The Environmental Monitoring Program in a GMP Environment

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KEY POINTS

The following key points are discussed in this article:

- The routine environmental monitoring program is a critical aspect of documenting the state of control of the facility
- Recommendations for the selection of sample sites to be used in the qualification program are provided. These recommendations are directed at providing data to allow creation of a program useful in determination of the state of control of the facility
- The qualification study should provide data to allow determination of meaningful alert and action levels for that facility. It must be noted that there are significant technical and scientific issues with the regulatory guidelines for the areas of an aseptic core region—a suggestion consistent with proposed revisions to *United States Pharmacopeia* chapter <1116> "Microbiological Control and Monitoring Environments Used for the Manufacture of Healthcare Products" is provided
- Explicit examples are provided from publically-available sources (FDA-483 observations and warning letters) of enforcement activities based on good manufacturing practice failures in the environmental monitoring program
- A discussion is provided on the relative values of 483 observations and warning letters as useful indicators of US Food and Drug Administration policy.

INTRODUCTION

The qualification, or requalification, of an aseptic manufacturing facility depends in large part on the demonstration of controlled microbial conditions. The following are several areas where this is especially true:

- Cleaning studies
- Contamination control planning (1)
- Equipment hold time studies (establishment of clean and dirty hold times—process hold times are process-specific)
- Selection of sample sites for environmental monitoring
- Establishment of facility-relevant alert and action levels for controlled environments.

This article examines the environmental monitoring (EM) program, its sample sites, frequency of testing, and establishment of alert and action levels. A method to qualify and justify the selection of the sample sites within a facility used for routine environmental monitoring is presented. This discussion is not meant to describe the only possible approach to this selection but rather one that the author has used in the past with success. Due to the limitations of space, this discussion does not include sampling of the water system, gasses, or personnel which have distinct considerations.

WHAT IS THE POINT OF THE EM PROGRAM?

In trying to determine the appropriate parameters of a complex program such as environmental monitoring, we first have to agree upon the scope and purpose of the program. The purpose of the EM program is to document the state of control of the facility, not to determine the quality of the finished product. The US Food and Drug Administration guidance document (2) is very clear on this point in section X.A.1 and states:

"In aseptic processing, one of the most important laboratory controls is the environmental monitoring program. This program provides meaningful information on the quality of the aseptic processing environment (e.g., when a given batch is being manufactured) as well as environmental trends of ancillary clean areas. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs (211.42 and 211.113)."

Section X.A.2 of the guidance states, "Environmental monitoring data will provide information on the quality of the manufacturing environment."

Recent publications have reinforced the position that the EM program looks to document the state of control of the facility. Hussong and Madsen (3) point out that the microbiological assays used have limits of quantification higher than the customary control levels and so are subject to a great deal of variability. This consideration, by their argument, reduces the precision and predictive ability of the data. Therefore, the trend of the data is the critical aspect, and this information cannot be used in finished product quality decisions. In other words, pristine EM data for an aseptic processing facility speaks to the state of control of that facility, not to the "sterility" of products produced there.

Farrington expanded this thesis in a subsequent article (4). He observed that the relationship of EM data to finished product quality was an unproven, but commonly held belief. In the absence of data, we cannot assume it is true, but that it is undeniable that these data (and particulary the trending of these data) show the state of control of the facility. He argues that the regulatory concern over contamination from environment makes sense, but must be applied with judgment and scientific rigor. The major problem with EM data, of course, is the fundamental imprecision and variability of these data. This imprecision renders the data all but useless as quantitative predictors of the system, but valuable as raw data for the determination of trends in the facility as a whole. Farrington makes the interesting observation here that these concerns about traditional EM methods are also a concern for rapid methods.

Farrington is not the only worker to point out the fundamental problem using "rapid" methods to generate inherently imprecise and variable data. Sutton (5) has more than once pointed out the questionable value of generating bad data quickly over generating bad data slowly. The data are not inherently "better" for being read off an extremely expensive machine. This is not to say that the rapid methods are not needed or

desirable, only that they are not a panacea and must be applied with forethought.

SHOULD THE SAMPLE SITES BE IDENTIFIED?

