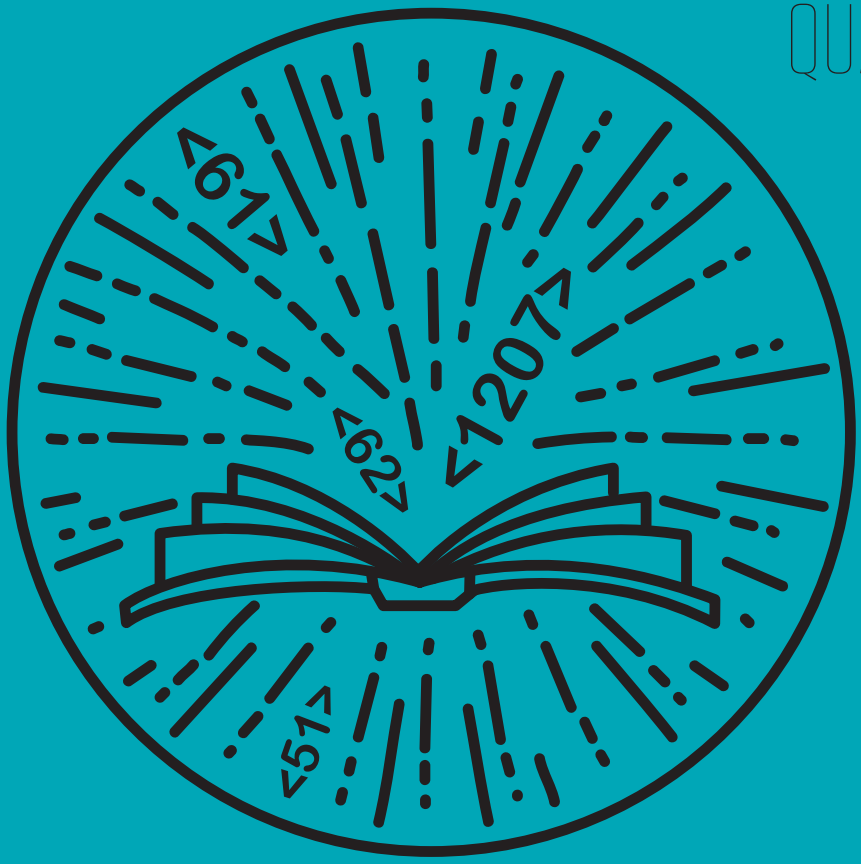

Minor Chapters, Major Impacts:

WHAT *UNITED STATES PHARMACOPEIA* CHAPTERS <51>, <61>, <62>, AND <1207> MEAN FOR YOUR COMPOUNDING PRACTICE

ABSTRACT

The United States Pharmacopeial Convention, Inc. recommends within the standards of the *United States Pharmacopeia* that compounding pharmacies have staff dedicated to quality assurance and quality control to ensure patients are receiving safe medications. The quality-control program must include testing. While compounding pharmacies have grown familiar with potency, sterility, and endotoxin testing, there are many more tests recommended within the *United States Pharmacopeia* that are critical for evaluating the quality of compounded preparations. This article discusses when a few of these tests should be utilized, how to assign acceptance criteria, and how test results are obtained.

Brian Kelley, BS

The author is the Director of Business Development for ARL Bio Pharma, Oklahoma City, Oklahoma.

QUALITY ASSURANCE AND QUALITY CONTROL

United States Pharmacopeia (USP) chapters <795> and <797> state that compounding pharmacies should have staff dedicated to quality assurance (QA) and quality control (QC). QA is responsible for procedures, activities, and oversight, while QC is responsible for sampling, testing, and documenting the test results to ensure that specifications have been met before dispensing compounded preparations. *USP* Chapter <1163> Quality Assurance in Pharmaceutical Compounding is referred to in chapters <795> and <797> because it provides guidance on how to set up QA/QC programs in a compounding pharmacy and makes recommendations for appropriate tests to conduct on compounded preparations.

TESTING

The goal of testing compounded preparations is to determine the adequacy of the compounding process and the quality of the preparation. Not only is testing the finished preparation recommended in *USP* Chapter <1163>, but so is testing of intermediates or stock solutions. Testing of stocks is important because the final preparation is likely to be out of specification (OOS) if the stock is not correct. Chapter <1163> also says that compounders must have a basic understanding of pharmaceutical analysis and that test acceptance criteria must be determined prior to testing. The Chapter acknowledges that testing of all preparations is not practical or required, but compounders should know the importance of:

- testing,
- when to test,
- what to test,
- the appropriate test method and equipment,
- how to interpret test results,
- limits of the test, and
- actions to take when a test result is OOS.

