Thank You

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