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Fundamentals of an Environmental Monitoring Program Annex 1: Environmental Monitoring of Facilities Manufacturing Low Bioburden Products

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1.0 Introduction

Environmental monitoring (EM) is used to evaluate the effectiveness of contamination controls used in the manufacture of pharmaceutical products. EM programs need to be designed and implemented based on the needs of the specific facility and processes involved. PDA *Technical Report No. 13 (Revised 2014): Fundamentals of an Environmental Monitoring Program* (TR 13) focuses on the environmental requirements for sterile product manufacturing (1). This addendum will provide elements to consider when designing a risk-based EM program to support the manufacture of low bioburden products using low bioburden processes.

Regulations and guidance are readily available for EM requirements supporting sterile, nonsterile, and advanced therapy medicinal products (ATMP) manufacturing processes (2–6). Guidance for EM supporting the manufacture of low bioburden products is very limited. Where it is, the documents often cite resources intended for aseptic processes and then recommend establishing a risk-based approach to designing an EM program to support low bioburden processes (7, 8). This is largely due to the fact that most manufacturing operations where low bioburden control is required combine elements of both sterile and nonsterile processing. However, no specific guidance identifies the elements to which these sterile and nonsterile guidelines should be applied.

This document provides a means of determining the critical aspects, assessing the associated risks, and designing the appropriate EM program for areas where bioburden control of manufacturing processes is required. It can be applied across many types of manufacturing operations used to produce pharmaceutical products including biologics, small molecules, ATMPs, and others. This document should be viewed as technical guidance and is not intended to establish any voluntary or mandatory standards.

1.1 Purpose

This addendum complements the existing PDA TR-13 and is not meant to change or modify its content. The addendum provides recommendations for the development of an environmental control and monitoring program for classified areas and the associated GMP processes used for manufacturing operations requiring bioburden control in the biotechnology and pharmaceutical industries. The content includes a review of regulatory requirements and the development of risk assessments based on the criticality and complexity of processes, as well as industry examples of these risk-based approaches.

Risk assessment tools such as Failure Mode Effects Analysis (FMEA), Hazard Analysis and Critical Control Points (HACCP), or hybrid approaches can be used for these evaluations. This addendum presents a hybrid approach that is intended to help analyze operational risk in order to develop appropriate levels of EM required to monitor operations. When implementing these tools in the design of any EM program, the resulting program should fit the intended purpose. It should not unnecessarily impede the operation or introduce additional risk to the process.

1.2 Scope

TR-13-2 focuses on environmental controls and monitoring programs for classified areas where manufacturing processes are required to ensure a low bioburden level of the material being produced. Although a comprehensive EM program addresses both viable and nonviable aspects of the facility, this addendum concentrates primarily on the viable aspects as these parameters have a greater potential to impact product and process quality related to bioburden. This document is not intended to address EM programs for traditional aseptic or sterile manufacturing, which are covered in TR-13, nor does it address traditional nonsterile dosage forms.

2.0 Glossary

The terms and definitions contained in this glossary are specific to the content of this technical report. Although some of these definitions will match those terms as defined in PDA TR-13 and/or other PDA technical reports (noted for each definition), others have been intentionally altered or developed to address the specific content and intent of this addendum and the attributes unique to facilities used to manufacture low bioburden products.

Adverse Trend

EM data (including microbial and particulate) that is consistently increasing in one direction. Adverse trends are system- or area-specific, should be evaluated on a case-by-case basis, and should consider factors such as contamination recovery rate, excursion rate, and individual results.

Airborne Particulate Count (Total Particulate Count)

The total number of particles of a specific size per unit volume of air (*1*).

Airborne Viable Particulate Count (Total Airborne Microbial Count)

The recovered number of colony-forming units per unit volume of air (*1*).

Bioburden

The total number of microorganisms per unit of material prior to sterilization (*1*).

Bioburden Reduction Step

A process utilizing a method that has been demonstrated to lower the bioburden level in a given sample.

Processing Area

The area in which processing occurs, with the appropriate environmental (e.g., gowning, cleaning/disinfection, training) and engineering (e.g., HVAC, facility design, material/personnel flows, differential pressures) controls in place to reduce the risk of microbial or particulate contamination.

Classified Area

An area typically classified according to ISO standards.

Cleaning

Chemical or physical means used to remove soil and/or microorganisms from surfaces (*1*).

Cleanroom

A room designed, maintained, and controlled to prevent particle and microbiological contamination of a drug product. A cleanroom is assigned and reproducibly meets an appropriate air cleanliness classification (*1*).

Critical Operations Monitoring

Monitoring performed throughout the duration of a process using methods designed to monitor the environmental quality of the process and to capture all interventions, transient events, and any system deterioration. The design and degree of the monitoring performed should be based on the risk to the process or product being monitored (e.g., closed vs. open systems, use of biological safety cabinet, unidirectional flow hood, or other containment systems).