Chapter <1163> lists many tests and provides details on the appropriateness of each test. This article focuses on three tests in *USP* Chapter <1163> and one from the U.S. Food and Drug Administration (FDA) that are not well-known but are important for checking the quality of compounded nonsterile and sterile preparations for release and beyond-use dating (BUD).

The tests listed in Chapter <1163> and discussed in this article relate to chapters:

- <61> Microbial Enumeration Tests (applies to nonsterile products)
- <62> Tests for Specified Organisms (a recommended test on nonsterile products)
- <51> Antimicrobial Effectiveness Testing (applies to preserved multi-dose nonsterile and sterile aqueous products)
- <1207> Package Integrity Testing – Sterile Products (applies to sterile and nonsterile preparations)

- **<61> Microbial Enumeration Tests** (applies to nonsterile products)
- **<62> Tests for Specified Organisms** (a recommended test on nonsterile products)
- **<51> Antimicrobial Effectiveness Testing** (applies to preserved multi-dose nonsterile and sterile aqueous products)
- **<1207> Package Integrity Testing – Sterile Products** (applies to sterile and nonsterile preparations)

TABLE 1 OF *USP* CHAPTER <1111>.

***UNITED STATES PHARMACOPEIA* CHAPTER <1111> 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 *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	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Gingival use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Cutaneous use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Nasal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
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 (1 g or 1 mL)

cfu = colony-forming agents

Source: United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary*. Rockville, MD: United States Pharmacopeial Convention, Inc.; Current Edition.

<61>

UNITED STATES PHARMACOPEIA CHAPTER <61> MICROBIAL ENUMERATION TESTS

USP <61> applies to nonsterile products, which includes finished nonsterile compounded preparations, and may be used to assess intermediates of sterile compounds. This is a test that determines how many microorganisms are present in nonsterile drug products and sterile products that are made using nonsterile components prior to sterilization of the final preparation. The microbial enumeration test is often referred to as "bioburden" or "microbial limits." In 483s issued to 503A pharmacies, the FDA has also referred to these tests as "yeast and mold counts" and "presence of microorganisms." As stated in Chapter <1163>, the acceptance criteria must be defined prior to test initiation. Acceptance criteria are not provided in Chapter <61>. Instead, acceptance criteria recommendations are provided in *USP* Chapter <1111> or the *USP* monograph. The limits listed in Table 1 of *USP* Chapter <1111> list how many microorganisms can be present in nonsterile compounded preparations. Separate criteria are provided for each of the two tests included in *USP* Chapter <61>.

TABLE 2 OF *USP* CHAPTER <1111>.

UNITED STATES PHARMACOPEIA **CHAPTER <1111> 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

Source: United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary.* Rockville, MD: United States Pharmacopeial Convention, Inc.; Current Edition.

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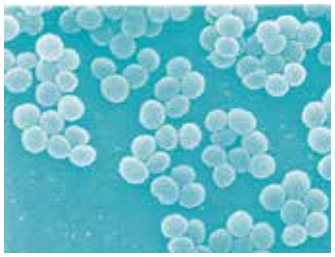
Table 2 of *USP* Chapter <1111> provides recommended limits for nonsterile components used to produce sterile preparations. *USP* Chapter <61> states the compounder must also consider the acceptance criteria of a nonsterile product or component when considering its use, to include:

- the nature of a nonsterile product,
- the method of application,
- the patient,
- the use of immunosuppressive agents/corticosteroids, and
- the presence of disease, wounds, and organ damage.

USP Chapter <61> testing is performed by plating the prepared sample onto two types of growth media. The sample preparation details are determined during method suitability. The growth medias and sample mixtures are incubated at defined temperatures and durations. After the incubation period, the colony numbers are counted, and the results are calculated to correct for any dilution of the compounded preparation that occurred during test-sample preparation. The test results are then compared to the defined acceptance criteria to determine if the nonsterile preparation passes or fails the test. The goal of *USP* Chapter <61> testing is to ensure that there is low bioburden in nonsterile compounded preparations and intermediates.



