

ranges.<sup>3</sup> Acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. Acceptance criteria should be consistent with historical data, and there is an expectation that acceptable batches (e.g., no significant differences in in vivo performance, composition, or manufacturing procedure) will have results that fall within the acceptance criteria.

<1101> MEDICINE DROPPER

The Pharmacopeial medicine dropper consists of a tube made of glass or other suitable transparent material that generally is fitted with a collapsible bulb and, while varying in capacity, is constricted at the delivery end to a round opening having an external diameter of about 3 mm. The dropper, when held vertically, delivers water in drops each of which weighs between 45 mg and 55 mg.

In using a medicine dropper, one should keep in mind that most medicinal liquids do not have the same surface tension and viscosity characteristics as water, and therefore the size of drops will vary from one preparation to another.

Where accuracy of dosage is important, a dropper that has been calibrated specifically for the preparation with which it is supplied should be employed. The volume error incurred in measuring any liquid by means of a calibrated dropper should not exceed 15% under normal use conditions.

<sup>3</sup>See the FDA Guidance for Industry: Dissolution Testing of Immediate-Release Solid Oral Dosage Forms, August 1997; <http://www.fda.gov/cder/guidance/1713bp1.pdf>, accessed 6/22/2005.

<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<sup>1</sup> cfu: maximum acceptable count = 20;
- 10<sup>2</sup> cfu: maximum acceptable count = 200;
- 10<sup>3</sup> 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 <sup>3</sup>	10 <sup>2</sup>	Absence of <i>Escherichia coli</i> (1 g or 1 mL)
Aqueous preparations for oral use	10 <sup>2</sup>	10 <sup>1</sup>	Absence of <i>Escherichia coli</i> (1 g or 1 mL)
Rectal use	10 <sup>3</sup>	10 <sup>2</sup>	—
Oromucosal use	10 <sup>2</sup>	10 <sup>1</sup>	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 <sup>2</sup>	10 <sup>1</sup>	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 <sup>2</sup>	10 <sup>1</sup>	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 <sup>2</sup>	10 <sup>1</sup>	Absence of <i>Staphylococcus aureus</i> (1 g or 1 mL) Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 mL)

**Table 1. Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms** (Continued)

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)
Auricular use	10 <sup>2</sup>	10 <sup>1</sup>	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 <sup>2</sup>	10 <sup>1</sup>	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 <sup>2</sup>	10 <sup>1</sup>	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 <sup>2</sup>	10 <sup>1</sup>	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 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.

**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 <sup>3</sup>	10 <sup>2</sup>

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.

## <1112> APPLICATION OF WATER ACTIVITY DETERMINATION TO NONSTERILE PHARMACEUTICAL PRODUCTS

The determination of the water activity of nonsterile pharmaceutical dosage forms aids in the decisions relating to the following:

- optimizing product formulations to improve antimicrobial effectiveness of preservative systems,
- reducing the degradation of active pharmaceutical ingredients within product formulations susceptible to chemical hydrolysis,
- reducing the susceptibility of formulations (especially liquids, ointments, lotions, and creams) to microbial contamination, and
- providing a tool for the rationale for reducing the frequency of microbial limit testing and screening for objectionable microorganisms for product release and stability testing using methods contained in the general test chapter *Microbial Enumeration Tests* <61> and *Tests for Specified Microorganisms* <62>.

Reduced water activity ( $a_w$ ) will greatly assist in the prevention of microbial proliferation in pharmaceutical products; and the formulation, manufacturing steps, and testing of nonsterile dosage forms should reflect this parameter.

Low water activity has traditionally been used to control microbial deterioration of foodstuffs. Examples where the available moisture is reduced are dried fruit, syrups, and pickled meats and vegetables. Low water activities make these materials self-preserved. Low water activity will also prevent microbial growth within pharmaceutical drug products. Other product attributes, for example, low or high pH, absence of nutrients, presence of surfactants, and addition of antimicrobial agents, as well as low water activity, help to prevent microbial growth. However, it should be noted that more resistant microorganisms, including spore-forming *Clostridium* spp., *Bacillus* spp., *Salmonella* spp. and filamentous fungi, although they may not proliferate in a drug product with a low water activity, may persist within the product.

When formulating an aqueous oral or topical dosage form, candidate formulations should be evaluated for water activity so that the drug product may be self-preserving, if possible. For example, small changes in the concentration of sodium chloride, sucrose, alcohol, propylene glycol, or glycerin in a formulation may result in the creation of a drug