Disinfection

The chemical or physical inactivation of a bioburden on inanimate surfaces. Typically, this requires a minimum three-log (3-log) reduction of vegetative microorganisms and a two-log (2-log) reduction of bacterial spores to be achieved in validation (*9*).

Environmental Control Parameters

Conditions and corresponding measurements as associated with facilities and equipment used in the control of a manufacturing area that may impact the identity, strength, quality, or purity of a product. Among such parameters are airflow rates and patterns, pressure differentials, materials and personnel flow, temperature, and relative humidity, as well as nonviable and viable particulates (*1*).

Environmental Monitoring

Dynamic (Operational) Monitoring

The condition where production operations are actively occurring as defined by the individual firm. Personnel may or may not be present at this time.

Routine Monitoring – Frequency-Based/ Predetermined/Nonbatch-related

Monitoring of a facility at a predetermined frequency, as defined by an approved procedure, to provide an overall assessment of the state of control of the facility.

Batch-related – In-Process or During-Process Monitoring

Monitoring performed during predetermined steps of the production process, as defined by

an approved batch record and/or approved procedures or protocols. This can be performed either in the presence or absence of the product.

Continuous

Batch-related monitoring, as defined by an approved batch record, to ensure that a state of control is maintained during processing and that any aberrant events are detected. Frequency of monitoring is determined by a risk assessment.

Closed System

A process system with equipment designed and operated such that the product is not exposed to the room environment at any point in the process. For most biological operations, the system or fluid pathway must remain free of extraneous contamination. Examples include, but are not limited to, a cell culture bioreactor or cell therapy bag assembly.

Functionally Closed System

A process system that may be routinely opened (e.g., to install a filter or make a connection), but is returned to a closed state during processing. In biological operations, for example, a functionally closed system is often employed when a low level of extraneous contamination may be permissible (such as purification skids used in cell-culture operations).

Open System

A process system that exposes the product to the room environment. In this type of system, the room environment is controlled to minimize the risk of extraneous product contamination. Examples include, but are not limited to, processing steps, such as media preparation or supplementation, or inoculum preparation.

Low Bioburden Product

Product manufactured within a controlled and monitored environment in which the final drug product or process intermediate, as applicable, requires bioburden control, but is not required to be sterile (e.g., biological drug substance produced by mammalian cell culture).

Nonviable

A term used in reference to particulates that are not capable of living, growing, or developing and functioning successfully (“unable to divide” or “not capable of reproducing”) (*1*).

Process Control Parameters

Conditions and corresponding measurements associated with the manufacturing process that may affect the identity, strength, quality, potency, and purity of a product. Examples of parameters of concern include bioburden, process rate, weight, volume, temperature, and pressure (*1*).

Risk Analysis

The estimation of the risk associated with the identified hazards (*1*). The following are commonly used tools that can be used to perform risk analysis (*10, 11*).

- FMEA – Failure Mode Effects Analysis
- HACCP – Hazard Analysis and Critical Control Points

Sanitization

Reduction of microbial contaminants to safe levels as judged by public health requirements for the specific country (*1*).

Sterilization

Validated process used to render product free from viable microorganisms (*1*).

3.0 Low Bioburden Products and Processes versus Traditional Sterile and Nonsterile Products and Processes

Sterile drug manufacturing is designed to produce a final sterile product through sterilizing process steps and subsequent manufacturing processes and controls. In contrast, manufacturing processes that require bioburden control are designed to limit the introduction of microorganisms into the process.

Based on the physical properties of the materials being manufactured or, in some cases, regulatory requirements, mitigative steps designed as bioburden control mechanisms, such as the use of antibiotics, preservatives, solvents, low or high pH, sterile filtration and heat, may not be possible. In many cases, the process streams for these processes support the proliferation of any microorganisms present, often requiring control mechanisms during manufacturing operations to prevent or reduce microbial growth. Specific process steps taken if microorganisms are present, such as purification and ultrafiltration, often reduce bioburden levels although, in general, they are not specifically designed to do so. Due to the inherent susceptibility of the manufacturing process in these cases, an added focus must be placed on minimizing the ingress and proliferation of microorganisms and their metabolites that can affect product quality, safety, and stability.

Control of the process and processing environment is a major component of reducing the potential for product stream bioburden. Elements of control include the design of the facilities, utilities, and processing equipment (closed/open), as well as personnel and procedural measures. EM is used as a tool to measure the efficacy of these controls in a manufacturing facility.

The use of a local unidirectional airflow hood (UDF) for specific open manufacturing steps is a common practice where bioburden control is desired. These units are designed to produce a localized EU Grade A/ISO 5 environment. In this application, the units are not being used to provide protection for a sterile manufacturing-related operation but rather a nonsterile manufacturing operation as part of a bioburden control program. In such cases, based on their use and a thorough risk assessment, the placement of the UDF in Grade C environments is often acceptable. The level of gowning associated with their use should also be evaluated and requirements set based on the operation being performed and the level of control required.