<62>

UNITED STATES PHARMACOPEIA CHAPTER <62> TESTS FOR SPECIFIED ORGANISMS

While *USP* Chapter <61> demonstrates the total number of microorganisms, *USP* Chapter <62> tests for the presence of specific organisms. The FDA refers to this in 483s as tests for "objectionable organisms" or lists "specific organisms" that cannot be present in nonsterile preparations. For example, the FDA has stated "freedom from *Pseudomonas aeruginosa*" or "absence of bile-tolerant Gram-negative bacteria" when referring to lack of Chapter <62> testing. To determine which organisms listed in *USP* Chapter <62> should not be present in nonsterile preparations, you should consider the route of administration and *USP* Chapter <1111>. These tests are performed similarly to *USP* Chapter <61> but utilize growth media designed to promote the growth of the specific target microorganism and inhibit the growth of others. Method suitability is required to determine the appropriate sample preparation steps necessary to overcome any antimicrobial properties of the compounded preparation. This ensures that the test will detect the objectionable microorganism if present. At the conclusion of the incubation, a result of "pass" or "fail" is generated. A passing result means that the target organism was not detected in the sample. A failing result means the objectionable microorganism was found. The goal of *USP* Chapter <62> testing is to ensure that nonsterile compounded preparations do not contain specific microorganisms of concern.

TABLE 1.

COMMON PHARMACEUTICAL PRESERVATIVES.

PRESERVATIVE	FORMULATION	CONCENTRATION (%)	OPTIMAL pH	SPECTRUM
4-Chlorocresol	Oral, Topical	Up to 0.2	<9.0	• Bacteria, spores, molds, and yeasts • Active in acidic media
4-Chloroxylenol	Topical	0.1 to 0.8	——	• Gram (+) bacteria • Less active vs Gram (-) bacteria • Synergistic with EDTA
Benzalkonium	Oral, Ophthalmic, Topical	0.01 to 0.02	4 to 10	• Gram (+) > Gram (-) bacteria • Ineffective vs resistant P. aeruginosa strains • Minimal activity vs bacterial endospores, acid-fast bacteria
Benzethonium chloride	Topical, Ophthalmic	Up to 0.5	4 to 10	• Bacteria, fungi, and molds • Synergistic with ethanol • Reduced efficacy by soaps and other anionic surfactants
Benzoic acid	Oral, Parenteral, Topical	0.1 to 0.2	2.5 to 4.5	• Moderate activity vs Gram (+) < Gram (-) • Moderate activity vs fungal • Moderate activity vs mold
Benzyl Alcohol	Parenteral, Topical	0.2	2.5 to 4.5	• Bacteria, fungi, molds, and yeasts • Moderate activity vs Gram (+) < Gram (-)
Cetrimide	Ophthalmic, Topical	• Ophthalmic: 0.005 • Topical: 0.1 to 1.0	Neutral or slightly alkaline	• Gram (+) > Gram (-) bacteria • Synergistic with alcohols • Variable activity vs fungi • Synergistic with EDTA vs resistant strains of P. aeruginosa, A. niger, C. albicans
Chlorhexidine	Ophthalmic	0.01	5 to 7	• Gram (+) > Gram (-) • Weak activity vs Proteus and Pseudomonas • Inactive vs acid-fast bacilli • Weak activity vs molds, yeasts
Chlorobutanol	Parenteral	Up to 0.5	<5.5	• Activity Gram (+), Gram (-), and some fungi
Imidurea	Topical, Ophthalmic	0.03 to 0.5	3 to 9	• Broad-spectrum antibacteria • Some antifungal properties • Synergistic with parabens vs fungi
m-Cresol	Parenteral	0.15 to 0.3	<9.0	• Moderately Gram (+) > Gram (-) • Weak activity vs yeasts and molds
Methylparaben	Oral, Parenteral	0.0018	4 to 8	• Broad spectrum antimicrobial activity • Most effective vs yeasts and molds
Phenols 0.5%	Parenteral	0.01	<9	• Moderate activity vs Gram (+) < Gram (-) • Weak activity vs yeasts and molds
Phenoxyethanol	Parenteral, Topical	0.5 to 2.2	<7	• Antibacterial vs P. aeruginosa < Proteus vulgaris • Weak activity vs Gram (-) • Frequently used in combination with other preservatives
Potassium sorbate	Oral, Topical	0.1 to 0.2	<6	• Predominantly antifungal • Moderate antibacterial

TABLE 1.

COMMON PHARMACEUTICAL PRESERVATIVES CONTINUED.

