USP 40 General Requirements for Tests and Assays

(Microbiological Tests)

ลัดดา พูลสวัสดิ์

สำนักยาและวัตถุเสพติด

<1> INJECTIONS AND IMPLANTED DRUG PRODUCTS (PARENTERALS)-PRODUCT QUALILTY TESTS

- Universal Tests
  - Sterility
    - The sterility of all drug products intended for parenteral administration should be **confirmed** by the use of methods described in *Sterility Tests* <71> or by an approved alternative method.
  - Bacterial endotoxins
    - All articles intended for parenteral administration should be **prepared** in a manner designed to limit bacterial endotoxins as defined in *Bacterial Endotoxins Test* <85> or *Pyrogen Test* <151>

<2> ORAL DRUG PRODUCTS-PRODUCT QUALITY TESTS

- Specific Tests for liquid
  - Microbial content
    - 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. Some liquid oral products can be subject to extreme microbiological control, and others require none. The needed microbial specification for a given liquid oral product depends on its formulation and use and is indicated in the monograph.

<3> TOPICAL AND TRANSDERMAL DRUG PRODUCTS-PRODUCT QUALITY TESTS

- Specific Tests
  - Microbial limit
    - Microbial examination of nonsterile products is performed according to the method given in *Microbial Enumeration Tests* <61> and *Tests for Specified Microorganisms* <62>, unless the formulation itself is demonstrated to have antimicrobial properties. Acceptance criteria for nonsterile pharmaceutical products based on total aerobic microbial count and total combined yeasts and moulds count are given in *Microbiological Examination of Nonsterile products: Acceptace Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use* <1111>

<3> TOPICAL AND TRANSDERMAL DRUG PRODUCTS-PRODUCT QUALITY TESTS

– Sterility
  - Depending on the use of the dosage form (e.g., products that will be applied to open wounds or burned areas), sterility of the product should be demonstrated as appropriate (see *Sterility Tests* <71>)

<4> MUCOSAL DRUG PRODUCTS - PRODUCT QUALITY TESTS

- Specific Mucosal Route and Product-Specific Tests
  - Specific quality tests across routes of administration

<4> MUCOSAL DRUG PRODUCTS - PRODUCT QUALITY TESTS

- Otic route
  - Inner ear, eardrum damaged
    - Sterility
  - Others
    - Microbial Limit

<4> MUCOSAL DRUG PRODUCTS - PRODUCT QUALITY TESTS

- Ophthalmic route:
  - Ophthalmic dosage forms
    - Sterility Tests
  - Irrigations and inserts
    - Sterility Tests
    - Bacterial Endotoxins Test

<4> MUCOSAL DRUG PRODUCTS - PRODUCT QUALITY TESTS

- Nasal route
  - Aerosol <5>
    - Microbial Limit
  - Gels <3>
    - Microbial Limit
  - Ointments <3>
    - Microbial Limit
  - Sprays <5>
    - Microbial Limit
    - Sterility (pre metered)
  - Solutions <5>
    - Microbial Limit

<4> MUCOSAL DRUG PRODUCTS - PRODUCT QUALITY TESTS

- Oropharyngeal route
  - Buccal patches <3>
    - Microbial Limit
  - Gels <3>
    - Microbial Limit
  - Ointments <3>
    - Microbial Limit
  - Sprays <5>
    - Microbial Limit
  - Tablets <2>
  - Films, gums, lozenges, solutions
    - Currently no specific tests (additional specific monograph requirements may apply)

<4> MUCOSAL DRUG PRODUCTS - PRODUCT QUALITY TESTS

- Urethral route
  - Chapters <61> and <62> may apply
- Vaginal route
  - Chapters <61> and <62> may apply
  - Creams, Gels <3>
- Rectal route
  - Ointments <3>

<5> INHALATION AND NASAL DRUG PRODUCTS – GENERAL INFORMATION AND PRODUCT QUALITY TESTS

General Quality Tests for Inhalation Drug Products

- Inhalation Solution
  - Sterility
- Inhalation suspension
  - Sterility
- Solution for Inhalation
  - Sterility
- Drug for Inhalation Solution
  - Sterility
- Inhalation Spray
  - Sterility
- Inhalation Aerosol
  - Microbial Limit
- Inhalation Powder
  - Microbial Limit

- All inhalation water based dosage forms are sterile preparations and should meet the requirements of *Sterility Tests* <71>

<5> INHALATION AND NASAL DRUG PRODUCTS – GENERAL INFORMATION AND PRODUCT QUALITY TESTS

General Quality Tests for Nasal Drug Products

- Nasal Aerosol
  - Microbial Limit
- Nasal Spray
  - Microbial Limit
  - Sterility (premetered)
- Nasal Powder
  - Microbial Limit
- Nasal Solution
  - Microbial Limit

Microbial Limits

- Acceptance criteria can be expressed on a per-container basis.

<1111> Table 1.Acceptance criteria for microbiological quality of non-sterile dosage forms-Acceptance criteria for microbiological quality of non-sterile dosage forms

Route of administration	TAMC (CFU/g or CFU/mL)	TYMC (CFU/g or CFU/mL)	Specified micro-organisms
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 nebulisation)	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)

TAMC and TYMC

- 10^1 CFU: Maximum acceptable count = 20
- 10^2 CFU: Maximum acceptable count = 200
- 10^3 CFU: Maximum acceptable count = 2000

Example: Oral dosage forms

- Amoxicillin Capsule
- Amoxicillin for Oral suspension
- Amoxicillin Tablets
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: The total aerobic microbial count does not exceed 10^3 cfu/g, and total combined yeasts and moulds does not exceed 10^2 cfu/g

- Amoxicillin Oral Suspension
- Amoxicillin Tablets for Oral Suspension
  - Not indicated in monograph

- Amoxicillin and Clavulanate Potassium for Oral Suspension
- Amoxicillin and Clavulanate Potassium Tablets
- Amoxicillin and Clavulanic Acid Extended-Release Tablets
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: The total aerobic microbial count does not exceed 10^3 cfu/g, and total combined yeasts and moulds does not exceed 10^2 cfu/g

- Alumina and Magnesia Oral Suspension
- Alumina, Magnesia, and Calcium Carbonate Oral Suspension
- Alumina, Magnesia, and Simethicone Oral Suspension
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: The total aerobic microbial count does not exceed 10^2 cfu/ml, and it meets the requirements of the test for the absence of *Escherichia coli.*
- Alumina and Magnesium Carbonate Oral Suspension
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: The total aerobic microbial count does not exceed 100 cfu/ml, and it meets the requirements of the test for the absence of *Escherichia coli, Salmonella* species, *Staphylococcus aureus,* and *Pseudomonas aeruginosa.*
- Alumina and Magnesium Trisillicate Oral Suspension
  - Not indicated in monograph

- Oral Solution Containing at Least Three of the Following-Acetaminophen and salts of Chorpheniramine, Dextromethorphan, and Pseudoephedrine
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: The total aerobic microbial count does not exceed 100 cfu/ml, and total combined yeasts and moulds does not exceed 10 cfu/ml, and it meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

- Acyclovir Oral Suspension
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: Its total count does not exceed 10^1 cfu/ml, and it meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

Example: Topical dosage forms

- Acyclovir ointment
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: It meets the requirements of the tests for the absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

- Adapalene gel
  - Microbial Enumeration Tests <61> and Tests for Specified Microorganisms <62>: The total aerobic microbial count is NMT 10^2 cfu/g. The total combined yeasts and moulds is NMT 10^1 cfu/g. It meets the requirements of the tests for the absence of *Escherichia coli, Salmonella* species, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

THANK YOU