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

5.2 Environmental Monitoring Program for Classified Areas

An environmental monitoring program must be established for all classified areas. The program provides meaningful information on the quality of the aseptic environment (e.g. when a batch is being manufactured) as well as environmental trends of ancillary areas.

All environmental conditions for clean areas must be classified and maintained in accordance with requirements in ISO 14644-1, EU GMP Annex 1 and FDA 21 CFR and Guidance for Industry "Sterile Drug Products Produced By Aseptic Processing", September 2004 as appropriate.

Action levels for particles and microbiological organisms must be established in accordance with Appendix A - B.

An effective Environmental Monitoring Program should assess the microbiological and particulate levels of the environment, the effectiveness of cleaning and sanitization procedures, monitor gowning and hand sanitization practices, and assess product risk, where and when appropriate. The monitoring program should cover all production shifts and include air, walls, floors, and equipment surfaces including critical surfaces that come in contact with product, containers, and closures. 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.

5.2.1 Procedures

5.2.1.1 Methods or Standard Operating Procedures (SOPs) must be established, documented and maintained and should outline the following:

(a) Sampling Locations
(b) Sampling Type
(c) Frequency of Sampling
(d) Duration of Sampling
(e) Sample Size
(f) Sample Incubation
(g) Alert and Action Levels and Adverse Trend
(h) Criteria for Establishing Corrective Actions
(i) Criteria for Maintenance of Database and Data Trending
(j) Criteria for Performing Microbiological Identification

5.2.2 Sampling for Non-Viable and Viable Particulates

Environmental monitoring must occur primarily during routine operations and/or immediately following operations but prior to cleaning/sanitizing.

Mapping studies should be performed during periods of inactivity (static) and during periods of simulated or actual production (dynamic). The data generated by the mapping studies are intended to provide the initial baseline for the

6 Appendices

Appendix A. Comparison table particles ISO 14644-1, EU GMP Annex 1 and FDA.

EN ISO 14644-1						EU GMP Annex 1				FDA	
At rest			In operation			Grade	At rest		In operation		Description	In operation
Maximum permitted number of **particles/m^3** equal to or above			Maximum permitted number of **particles/m^3** equal to or above				Maximum permitted number of **particles/m^3(ft^3)** equal to or above		Maximum permitted number of **particles/m^3(ft^3)** equal to or above			Maximum permitted number of **particles/ ft^3 (m^3)** equal to or above
0,5 µm	5 µm	ISO Class	0,5 µm	5 µm	ISO Class		0,5 µm	5 µm	0,5 µm	5 µm		0,5 µm
3,520	29	5	3,520	29	5	A	3,500 (100)	1	3,500 (100)	1	Critical	100 (3,520)
3,520	29	5	352,000	2,930	7	B	3,500 (100)	1	350,000 (10,000)	2,000 (57)	Supporting Clean Area	10.000 (352,000)
352,000	2,930	7	3,520,000	29,300	8	C	350.000 (10.000)	2.000 (57)	3,500,000 (100,000)	20,000 (570)	Controlled	100.000 (3,520,000)
3,520,000	29,300	8	-	-	-	D	3,500,000 (100,000)	20,000 (570)	-	-	-	-
35,200,000	293,000	9	-	-	-	-	-	-	-	-	-	-

* - = not defined

Note: Additional reference for monitoring is USP Chapter 1116.