There is a school of thought that believes that sample sites for the EM program should not be defined, that sampling from a defined location will encourage the cleaners to pay particular attention to those sites and skew the data. This is incorrect and contrary to good manufacturing practice (GMP). For example, the FDA aseptic processing guideline (2, Section X.A.1) states:

"It is important that locations posing the most microbiological risk to the product be a key part of the program. It is especially important to monitor the microbiological quality of the critical area to determine whether or not aseptic conditions are maintained during filling and closing activities. Air and surface samples should be taken at the locations where significant activity or product exposure occurs during production. Critical surfaces that come in contact with the sterile product should remain sterile throughout an operation. When identifying critical sites to be sampled, consideration should be given to the points of contamination risk in a process, including factors such as difficulty of setup, length of processing time, and impact of interventions. . .

"All environmental monitoring locations should be described in SOPs with sufficient detail to allow for reproducible sampling of a given location surveyed. Written SOPs should also address elements such as 1. frequency of sampling, 2. when the samples are taken (i.e., during or at the conclusion of operations), 3. duration of sampling, 4. sample size (e.g., surface area, air volume), 5. specific sampling equipment and techniques, 6. alert and action levels, and 7. appropriate response to deviations from alert or action levels."

In other words, the sites used in the routine EM program must be justified and identified. Section X.A.2 states, "Microbiological monitoring levels should be established based on the relationship of the sampled location to the operation. The levels should be based on the need to maintain adequate microbiological control throughout the entire sterile manufacturing facility. . . Environmental monitoring data will provide information on the quality of the manufacturing environment."

This concern also appears in 483 observations and warning letters. Warning letters and many 483 observations are posted on FDA's website (6). The following 483 observation dealt with significant issues in justification of the EM sample sites (7):

"Regarding the increased non-routine surveillance monitoring performed to further evaluate the Building 37 Flu manufacturing facility, there was no plan in place specifying the locations to be tested, method of sampling, and actions to be taken when microbial contamination was noted. Samples containing colony forming units (CFU) were evaluated for morphological characteristics, and only colonies exhibiting Gram-negative characteristics were Gram stained and identified.

- The [redacted] method used for increased surveillance monitoring of the environment has not been qualified."

So, clearly it is important to have a rationale for the location, frequency and number of sample sites. This can be done by a qualification study that will utilize many more sample sites than will be present in the routine program, but will serve to identify those sites most useful to routine monitoring.

NUMBER OF SITES FOR QUALIFICATION STUDIES

International Organization for Standardization (ISO) 14644-1 (8) describes a method to determine the number of sampling sites for site qualification. Annex B states that we should determine the minimum number of sample sites by the following equation:

$$N_L = \sqrt{A}$$

where

N_L is the minimum number of sampling locations (rounded up to a whole number)
A is the area of the clean room or zone in meters^2 .

This might work well enough for non-viable particulate measures (which is the intent and scope

of 14644-1), but we also wish to consider viable air sampling (both passive and active) and viable surface monitoring. Frequently, the sample site study is worked into the facility HVAC performance qualification study for ease of documentation and logistic considerations. For the initial facility HVAC qualification protocol, both viable and non-viable active air sampling sites should be done at the same locations (or as close as practical to avoid compromising the other measure or the product integrity). This leaves determination of the number of sites for passive air sampling and surface sampling.

PASSIVE AIR SAMPLING

Passive air sampling (i.e., settle plates) is a frequently-used measure of clean room (or controlled zone) monitoring. Settle plates have several advantages in this regard, chief among them the ability to remain in continuous exposure for up to four hours (four hours is cited in European Union [EU] 2008 guidance [9]—extended exposure times must be demonstrated via demonstration of the growth promoting capabilities of the aged and exposed media). In addition, passive viable monitoring (settle plates) is not disruptive to the immediate environment and so may possibly sample sites very near product exposure points (see reference 10 for a discussion of these, and other, advantages). In addition, settle plates are not as prone to variation among different vendors as are active samplers (11). However, it is not clear whether all the advantages cited for passive sampling apply in areas of laminar air flow at the rates used for modern clean rooms. In addition, settle plates may be particularly susceptible to handling, transport, and lab contamination. However you view their usefulness, current regulatory expectation for air monitoring includes their use and the justification of sampling sites. A prudent measure is to use the same number of sampling sites for settle plates as used for the active viable and non-viable sampling programs. These will not be the same sites but will be similar in number.