PRESERVATIVE	FORMULATION	CONCENTRATION (%)	OPTIMAL pH	SPECTRUM
Propionic acid	Oral, Topical	————	3.9	• Bacteria, fungi, and molds
Propylparaben	Oral, Parenteral	0.0002	4 to 8	• Activity vs yeasts and molds > bacteria • Gram (+) > Gram (-) bacteria
Sodium benzoate	Oral, Parenteral	Oral: 0.02 to 0.5 Parenteral: 0.5	2 to 5	• Bacteriostatic • Antifungal
Sorbic acid	Oral, Topical	0.05 to 0.2	4.5	• Primarily antifungal • Weak antimicrobial • Synergy with glycol
Thimerosal	Ophthalmic, Parenteral	0.001 to 0.01	7 to 8	• Bactericidal at acidic pH • Bacteriostatic and fungistatic at alkaline or neutral pH • Ineffective vs spore-forming organisms

Source: United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary.* Rockville, MD: United States Pharmacopeial Convention, Inc.; Current Edition.

TABLE 1 OF *USP* CHAPTER <51>.

***UNITED STATES PHARMACOPEIA* CHAPTER <51> TABLE 1. COMPENDIAL PRODUCT CATEGORIES.**

CATEGORY	PRODUCT DESCRIPTION
1	Injections; other parenterals including emulsions, otic products, sterile nasal products, and ophthalmic products made with aqueous bases or vehicles
2	Topically used products made with aqueous bases or vehicles; nonsterile nasal products and emulsions, including those applied to mucous membranes
3	Oral products other than antacids, made with aqueous bases or vehicles
4	Antacids made with an aqueous base

Source: United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary.* Rockville, MD: United States Pharmacopeial Convention, Inc.; Current Edition.

TABLE 3 OF *USP* CHAPTER <51>.

***UNITED STATES PHARMACOPEIA* CHAPTER <51> TABLE 3. CRITERIA FOR TESTED MICROORGANISMS.**

FOR CATEGORY 1 PRODUCTS	
Bacteria	NLT 1.0 log reduction from the initial calculated count at 7 days, NLT 3.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days
Yeast and molds	No increase from the initial calculated count at 7, 14, and 28 days
FOR CATEGORY 2 PRODUCTS	
Bacteria	NLT 2.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days
Yeast and molds	No increase from the initial calculated count at 14 and 28 days
FOR CATEGORY 3 PRODUCTS	
Bacteria	NLT 1.0 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days
Yeast and molds	No increase from the initial calculated count at 14 and 28 days
FOR CATEGORY 4 PRODUCTS	
Bacteria, yeast, and molds	No increase from the initial calculated count at 14 and 28 days

NLT = not less than

Source: United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary*. Rockville, MD: United States Pharmacopeial Convention, Inc.; Current Edition.

<51>

UNITED STATES PHARMACOPEIA CHAPTER <51> ANTIMICROBIAL EFFECTIVENESS TESTING

Many nonsterile and sterile compounded preparations contain antimicrobial preservatives to prevent the growth of microbial contamination throughout the BUD. The preservatives are needed because end users may introduce microorganisms into their compounded medication. Table 1 of this article lists common pharmaceutical preservatives, the type of formulation that is used, the effective concentration, optimal pH, and the types of organism the preservative is effective against.

Examples of when microorganisms can be introduced into the compounded preparation are 1) when a patient puts unclean hands into their topical cream or 2) by repeated use of an oral product. Entry into a vial without proper aseptic technique can introduce microorganisms into sterile preparations. The test procedure described in *USP* Chapter <51> simulates these contamination events by adding high concentrations of 5 microorganisms to the compounded preparation. The effectiveness of the antimicrobial preservative is determined by counting the number of microorganisms present for 28 days following the contamination event. The counts occur similarly to *USP* Chapter <61> where the test sample is prepared, inoculated onto growth media, incubated, microorganisms counted, and results calculated to correct for any dilution of the compounded preparation while making the sample for counts. The sample preparation procedure for counting is determined during method suitability. The acceptance criteria for *USP* Chapter <51> vary based on the type of product and the type of organism. Table 1 in *USP* Chapter <51> divides the types of product into 4 categories based on the type of product and route of administration.

Table 3 of *USP* Chapter <51> provides the acceptance criteria for each product category. Notice that each product category has 2 acceptance criteria. One is for bacteria, and the other is for yeast and molds. The goal of *USP* Chapter <51> testing is to prove that antimicrobial preservatives kill introduced microorganisms or prevent their proliferation.

