# *Quality Control: Microbial Limit Tests for Nonsterile Pharmaceuticals, Part 2*

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*This article represents part 2 of a 2-part article on the topic of microbial limit tests for nonsterile pharmaceuticals. Part 1, which was published in the International Journal of Pharmaceutical Compounding's May-June 2014 issue (Volume 18, No. 3), provided an introduction to this topic as well as a discussion on the acceptance criteria for microbiological quality of nonsterile pharmaceuticals and an overview of United States Pharmacopeia Chapter <61>. Part 2 brings us back to this topic with an overview of United States Pharmacopeia Chapter <62>.*

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**ABSTRACT** **Cases of contaminated nonsterile products have been reported in increasing numbers. Often, these contaminated products are associated with the presence of objectionable microorganisms. The major contaminants of nonsterile pharmaceutical products and ingredients are bacteria, yeasts, and molds. The combination of parts 1 and 2 of this series of articles provides a thorough examination of microbiological quality testing for nonsterile products.**

Part 1 of this 2-part article contains important facts about the topic of microbial limit tests for nonsterile pharmaceuticals, including the following statements[1]:

- Nonsterile pharmaceuticals are not produced by aseptic processes and, therefore, are not expected to be totally free from microbial contaminations.
- The degree of contamination in nonsterile products is regulated, and is based on the acceptance criteria for microbiological quality established in Pharmacopeial monographs.
- The major contaminants of nonsterile pharmaceutical products and ingredients are bacteria, yeast, and molds.[1,2]

Also, the following excerpt from part 1 of this topic stated[1]:

> *United States Pharmacopeia (USP)* Chapters <61> *Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests and* <62> *Microbiological Examination of Non-Sterile products: Tests for Specified Microorganisms* provide protocols that allow quantitative enumeration of the presence of bacteria and fungi. The tests help determine whether a nonsterile product complies with an established specification for microbiological quality. Additionally, these two *USP* chapters provide guidance on determining the absence of, or the limited occurrence of, specified microorganisms that may be detected under the conditions of the tests.[3] It is necessary to emphasize here that the *USP* provides methodologies for selected indicator organisms, but not all "objectionable" organisms in the FDA opinions.[4]

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Part 1 of this 2-part series of articles provided an overview of *USP* Chapter <61>, as well as a discussion on other chapters within the *USP* that relate to the microbiological quality of nonsterile pharmaceuticals. This article provides an overview of *USP* Chapter <62>.

## OVERVIEW OF *UNITED STATES PHARMACOPEIA* CHAPTER <62>: TESTS FOR SPECIFIED MICROORGANISMS

*USP* Chapter <62> provides procedures and test conditions for determining whether the product under examination meets the acceptance criteria for the specified microorganisms that have been identified as objectionable (Table 1).[3] Alternative methods may be applied if their equivalence to Pharmacopeial procedures has been demonstrated. As with all microbiological tests, growth properties of the media must be demonstrated, and the method must show to be suitable for microbial recovery in the presence of a product using the test strains listed in Table 2. The challenge microbial species must be detected with the same indication reactions described in *USP* Chapter <62> under the Testing of Products section.

**TABLE 1. *United States Pharmacopeial* (Chapter <1111>) Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms.[3]**

| ROUTE OF ADMINISTRATION | TAMC (CFU/G, CFU/ML) | TYMC (CFU/G, CFU/ML) | ABSENCE OF SPECIFIED MICROORGANISM(S) (1 G, 1 ML)[a] |
|---|---|---|---|
| Oral (non-aqueous) | $10^3$ | $10^2$ | *Escherichia coli* |
| Oral (aqueous) | $10^2$ | $10^1$ | *Escherichia coli* |
| Rectal | $10^3$ | $10^2$ | None designated |
| Oromucosal | $10^2$ | $10^1$ | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa* |
| Gingival | $10^2$ | $10^1$ | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa* |
| Cutaneous | $10^2$ | $10^1$ | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa* |
| Nasal | $10^2$ | $10^1$ | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa* |
| Auricular | $10^2$ | $10^1$ | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa* |
| Vaginal | $10^2$ | $10^1$ | *Pseudomonas aeruginosa*<br>*Staphylococcus aureus*<br>*Candida albicans* |
| Transdermal Patch (drug matrix, adhesive layer and backing) | $10^2$ | $10^1$ | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa* |
| Inhalation | $10^2$ | $10^1$ | *Staphylococcus aureus*<br>*Pseudomonas aeruginosa*<br>Bile-tolerant Gram-negative bacteria |
| Pharmaceutical substances | $10^3$ | $10^2$ | None designated |

