1 Purpose

The purpose of this Guideline is to provide requirements for environmental monitoring. This guideline provides recommendations on how to achieve compliance with the requirements. This guideline will aid in assuring that the commercial and investigational medicinal products manufactured will meet the appropriate regulatory and company requirements.

2 Scope and Applicability

The guideline provides the requirements for non-viable and microbiological environmental monitoring. This Guideline is applicable to all Operations and Research and Development (R&D) sites, functions and departments undertaking work, or providing support services, required to meet Good Manufacturing Practice (GMP) or, in the absence of a GMP standard, International Organization for Standardization (ISO) standards.

Where required: This Guideline is also applicable to service providers carrying out work on behalf of sponsor Operations and Research and Development (R&D) when those activities are covered under GMP and/or ISO standards. It is recognized that it may not be required to achieve an equivalent level of validation or qualification and documentation at all phases of the product development process and a sliding scale towards GMP should be applied. Nonetheless, the extent of validation or qualification performed shall be sufficient to ensure all research and development products are fit for their intended purpose. Risk management should be used to maximize potential opportunities, manage and control uncertainties and minimize potential threats, particularly risks to the patient. Risk management, when based on scientific and historical data, provides a means to focus resources on those GMP areas of greatest need.

3 Definitions

3.1 Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

3.2 Sliding Scale

An approach to different levels of approval depending upon the quality class. Ensures efficiency and flexibility where appropriate to the Phase of development within the R&D environment. Some examples where sliding scale is used are Masters, Master Batch Records and Releases.

3.3 Alert Level

processing.

4 Responsibilities

Each manufacturing site and R&D function is responsible for compliance with appropriate guideline like this.

5 Guideline

5.1 General Requirements

An environmental monitoring program provides information on the non-viable particulate and microbiological quality of the environment being monitored. Such data provides an insight into the effectiveness of the control programs (e.g. cleaning, housekeeping, gowning) that are in place.

Classified environments (sometimes referred to as controlled environments) must be monitored using the appropriate regulatory, guideline and industry practices. Areas defined as classified environments must be monitored as appropriate for that environment. Monitoring programs must be designed based on the processing requirements of the area and the risk assessment of the area.

In non-classified areas, a level of microbiological monitoring is necessary as part of an ongoing risk assessment to maintain awareness of the microbiological environmental conditions during manufacturing activities.

The monitoring programs must be performed and analyzed by appropriately trained personnel.

A program must be established for sampling equipment and instrument calibration.

Samples should be collected from areas in which product or components are exposed to the environment, such as critical processing zones and filling lines, where such sampling does not interfere with the process being monitored or increase the risk of product contamination.

Intensified environmental monitoring should be performed during the initial area start-up and following periods of extended shut-down or considered after area, system or equipment modifications or if significant atypical results or trends are observed in the data. Factors that may have an impact on the integrity of the environment must be evaluated and controlled (e.g. Sterile-filtered gases that come in contact with product, primary containers or direct product contact surfaces and sanitizing agents). The frequency should be based on assessment of risk to product failure.

Reports must be periodically issued to management describing the results of the environmental monitoring program including any recommended corrective actions. Statistical analysis of the data and establishing the historical profile or trend of the data allows for the detection of deviations away from the normal operational state and should be performed on a routine basis.

historical databases that will be used to establish the normal operating ranges for the area. The routine environmental monitoring program provides a continuing input of data and, through trend analysis, aids in assuring that the area continues to perform in an acceptable manner within the established normal operating ranges. Environmental monitoring data should be used to establish alert and action limits if not specified by regulatory guidelines.

5.2.2.1 Sampling Locations and Frequencies

(a) Sampling locations and frequencies shall be based on the appropriate rationale (product risk assessment, mapping studies, etc.) and applicable regulatory guidelines.

(b) Critical surfaces in the ISO 5 zone (Grade A) that are accessible during manufacturing should be monitored with every batch in a manner that will not increase the risk of product contamination, typically at the conclusion of the aseptic process. Typically representative critical surfaces (filling needles, insides stopper bowls, and stopper chutes) are monitored on a per batch basis.

(c) Monitoring for other micro-organisms, where appropriate (e.g. anaerobic micro-organisms) should be performed on an as needed basis and should be based on historical data and the risk to the product involved.

5.2.2.2 Sampling Types

(a) Non-Viable Particulates

Non-viable particulate monitoring should be used to determine the general particulate quality of the area being monitored according to the classification of the area. It should be employed for areas or equipment where product quality may be affected by the environmental conditions or particulate matter.

(b) Microbiological

(i) Air sampling should employ an acceptable volumetric method such as Reuter Centrifugal Sampler (RCS), Slit-To-Agar (STA) or other methods as appropriate for monitoring viable particles within the specific environment. Settle plates are another useful way of monitoring air quality.

(ii) Surface sampling should employ methods such as contact plates or swabs as appropriate for determining the microbial bioburden of surface areas within the specific environment.

The use of neutralizing agents to negate the inhibitory effect of sanitizing agents/antibiotics may be required.

(iii) The monitoring program, including culture media selection and incubation conditions, should be designed to provide for detection of bacteria and yeast and molds.

monitoring data.

5.3 Environmental Monitoring Program for Non-Classified Areas

A level of microbiological monitoring is necessary as part of an ongoing risk assessment to maintain awareness of the microbiological environmental conditions during manufacturing activities. The frequency and extent of the monitoring program should be made using professional judgment, development experience, historical knowledge of environmental conditions and the nature of the raw materials, production conditions (i.e. elevated processing temperatures, environmental exposure, handling, etc.) and the physical form of the drug product. The manufacture of oral solid dosage forms, in particular, is generally a low risk operation in terms of the potential for contamination via the environment.

All open product manufacturing requires that an environmental monitoring program be established. Environmental monitoring should be conducted at the final isolation step for all active pharmaceutical ingredient (API) manufacturing.

There are no cGMP requirements to classify these areas. Non-viable particulate monitoring is not required for any unclassified areas.

An effective Environmental Monitoring Program for non-classified areas should assess the microbiological levels of the environment, the effectiveness of cleaning and sanitization procedures, and product risk, where and when appropriate. Monitoring should be routinely conducted (e.g., Weekly, monthly, or quarterly depending on the product.). Monitoring locations should be selected on the basis of product contamination risk assessment.

Alert and action levels should be established on the basis of system capabilities and from historical data and should be evaluated on an ongoing basis.

An environmental monitoring program may be established and coordinated using a pre-approved protocol. The purpose of the protocol is to establish a base line for the indigenous flora in the manufacturing operation. The initial monitoring frequency should be frequent and for a defined duration, for example, 1X/wk for a period of 12 weeks, after which time preliminary alert and action levels may be established. The protocol should state that preliminary alert and action levels should be established at the conclusion of the first 12 weekly sampling.

Routine environmental monitoring should provide an information base of sufficient size and detail to make decisions regarding the operational status of the area and to ensure that the appropriate level of control is being maintained.

6 Appendices