The implementation and utilization of a quality risk management program provides scientific rationale for the manufacturing controls and EM program developed for these types of manufacturing processes (10, 12). Quality risk management is predicated on understanding the specific risk factors of the environment and the process used to manufacture the product.

Once the manufacturing process and the potential contributors to the level of bioburden (e.g., environmental factors, facility and/or equipment design) have been identified and characterized, a thorough and well-documented risk assessment should be conducted to identify the points of potential microbial ingress. The manufacturer may incorporate specific components of a regulation or guidance document into the risk assessment as it applies to a particular process or step; this addition may vary depending on the intent of the risk assessment. Upon completion of the risk assessment, supporting programs can be developed to mitigate the risks identified. While all risks may need to be monitored for a period of time, any risk that cannot be mitigated should continue to be monitored.

When a manufacturing area has been classified in line with a regulatory or industry classification scheme, the EM program is often expected to meet the applicable requirements regardless of how the area is used. For example, if an area is classified as EU Grade A, the EM program and other supporting programs (e.g., gowning, cleaning, and sanitization) must reflect the requirements contained in the corresponding regulatory document. In many cases, these guidance documents are designed specifically to address the manufacture of sterile medicinal products, not nonsterile manufacturing operations designed to control but not eliminate the bioburden load present.

Consider the scenario of an aseptic transfer of materials in the UDF to minimize the introduction of additional bioburden. This is a nonsterile manufacturing step. A risk assessment may demonstrate

that only certain aspects of the EU Grade A classification requirements are pertinent to the process. Monitoring performed during the manufacturing process should be aligned with the risk assessment and reflect the monitoring needed to support the process. For example, in a situation where the concern is focused on the addition of bioburden (microorganisms) to the manufacturing operation the risk assessment may conclude that the need to perform total particulate monitoring during the manufacturing operation should be reduced or eliminated. In that case, the total particulate monitoring would still be performed at a set frequency to ensure the UDF is continuing to operate appropriately but not during the actual manufacturing step. Similarly, the surrounding room environment should be determined based on the assessment of the manufacturing process and the control needed. For traditional nonsterile operations, for example, the EU Grade C requirements may be more appropriate based on the operation being performed. An alternative could be to classify the area according to ISO 14644 (e.g., ISO 5, 7, 8), as appropriate for the specific process and area (13). This approach must be documented in the site risk assessment. The supporting EM and other control programs should be designed to monitor the room or facility to the levels needed for the specific processes being performed.

An additional example where the use of a risk assessment may be of value is in the use of a UDF where preparation of the inoculum used for seeding of a bioreactor is being performed. In this example, during mammalian cell culture preparation, a designated room is used to prepare the inoculum for seeding the bioreactor. In the scale-up process, aseptic techniques are used to transfer the contents of a thawed cryovial to a sterile T-flask (or similar container). This activity is performed in a UDF to protect the process from the introduction of microorganisms, as microbial contamination would be the largest concern. The UDF is classified as EU Grade A because an aseptic technique must be performed in order to exclude the introduction of extraneous contaminants. This process takes less than two minutes to execute. Based on the air quality criteria described in *EudraLex, Volume 4, Annex 1: Manufacture of Sterile Medicinal Products*, both continuous nonviable particulate counts and active airborne viable monitoring would be required during the manufacturing process based on the UDF classification as Grade A (2). This would present some challenges if applied. Annex 1 has generally been interpreted to expect a sample size of one cubic meter of air for both types of monitoring, which takes between 5 and 35 minutes to collect depending on the type of equipment used. Considering that the scale-up process takes only two minutes to execute, the requirements for the sample volumes would be difficult to satisfy; however, if the process only takes two minutes, the monitoring would encompass the entire process and meet the intent of the regulation. In this case, a risk assessment should be completed to evaluate the process and monitoring requirements. If the primary concern is the introduction of viable organisms, the risk assessment may conclude that performing in-process total particulate counts not only provides little value but increases the risk to the operation based on the distraction it creates for the operator (assuming the use of manually operated particulate counters) and should not be conducted during the process while viable monitoring is of greater importance. As presented in the aseptic transfer example above, total particulate monitoring would be expected at an established frequency to ensure the biological safety cabinet is performing properly.

A number of well-known risk assessment tools are available, such as flow charts, check sheets, FMEA, and HACCP. In order to perform a successful risk assessment, the following must be included to ensure that all aspects of the process are appropriately addressed:

- Knowledgeable representation from the functional areas involved in the process (e.g., validation, manufacturing, quality, facilities, microbiology)
- Defined risk questions
- Detailed process map
- Facility map, including personnel and material movements
- Production batch records and standard operating procedures