[a]Minimum amount of product to be used in sample preparation
cfu = colony-forming unit; TAMC = total aerobic microbial count; TYMC = total combined yeasts and molds count

**TABLE 2. Representative Microorganisms for Use in Validation of *United States Pharmacopeia* Chapters <61> and <62>.[3]**

| ORGANISM | ATCC | NCIMB | CIP | NBRC | NCTC | NCPF | IP |
|---|---|---|---|---|---|---|---|
| *Staphylococcus aureus* | 6538 | 9518 | 4.83 | 13276 | NA | NA | NA |
| *Pseudomonas aeruginosa* | 9027 | 8626 | 82.118 | 13275 | NA | NA | NA |
| *Bacillus subtilis* | 6633 | 8054 | 52.62 | 3134 | NA | NA | NA |
| *Candida albicans* | 10231 | NA | NA | 1594 | NA | 3179 | 48.72 |
| *Escherichia coli* | 8739 | 8545 | 53.126 | 3972 | NA | NA | NA |
| *Salmonella enterica* subsp: *serovar* typhimurium or *serovar* abony | 14028<br>NA | NA | NA<br>80.39 | NA<br>100797 | NA<br>6017 | NA | NA |
| *Clostridium sporogenes* | 11437 or 19404 | 12343 | 100651 or 79.3 | 14293 | 532 | NA | NA |

## TESTING OF PRODUCTS BY *UNITED STATES PHARMACOPEIA* CHAPTER <62>

The procedure for the preparation of test samples follows the same principle as previously described for microbial enumeration testing (*USP* <61>). If neutralization of antimicrobial activities cannot be accomplished, then it may be assumed that the inhibited microorganisms will not be present in the product. In most instances, the product is diluted 1:10 in a general purpose medium (e.g., TSB or SCD broth), and then incubated for a defined time to resuscitate but not to promote growth of microbial species in the product. After the resuscitation step, an aliquot of the sample solution equivalent to 1 g (or 1 mL) of the product is transferred to an enrichment medium for culturing under conditions optimal for growth of the target species, and then sub-cultured on selective medium for indication tests. The properties of selective media employed in testing by *USP* <62> are summarized in Table 3.

### *Test for Absence of Specified Microorganism*

*USP* Chapter <62> entails procedures to test for absence of Bile-Tolerant Gram-negative Bacteria, *Escherichia coli, Samonella, Pseudomonas aeruginosa, Staphylococcus aureus, Clostridia,* and *Candida albicans.* While most procedures specify a sample volume equivalent to 1 g (or 1 mL) of the product, the *Samonella* test is the only case that requires that a sample volume equivalent to 10 g (or 10 mL) of the product be used. In the test for Clostridia, a portion of the diluted sample is heated to 80°C for 10 minutes and then cooled

**TABLE 3. Properties of Selective Media Used in Testing by *United States Pharmacopeia* Chapter <62>.[3]**

| MEDIUM | GROWTH PROMOTION | GROWTH INHIBITION | INDICATIVE REACTION |
|---|---|---|---|
| Mossel Enterobacteria Enrichment Broth | *E. coli*<br>*P. aeruginosa* | *S. aureus* | |
| Violet Red Bile Glucose Agar | *E. coli*<br>*P. aeruginosa* | | *E. coli*<br>*P. aeruginosa* |
| MacConkey Broth | *E. coli* | *S. aureus* | |
| MacConkey Agar | *E. coli* | | *E. coli* |
| Rappaport Vassiliadis Samonella Enrichment Broth | *S. enterica* | *S. aureus* | |
| Xylose Lysine Deoxycholate Agar | *S. enterica* | | *S. enterica* |
| Cetrimide Agar | *P. aeruginosa* | *E. coli* | |
| Manitol Salt Agar | *S. aureus* | *E. coli* | |
| Reinforced Medium for Clostridia | *Cl. Sporogenes* | | |
| Columbia Agar | *Cl. Sporogenes* | | |
| Sabouraud Dextrose Broth | *C. albicans* | | |
| Sabouraud Dextrose Agar | *C. albicans* | | *C. albicans* |