SURFACE SAMPLING

This leaves us with determination of the number of surface sampling sites for the qualification study. There is no regulatory guidance directed to this point for the international pharmaceutical industry. Even the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), which generally can be counted on to provide details on almost everything microbiological, is silent on this point (12). Oddly enough, even the Parenteral Drug Association (PDA)'s *Technical Report #13* (13) offers no help here. We are left to our own devices. One approach to determination of the number of sites would be to address it in a manner similar to that of ISO 14644-1 for the walls and floors (as relevant). Each surface would then be treated as a separate item and the minimum number of sites determined for each. While this might work for walls and floors, the number of surface sampling sites for equipment remains unanswered and is not noticeably amenable to this approach. This, quite frankly, may well be something that must be left to determination at each individual site—the numbers could be driven by the nature of the equipment and the associated manufacturing process.

SELECTION OF SAMPLE SITES FOR THE QUALIFICATION STUDY

Having determined the number of sites for each room, we now need to determine their location for this qualification study. One of the goals of this study is to provide data to assist in the determination of appropriate sample sites. This method of determining sample site number will provide an unreasonably large number of sample sites for routine surface sampling. It is from the data collected that the determination of the routine surface and air sample sites will be decided.

The selection of sample sites should be designed to provide useful information for eventual selection of routine sample sites. Several technical and guidance documents from PDA, FDA, EU, and the United States Pharmacopeia (USP) are relevant.

Parenteral Drug Association

PDA *Technical Report #13* provides the following guidance in this regard:

"Factors to consider in selecting sites for routine surveillance are:

- 1. At which sites would microbial contamination most likely have an adverse effect on product quality?
- 2. What sites would most likely demonstrate heaviest microbial proliferation during actual production?
- 3. Should site selection involve a statistical design (e.g., following the calculations in Federal Standard 209E) or should site selection be made on the basis of grid profiling? Should some sites for routine monitoring be rotated? *[Note from author: As 209e has been withdrawn in favor of ISO 14644, the answer is "No"]*
- 4. What sites would represent the most inaccessible or difficult areas to clean, sanitize, or disinfect?
- 5. What activities in the area contribute to the spread of contamination?
- 6. Would the act of sampling at a given site disturb the environment sufficiently to cause erroneous data to be collected or contaminate product?" (13).

The US Food and Drug Administration

The FDA aseptic processing guidance document (2) states in section IVA:

"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 µm and larger when counted at representative locations normally not more than one foot away from the work site, within the airflow, and during filling/closing operations. This level of air cleanliness is also known as Class 100 (ISO 5). We recommend that measurements to confirm air cleanliness in critical areas be taken at sites where there is most potential risk to the exposed sterilized product, containers, and closures. The particle counting probe should be placed in an orientation demonstrated to obtain a meaningful sample. Regular monitoring should be performed during each production shift. We recommend conducting nonviable particle monitoring with a remote counting system. These systems are capable of collecting more comprehensive data and are generally less invasive than portable particle counters. See Section X.E. for additional guidance on particle monitoring.

"Some operations can generate high levels of product (e.g., powder) particles that, by their nature, do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the one-foot distance and still differentiate background levels of particles from air contaminants. In these instances, air can be sampled in a manner that, to the extent possible, characterizes the true level of extrinsic particle contamination to which the product is exposed. Initial qualification of the area under dynamic conditions without the actual filling function provides some baseline information on the non-product particle generation of the operation."

Further, Section X.A. states:

"Sample timing, frequency, and location should be carefully selected based upon their relationship to the operation performed. …

"It is important that locations posing the most microbiological risk to the product be a key part of the program. It is especially important to monitor the microbiological quality of the critical area to determine whether or not aseptic conditions are maintained during filling and closing activities. Air and surface samples should be taken at the locations where significant activity or product exposure occurs during production. Critical surfaces that come in contact with the sterile product should remain sterile throughout an operation. When identifying critical sites to be sampled, consideration should be given to the points of contamination risk in a process, including factors such as difficulty of setup, length of processing time, and impact of interventions."

European Union

The EU guidance document *Manufacture of Sterile Medicinal Products* (9) provides some site selection guidance:

"18. Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air, and surface sampling (e.g., swabs and contact plates). Sampling methods used in operation should not interfere with zone protection."

