Microbiological quality of non-sterile products: recommended acceptance criteria for pharmaceutical preparations

This text is based on the internationally-harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). Some editorial modifications have been made in order to be in line with the style used in The International Pharmacopoeia *. It should be noted, however, that acceptance criteria for oral dosage forms, other than herbal medicines, containing raw material of natural origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 103 CFU/g or CFU/mL (see Table 1), were exempted from the PDG harmonization.*

The text is provided to give information and guidance and is not regarded as an analytical requirement. The acceptance criteria do not apply to herbal medicines (i.e. herbs, herbal materials, herbal preparations and finished herbal products). For such preparations reference should be made to Quality control methods for herbal materials: Determination of microorganisms (World Health Organization, 2011), and WHO guideline on assessing quality of herbal medicines with reference to contaminants and residues (Determination of microbial contaminants; Annex 5 – Determination of microorganism) (World Health Organization, 2007).

The presence of certain microorganisms in non-sterile 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 (GMP) during the manufacture, storage and distribution of pharmaceutical preparations.

Microbial examination of non-sterile products is performed according to the methods given in the texts on 3.3.1 Microbial enumeration tests and 3.3.2 Tests for specified microorganisms. Acceptance criteria for non-sterile pharmaceutical products based upon the total aerobic microbial count (TAMC) and the total combined yeasts/moulds count (TYMC) are given in Table 1. Acceptance criteria are based on individual results or on the average of replicate counts when replicate counts are performed (e.g. direct plating methods).

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.

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. Recommended acceptance criteria for microbiological quality of non-sterile dosage forms

Route of administration	Total aerobic microbial count (CFU/g or CFU/ mL)	Total combined yeasts/moulds count (CFU/g or CFU/ mL)	Specified microorganism
Non-aqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli* (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of *Escherichia coli* (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 (1g or 1 mL)
Oral dosage forms, other than herbal medicines, containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the relevant national or regional authority accepts TAMC of the raw material exceeding 10^3 CFU/g or CFU/mL.	10^4	10^2	Not more than 10^2 CFU of bile-tolerant gram-negative bacteria (1 g or 1 mL) Absence of *Salmonella* (10 g or 10 mL) Absence of *Escherichia coli* (1 g or 1 mL) Absence of *Staphylococcus aureus* (1 g or 1 mL)

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 use of the product: hazard varies according to the route of administration (eye, nose, respiratory tract);

-the nature of the product: its ability to support growth, the presence of adequate antimicrobial preservation;

-the method of application;

-the intended recipient – risk may differ for neonates, infants, the debilitated;

-use of immunosuppressive agents, corticosteroids;

-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 the interpretation of microbiological data. For raw materials the assessment takes account of processing to which the product is subjected, the current technology of testing and the availability of materials of the desired quality.