

<1111> MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE

The presence of certain microorganisms in nonsterile preparations may have the potential to reduce or even inactivate the therapeutic activity of the product and has a potential to adversely affect the health of the patient. Manufacturers have therefore to ensure a low bioburden of finished dosage forms by implementing current guidelines on Good Manufacturing Practice during the manufacture, storage, and distribution of pharmaceutical preparations.

Microbial examination of nonsterile products is performed according to the methods given in the texts on *Microbial Enumeration Tests* (61) and *Tests for Specified Microorganisms* (62). Acceptance criteria for nonsterile pharmaceutical products based upon the total aerobic microbial count (TAMC) and the total combined yeasts and molds count (TYMC) are given in *Tables 1* and *2*. Acceptance criteria are based on individual results or on the average of replicate counts when replicate counts are performed (e.g., direct plating methods).

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.

Table 1. Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms

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

Table 2. Acceptance Criteria for Microbiological Quality of Nonsterile Substances for Pharmaceutical Use

	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)
Substances for pharmaceutical use	10^3	10^2

Table 1 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.

If it has been shown that none of the prescribed tests will allow valid enumeration of microorganisms at the level prescribed, a validated method with a limit of detection as close as possible to the indicated acceptance criterion is used.

In addition to the microorganisms listed in *Table 1*, the significance of other microorganisms recovered should be evaluated in terms of the following:

- The use of the product: hazard varies according to the route of administration (eye, nose, respiratory tract).
- The nature of the product: does the product support growth? does it have adequate antimicrobial preservation?
- The method of application.
- The intended recipient: risk may differ for neonates, infants, the debilitated.
- Use of immunosuppressive agents, corticosteroids.
- The presence of disease, wounds, organ damage.

Where warranted, a risk-based assessment of the relevant factors is conducted by personnel with specialized training in microbiology and in the interpretation of microbiological data. For raw materials, the assessment takes account of the processing to which the product is subjected, the current technology of testing, and the availability of materials of the desired quality.

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