United States Pharmacopeia

Similarly, the following guidance in the proposed revision to *USP* chapter <1116> (14) is of general interest:

"Microbiological sampling sites are best selected when human activity during manufacturing operations are considered. Careful observation and mapping of a clean room during the qualification phase can provide information concerning the movement and positioning of personnel within these rooms. Such observation can also yield important information about the most frequently conducted manipulations and interventions.

"Other areas of concern relative to introduction of contamination into clean rooms are at entry points where equipment and materials move from areas of lower classification to those of higher classification. Therefore, areas within and around doors and airlocks should be included in the monitoring scheme."

Specific considerations for sample site selection in the qualification study can be distilled from these different sources. After the minimal number of sites in a room is determined, their most useful location must be determined. This determination should be documented in a written justification and should consider the following:

- Contamination vectors (e.g., handles, control panels, doors, etc.)
- High traffic areas
- Personnel flow
- Material flow
- Waste flow
- Surfaces that are difficult to disinfect
- HVAC returns
- Product risk
- Extent of product exposure
- The type of activity performed near that site
- Interventions and manipulations
- Surfaces that are difficult to disinfect.

SAMPLING FREQUENCY FOR THE QUALIFICATION STUDY

The sampling frequency for the qualification of a specific controlled environment should, in general, follow that of the regulatory recommendations for that level of control. This is a matter of some discussion as the recommendations in Europe (EU Annex 1), ISO, and the US (USP) are not in complete agreement. The qualification study may benefit from more frequent sampling and under more conditions (e.g., sampling under both dynamic and at-rest conditions) than are planned for the routine monitoring program.

The EM qualification protocol should allow for the sampling frequency to be described in detail and justified. As this justification will rely on the selection of sites that show consistently higher colony forming unit (CFU) recovered, there will need to be enough sampling to allow the sites to be identified. It is recommended that the frequency of sampling be accelerated (particularly in lower class-controlled environments) during the qualification study to allow collection of sufficient data from each site to all this determination of meaningful routine sample sites.

DURATION OF QUALIFICATION STUDY

The duration of the qualification study should be determined by the need to acquire sufficient data and the frequency of testing for that sample site. A site tested on a weekly basis may require three months of data (at least 12-14 data points) before enough data are available. The qualification protocol should justify the duration of the study on this basis (and not what best fits the mandated timeline for facility qualification).

SELECTION OF ROUTINE SITES

The qualification study should include sufficient replicates under conditions both "at rest" and "dynamic" to allow identification of sites that provide useful information. It should be clarified that the term "useful information" is not meant to describe "those sites that give the most desireable counts" but rather those sites that either give the highest counts (i.e., serve as the most sensitive measure of the state of control of the room) or were shown to be appropriately placed to herald a problem in the room. The number of sites in a room or zone should similarly be driven by data generated during this study. Both the number and location of sites or each clean room or zone should be justified in the report from this qualification study.

The following section (X.A.1) from the FDA guidance (2) is relevant for consideration:

"All environmental monitoring locations should be described in SOPs with sufficient detail to allow for reproducible sampling of a given location surveyed. Written SOPs should also address elements such as 1. frequency of sampling, 2. when the samples are taken (i.e., during or at the conclusion of operations), 3. duration of sampling, 4. sample size (e.g., surface area, air volume), 5. specific sampling equipment and techniques, 6. alert and action levels, and 7. appropriate response to deviations from alert or action levels."

The generation of relevant data to justify sample sites is taken seriously by FDA. An example of this can be found in an FDA-issued warning letter (15):

"For environmental and personnel monitoring:

- Your active air-sampling unit in one aseptic filling room is not located in a critical area representative of exposure of open containers on the aseptic line. The active air sampling unit was observed positioned behind stoppered vials.

"You have not evaluated the microbiological burden generated from the manual aseptic connection from the source vessel to the XXX filling vessel."

It is not sufficient to pick a few sites around the room and then apply alert and action levels as recommended by some guidance document. The location, control levels, and frequency of sampling must be justified by data and a rational analysis.