<1207>

UNITED STATES PHARMACOPEIA CHAPTER <1207> PACKAGE INTEGRITY EVALUATION – STERILE PRODUCTS

USP Chapter <1207> describes the tests that are used to demonstrate that container-closure systems can maintain a sterile environment throughout the BUD. The FDA says testing container-closure integrity is more likely to detect problems than sterility testing throughout the storage period. *USP* Chapter <1207> also discusses the potential for drug product components to escape from the container-closure system and the product quality risks posed by leaks. Escaping drug product components can be problematic for both sterile and nonsterile compounded preparations. For example, if benzyl alcohol in a preserved preparation escapes from the packaging system, the concentration may fall below its effective concentration range. Other components, such as water, could also escape, increasing the compounded preparation's drug potency. Evaluating container-closure integrity is, therefore, important for both sterile and nonsterile compounded preparations.

Many container-closure integrity tests are described in Chapter <1207>. The goal of *USP* <1207> testing is to ensure that the product's package provides a level of protection required to meet physicochemical label-claim specifications and maintain product sterility until time of use. All the tests are designed to challenge the entire packaging system, not the individual components. Individual components are qualified by tests described in other *USP* chapters. *USP* Chapter <1207> divides the various tests into two categories: 1) deterministic and 2) probabilistic.

DETERMINISTIC TESTS

Deterministic methods are described as quantitative and definitive and preferred by the *USP*. Vacuum decay is a common deterministic method. Vacuum decay is performed by placing the entire

packaging system into a test chamber and drawing a vacuum on the chamber. The instrument then monitors for any changes in the vacuum level pulled on the chamber. Vacuum levels are monitored by the test instrument. Vacuum level changes indicate a leak in the packaging system. Because the test results are obtained from the instrument and not by an interpretation from the test operator, the *USP* prefers deterministic container-closure test methods.

PROBABILISTIC TESTS

Probabilistic methods are those that are qualitative and use human judgement. The *USP* considers these tests less desirable than deterministic methods. Dye ingress is a common probabilistic method. A common way to perform dye ingress testing is by submerging the container-closure system inside a chamber. The chamber is then filled with a dye and a vacuum pulled. The vacuum is then turned off and the chamber allowed to return to atmospheric pressures. Most of the time, the test articles are then visually examined for the presence of dye. The differences in color perception from one analyst to the next add variability to the test results. To overcome this variability, the drug product can be tested using an analytical instrument to test for the presence of dye. However, some drug products can oxidize the dye so even a high-performance liquid chromatogram with mass spectrometry would not detect the dye. Testing for container-closure integrity is important to determine if there is a leak in the packaging system that allows microorganisms to enter or if drug preparation components can escape. The *USP* considers probabilistic test methods, such as dye ingress, less desirable than deterministic test methods because analyst interpretation is often required to obtain the test results.

CONCLUSION

The *USP* has many resources for compounding pharmacists to ensure their patients receive quality compounded preparations. Compounders understand that *USP* Chapter <795> and *USP* Chapter <797> provide guidance on how to make quality preparations. Both chapters state that the compounding staff must be knowledgeable of the standards in *USP* Chapter <795> and/or *USP* Chapter <797> and must also be familiar with *USP* Chapter <1163>. This chapter provides information on QA and QC responsibilities within a compounding pharmacy. Part of QC's responsibility is to execute the testing program setup by the QA group. *USP* Chapter <1163> also provides recommendations on which tests to perform on different types of compounded preparations. Compounding is heavily regulated so compounding personnel should utilize as many tools as possible to educate themselves. Testing itself is not intended to be the QA/QC program. Testing is a lagging indicator that all the things QA is doing are working appropriately. Without testing, patient complaint or harm may be the only feedback.

RESOURCES

- United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary. USP* Chapter <795>; *USP* Chapter <797>; *USP* Chapter <1163>; *USP* Chapter <61>; *USP* Chapter <62>; *USP* Chapter <1111>; *USP* Chapter <51>; *USP* Chapter <1207>. Rockville, MD: United States Pharmacopeial Convention, Inc.; Current Edition.
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Address correspondence to Brian Kelley, Director of Business Development, ARL Bio Pharma, 840 Research Pkwy #546, Oklahoma City, OK 73104. E-mail: bkelley@arlok.com

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