**TABLE 4. Selective Media and Their Usage in *United States Pharmacopeia* Chapter <62>.[3]**

| TEST | MEDIUM | TEMPERATURE (°C) | TIME (HOUR) |
|---|---|---|---|
| Bile Tolerant Gram-negative | • Mossel Enterobacteria Enrichment Broth<br>• Violet Red Bile Glucose Agar | 30 to 35<br>30 to 35 | 24 to 48<br>18 to 24 |
| *E. coli* | • MacConkey Broth<br>• MacConkey Agar | 42 to 44<br>30 to 35 | 24 to 48<br>18 to 72 |
| *Samonella* | • Rappaport Vassiliadis Samonella Enrichment Broth<br>• Xylose Lysine Deoxycholate Agar | 30 to 35<br>30 to 35 | 18 to 24<br>18 to 48 |
| *P aeruginosa* | Cetrimide Agar | 30 to 35 | 18 to 72 |
| *S. aureus* | Manitol Salt Agar | 30 to 35 | 18 to 72 |
| *Clostridia* | • Reinforced Medium for Clostridia<br>• Columbia Agar | 30 to 35 (anaerobic)<br>30 to 35 (anaerobic) | 48<br>48 to 72 |
| *C. albicans* | • Sabouraud Dextrose Broth<br>• Sabouraud Dextrose Agar | 30 to 35<br>30 to 35 | 3 to 5 days<br>24 to 48 |

**TABLE 5. Interpretation of Quantitative Test by *United States Pharmacopeia* Chapter <62>.[3]**

| PRODUCT AMOUNT (G OR ML) | | | MPN |
|---|---|---|---|
| 0.1 | 0.01 | 0.001 | (PER G, ML) |
| + | + | + | $>10^3$ |
| + | + | ± | $>10^2$ to $<10^3$ |
| + | ± | ± | >10 to $<10^2$ |
| ± | ± | ± | <10 |

rapidly while another portion is kept at room temperature. The prepared portions are used separately to inoculate Reinforced Medium for Clostridia, which are then subcultured on Columbia Agar for an indication test. A list of the selective media and their usage in *USP* Chapter <62> procedures is provided in Table 4. In general, the presence of any colonies on these selective media indicates presumptive identification, which must be confirmed by suitable identification tests. The product complies with the test if no colonies are detected or confirmatory identification tests are negative.

### *Quantitative Test for Bile-Tolerant Gram-negative Bacteria*

The quantitation scheme is conducted similar to the Most Probable Number (MPN) method described in *USP* Chapter <61>. A set of 10-fold serial dilutions of the product in Mossel Enterobacteria Enrichment Broth containing products equivalent to 0.1, 0.01, and 0.001 g is prepared for enrichment at 30°C to 35°C for 24 to 48 hrs. The enriched samples are then sub-cultured to Violet Red Bile Glucose Agar and incubated at 30°C to 35°C for 18 to 24 hours. Growth of colonies are recorded, and the MPN of bacteria is determined according to Table 5.

## WHEN TO PERFORM *UNITED STATES PHARMACOPEIA* CHAPTERS <61> AND <62>

The International Conference on Harmonization (ICH Q4B) recommends that the official pharmacopeial texts concerning microbiological tests and acceptance criteria for nonsterile products be used interchangeably within the ICH regions. Therefore, both *USP* Chapters <61>: Microbial Enumeration Tests and <62>: Tests for Specified Microorganisms are harmonized with the *European Pharmacopeia (EP)* 7.0 Sections 2.6.12 and 2.6.13, also with the *Japanese Pharmacopeia (JP) XVI* Chapter 4.05 Microbial Limit Test. *USP* General Chapter <1111> Acceptance Criteria for Pharmaceutical Preparations and Drug Substances for Pharmaceutical Use is practically harmonized with the *EP* Section 5.1.4, and *JP* Chapter G4 (12).[5]

## TESTING FREQUENCY

### *In-process and Release Testing*

According to the Code of Federal Regulations (21 CFR 211), each lot of a component (e.g., in process or raw materials) or drug product that may potentially become contaminated with objectionable organisms during the manufacturing process or its period of intended use must first pass

microbiological testing. Written procedures to prevent objectionable organisms in nonsterile drug products must be in place, as well as appropriate laboratory testing for each batch. Additionally, in-process materials must be tested for identity, strength, quality (product and microbial), and purity, and be approved or rejected during all stages of production.[6]

> 21 CFR 211.84(d): Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.
>
> 21 CFR 211.113(a): Appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.
>
> 21 CFR 211.165(b): There shall be appropriate laboratory testing as necessary of each batch of drug product required to be free of objectionable microorganisms.