ESTABLISHMENT OF ALERT AND ACTION LEVELS

Data from the qualification study should be used to set the initial operating alert and action levels for the routine environmental monitoring program. A good rule of thumb is that the alert level should be at the 95th percentile of observed readings for a given period of time, the action level at the 99th percentile (see the PDA *Technical Report #13* for an excellent discussion of setting alert and action levels). While common industry practice is to uncritically accept regulatory recommendations for predefined clean zones, this practice is discouraged in the US (see reference 2, especially section X.A.2 "Establishing Levels and a Trending Program"). There is controversy over the regulatory guidance for highly controlled areas as well with concern that control levels set so far below the level of quantification for plate count assays (generally 25-30 CFU per plate, compared with regulatory guidance setting alert and action levels as low as single digits). This concern led USP to suggest a frequency distribution approach for these areas (14). An interesting discussion of this approach can be found in Caputo and Huffman (16).

Whichever approach is chosen to the determination of the inital alert and action levels, they should be one of the deliverables from the EM qualification program.

Once these are established there must be a mechanism in place to track and trend them in real time and to investigate excursions. The recent upset over vaccine production featured a failure to investigate repeated excursions that figured prominently in 483 observations (17) and in the associated warning letter (18). A second example of this enforcement stance can be seen in the warning letter from 2009 regarding manufacture control of a parenteral medication (19). Collection of data and then failure to use the data to determine the "state of control" for the facility is clearly at odds with GMP and will be cited.

We would be remiss if the role of the historical database was not discussed in the setting of alert and action levels. This expectation is described in the FDA aseptic processing guidance document (section X.A.2) as:

"Microbiological monitoring levels should be established based on the relationship of the sampled location to the operation. The levels should be based on the need to maintain adequate microbiological control throughout the entire sterile manufacturing facility. One should also consider environmental monitoring data from historical databases, media fills, cleanroom qualification, and sanitization studies, in developing monitoring levels" (2).

That this is a long-standing expectation of FDA is evidenced by an FDA-483 observation from 2001 that reads (in part), "44. The firm's microbial alert and action limits established for the XX to XXX manufacturing areas are not based on historical data taken from the EM Program" (20).

THE "MICROORGANISM CATALOG"

FDA has clearly recommended establishment of a listing of common microorganisms found in the

aseptic manufacturing environment. This expectation is laid out in section X.B. (2), as follows:

"Characterization of recovered microorganisms provides vital information for the environmental monitoring program. Environmental isolates often correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for an investigation. 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. In some cases, environmental trending data have revealed migration of microorganisms into the aseptic processing room from either uncontrolled or lesser controlled areas. Establishing an adequate program for differentiating microorganisms in the lesser-controlled environments, such as Class 100,000 (ISO 8), can often be instrumental in detecting such trends. At minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in these ancillary environments at frequent intervals to establish a valid, current database of contaminants present in the facility during processing (and to demonstrate that cleaning and sanitization procedures continue to be effective)."

The EM qualification study is an excellent opportunity to start this catalog, and to generate information on the effectiveness of the cleaning and sanitization program from a microbiological perspective. Make sure that the EM qualification program includes relevant evaluations.

A NOTE OF CAUTION ON 483S

There is a great deal of interest currently in the topic of "objectionable organisms." And in fact you might even find 483 observations that relate to "objectionable organisms" in an aseptic manufacturing arena (21). A quck check of the current good manufacturing practice (CGMP) guidance (22) shows the following three references to "objectionables":

- **21 CFR 211.84(d)(6).** "Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use."
- **21 CFR 211.113(a).** "Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed."
- **21 CFR 211.165(b).** "There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms."

There are two problems with referencing "objectionables" with aseptic manufacture: the first is that it begs the question of what "permissible" microorganisms might be in the aseptic environment, and secondly that it misrepresents the requirements in 21 CFR 211 which relate to non-sterile finished dosage forms. The point here is that we must be careful of over-interpreting 483 observations as teaching tools. While they can be enlightening, in the end they are only one inspector's opinion on that particular day and faced with a particular set of conditions. Everyone has an off day, and we may never know all the background that went into the 483 observation.

Having said that, the availability of warning letters provides a window into CGMP that can be very useful. Warning letters have been reviewed at the district, frequently have been reviewed at the national level, and can be considered to represent FDA policy.

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ARTICLE ACRONYM LISTING

CFR	Code of Federal Regulations
CFU	Colony Forming Unit
CGMP	Current Good Manufacturing Practice
USP	United States Pharmacopeia
EM	Environmental Monitoring
EU	European Union
FDA	US Food and Drug Administration
GMP	Good Manufacturing Practice
ISO	International Organization for Standardization
PDA	Parenteral Drug Association
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

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