1 Purpose

The purpose of this Guideline is to provide guidance for the microbiological testing of non-sterile products. This guideline should aid in assuring that the products manufactured at each of the company sites as well as by a contract manufacturer should meet the appropriate regulatory and company requirements and that there is a standardized, company-wide approach to the basic concept of microbiological quality control of non-sterile products.

The purpose of this guideline is also to outline the requirements for the analysis of non-sterile drug products as per the harmonized pharmacopoeia (Ph Eur, General Text 5.1.4; USP, General Information Chapter <1111>; JP, Chapter to be determined) General Text/Chapters on the microbiological quality of non-sterile pharmaceutical preparations. Herbal medicinal products are outside the scope of this guideline.

Note: These General Text/Chapters are published for information and guidance only; they are not a mandatory part of the pharmacopoeia.

2 Scope and Applicability

This guideline applies specifically to microbiological testing of non-sterile products, as it can be carried out at any site worldwide, as well as at third party testing labs.

In addition to the guideline, the following items should also be in place:

Standard Operating Procedures (SOPs)

SOPs should be developed by the appropriate operational units to provide clear direction for the execution of the testing procedures, material preparation, data analysis, and the development of the documentation referred to in this guideline.

Validation Protocols

Validation protocols should be generated by the appropriate operational units to verify and document that the methods and equipment used to perform microbiological testing can reliably and consistently detect micro-organisms that may be present in units being tested. These protocols, the data generated, and the associated validation reports should provide documentation of the acceptability of these methods and equipment for their intended use.

3 Definitions

3.1 Ph Eur

Ph Eur is the European Pharmacopoeia.

- Analysts or technicians must have appropriate training and documentation of that training should be on file and available for review.

- Validated test methods and or procedures must be approved, current and available for use by the analysts or technicians.

- Compendial test methods must demonstrate that they are suitable for their intended use.

- Non-compendial test methods must be validated and demonstrate that they are appropriate for their intended use.

- Samples must be taken in accordance with approved sampling procedures.

- All materials, controls and systems sourced externally must be covered by a suitable vendor assurance program.

5.1.2 Methods and Procedures

The following additional items or issues should also be addressed in approved methods and/or procedures:

- Sample Collection, Transport and Storage.
- Positive and Negative Controls (Growth Promotion) of media for cultivation.
- Incubation of Test Samples.
- Preparation, Testing, Approval and Storage of Test Media Reagents.
- Policy on identification of organisms.
- Gowning.
- Out of Specification (OOS) Result Investigation and Response.
- Test Failure Investigation and Response.
- Decontamination and Disposal of Testing Waste.
- Interpretation of Test Results.
- Retesting.
- Trending of Test Data.
- Change Control.
- Labeling media.
- Recording, storing and archiving data.

5.1.3 Validation

- Test methods and procedures, and equipment must be validated to assure the reliability of the data generated by the testing program.

- All proposed changes to validated systems, processes, equipment or methods must be reviewed for regulatory impact and approved by appropriate management prior to the change. Any changes that impact the status of a validated system process, equipment or methods may require revalidation of that system, process, equipment or method.

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Moulds Count (cfu/g or cfu/mL)	Specified Microorganism(s)
use			(1 g or 1 mL)
Rectal use	10^3	10^2	—
Oromucosal use Gingival use Cutaneous use Nasal use Auricular use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Vaginal use	10^2	10^1	Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
			Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Candida albicans* (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1 patch)
			Absence of *Pseudomonas aeruginosa* (1 patch)
Inhalation use (special requirements apply to liquid preparations for nebulization)	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL)
			Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
			Absence of bile-tolerant Gram-negative bacteria (1 g or 1 mL)

Note: When an acceptance criterion for microbiological quality is prescribed, it is interpreted as follows:

- 10^1 cfu: maximum acceptable count = 20;
- 10^2 cfu: maximum acceptable count = 200;
- 10^3 cfu: maximum acceptable count = 2000; and so forth.

Note: Table I includes a list of specified microorganisms for which acceptance criteria are set. The list is not necessarily exhaustive, and for a given preparation it may be necessary to test for other microorganisms depending on the nature of the starting materials and the manufacturing process.

*Note: Table I was copied directly from the USP General Information Chapter <1111>. This chapter is provided for guidance, but is not mandatory. The same information is also presented in the EP as Table 5.1.4.1.