### *Stability Testing*

Furthermore, a written testing program to assess stability of drug products should be established. Provided that a sufficient number of batches are tested, this information will determine appropriate storage conditions and expiration dates. The following information should be included in the testing program[6]:

1. Sample size and testing intervals based on statistical criteria
2. Storage conditions of samples retained for testing
3. Reliable and meaningful testing methods
4. Carrying out the test in the same container as the final marketed product
5. Testing drug products intended for reconstitution both at the time of dispensing and during the period of in-use

The following guidelines are expressed in ICH/FDA guidance documents:

> ICH Q1A(R2)/FDA: Testing performed during a stability program should include analyses for product attributes that are susceptible to change during storage and that are likely to influence the product's quality, safety, or efficacy[7]
>
> ICH Q6A/FDA: Acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria...These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience.[8]

Additional guidance is provided in *USP* Chapter <1163> Quality Assurance in Pharmaceutical Compounding[3] and <1191> Stability Consideration in Dispensing Practice[3] where microbiological quality is a condition of sample stability. Thus, microbial limit is one of the recommended tests, and frequency of testing should be sufficient to establish the stability profile of nonsterile preparations. For long-term stability study, the test is usually conducted at 6- to 12-month intervals.

## REPEAT TESTING

A procedure for investigating test results that fail to meet given microbial limit specifications should be established by the manufacturers, and this procedure should allow for confirmatory testing. However, the logic and rationale for conducting the retest should be based on sound scientific judgement.[4] In the event that a root cause cannot be determined, all values obtained (original and re-test) must be reported and taken into consideration when evaluating the microbial quality of the product. The FDA expressed the following opinions[4]:

> Data review must evaluate the relationship between the organisms found in test samples, and the potential for the existence of other objectionable conditions.
>
> The importance of identifying all isolates from either or both total plate count testing and enrichment testing will depend upon the product and its intended use. Obviously, if an oral solid dosage form such as tablet is tested, it may be acceptable to identify isolates when testing show high levels. However, for other products such as topicals, inhalants or nasal solutions where there is a major concern for microbiological contamination, isolates from plate counts, as well as enrichment testing should be identified.

So, the first consideration should be the total numbers of microorganisms present. High levels of bioburden may indicate a manufacturing process is out of control, or that a spoilage organism is proliferating in the product. If the numbers of organisms in the product are not large, the next consideration is whether those organisms are "objectionable." One approach is to transfer the enrichments prepared in the compendial test to non-selective media in addition to the required selective media. Any colonies recovered and identified should be evaluated using a risk-based approach suggested in *USP* Chapter <1111>.[9]

Table 6 lists microorganisms that are primarily foodborne, but some of these species can persist in pharmaceutical or healthcare products. One such example includes the many cases of contaminated alcohol wipes containing *Bacillus cereus* species, which contributed to one fatality in a child and eight other deaths that have not yet been positively linked. Of note, no yeast or mold species are officially included in the FDA's list. The information in Table 6 may potentially be of interest in determining which organisms should be added to an "objectionable" list. Additionally, any organisms that persist in high level within any manufacturing process should be strongly considered an "objectionable" candidate because they can adversely impact the quality and safety of the finished product.[10]

**TABLE 6. The U.S. Food and Drug Administration List of Objectionable Foodborne Organisms.[11]**

| |
|---|
| **GRAM-NEGATIVE ORGANISMS** |
| *Aeromonas hydrophila and other species* |
| *Brucella species* |
| *Campylobacter jejuni* |
| *Coxiella burnetii* |
| *Cronobacter species* |
| *Francisella tularensis* |
| **Miscellaneous bacterial enterics:** |
| *Plesiomonas shigelloides* |
| *Salmonella species* |
| *Shigella species* |
| *Vibrio cholerae Non-O1 Non-O139* |
| *Vibrio cholerae Serogroups O1 and O139* |
| *Vibrio parahaemolyticus* |
| *Vibrio vulnificus* |
| *Yersinia enterocolitica* |
| **GRAM-POSITIVE ORGANISMS** |
| *Bacillus cereus and other Bacillus species* |
| *Clostridium botulism* |
| *Clostridium perfringens* |
| *Enterococcus species* |
| *Listeria monocytogenes* |
| *Mycobacterium bovis* |
| *Staphylococcus aureus* |
| *Streptococcus species* |

## WATER ACTIVITY OF NON-STERILE PRODUCTS AND RELATIONSHIP TO MICROBIOLOGICAL QUALITY (*UNITED STATES PHARMACOPEIA* CHAPTER <1112>)

Traditionally, low-water activity has been used to control microbial deterioration of food. Reduced water activity (aW) greatly assists in the prevention of microbial proliferation in pharmaceutical products. Additionally, low-water activity promotes self-preservation and thereby prevents microbial growth within pharmaceutical drug products. However, it should be noted that resistant microorganisms, including spore-forming *Clostridium* spp., *Bacillus* spp., *Salmonella* spp., and filamentous fungi, may persist within the product although they may not proliferate. Non-aqueous liquids or dry solid dosage forms will not support spore germination or microbial growth due to their low-water activity.

When formulating an aqueous oral or topical dosage form, candidate formulations should be evaluated for aW so that the drug product may be self-preserving, if possible. For example, small changes in sodium chloride, sucrose, alcohol, propylene glycol, or glycerin in a formulation may result in the creation of a drug product with a lower aW that can discourage the proliferation of microorganisms in the product. This is particularly valuable with a multiple-use product that may be contaminated by the end-user.

Water activity is the ratio of water vapor pressure in the product (P) to vapor pressure of pure water (Po) at the same temperature. Water activity can be determined directly from the partial vapor pressure or dew point, or indirectly by determination of equilibrium relative humidity (ERH%). Pharmaceutical drug products with water activities well below 0.75 are excellent candidates for reduced microbial limit testing. Table 7 contains suggested microbial limit

testing strategies for typical pharmaceutical and OTC drug products based on estimated aW. Manufacturers are urged to test their products for aW before developing reduced test strategy.

## CONCLUSION

The microbial limit for nonsterile products must be within an acceptable range that does not pose health hazards to intended patient groups or diminish product stability. Objectionable organisms can be detected using procedures prescribed in *USP* <61> and <62>, but practitioners and manufacturers should be aware of the possibility for contamination by organisms not included in the *USP* list. Similarly, products with low-water activity may resist microbial proliferation, but contaminating microorganisms may remain viable and potentially be pathogenic. Therefore, aW measurements cannot solely be used to justify the elimination of microbial testing for product release. Contamination control is a preventive activity that demands conscientious adherence to GMP and good compounding practice.

**TABLE 7. Recommended Tests Based on Representative Water Activity of Pharmaceuticals and Over-the-counter Products.[3]**

| PRODUCTS | WATER ACTIVITY | GREATEST POTENTIAL CONTAMINANTS | RECOMMENDED TESTING |
|---|---|---|---|
| Nasal inhalant | 0.99 | Gram-negative bacteria | TAMC, TYMC, absence of *S. aureus* and *P. aeruginosa* |
| Hair shampoo | 0.99 | Gram-negative bacteria | TAMC, TYMC, absence of *S. aureus* and *P. aeruginosa* |
| Antacid | 0.99 | Gram-negative bacteria | TAMC, TYMC, absence of *E. coli* and *Salmonella spp.* |
| Topical cream | 0.97 | Gram-positive bacteria | TAMC, TYMC, absence of *S. aureus* and *P. aeruginosa* |
| Oral liquid | 0.9 | Gram-positive bacteria, fungi | TAMC, TYMC |
| Oral suspension | 0.87 | Fungi | TAMC, TYMC |
| Topical ointment | 0.55 | None | Reduced testing |
| Lip balm | 0.36 | None | Reduced testing |
| Suppositories (vaginal, rectal) | 0.3 | None | Reduced testing |
| Compressed tablets | 0.36 | None | Reduced testing |
| Liquid-filled capsule | 0.3 | None | Reduced testing |

TAMC = total aerobic microbial count; TYMC = total combined yeasts and molds count

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