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The designation on the cover of this publication, "USP NF 2014," is for ease of identification only. The publication contains two separate compendia: *The United States Pharmacopeia*, Thirty-Seventh Revision, and *The National Formulary*, Thirty-Second Edition.

THE UNITED STATES PHARMACOPEIAL CONVENTION
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SIX-MONTH IMPLEMENTATION GUIDELINE

The *United States Pharmacopeia–National Formulary* and its supplements become official **six months** after being released to the public. The *USP–NF*, which is released on November 1 of each year, becomes official on May 1 of the following year. This six-month implementation timing gives users more time to bring their methods and procedures into compliance with new and revised *USP–NF* requirements.

The table below describes the official dates of the *USP–NF* and its supplements. The 2013 *USP 36–NF 31*, and its supplements, *Interim Revision Announcements (IRAs)* and *Revision Bulletins* to that edition, will be official until May 1, 2014, at which time the *USP 37–NF 32* becomes official.

Publication	Release Date	Official Date	Official Until
USP 37–NF 32	November 1, 2013	May 1, 2014	May 1, 2015 (except as superseded by supplements, *IRAs*, and *Revision Bulletins*)
First Supplement to the USP 37–NF 32	February 1, 2014	August 1, 2014	May 1, 2015 (except as superseded by *Second Supplement*, *IRAs*, and *Revision Bulletins*)
Second Supplement to the USP 37–NF 32	June 1, 2014	December 1, 2014	May 1, 2015 (except as superseded by *IRAs* and *Revision Bulletins*)
USP 38–NF 33	November 1, 2014	May 1, 2015	May 1, 2016 (except as superseded by supplements, *IRAs*, and *Revision Bulletins*)

The table below gives the details of the *IRAs* that will apply to *USP 37–NF 32*.

IRA	PF Posting Date	Comment Due Date	IRA Posting Date	IRA Official Date
40(1)	January 2, 2014	March 31, 2014	May 30, 2014	July 1, 2014
40(2)	March 3, 2014	May 31, 2014	July 31, 2014	September 1, 2014
40(3)	May 1, 2014	July 31, 2014	September 26, 2014	November 1, 2014
40(4)	July 1, 2014	September 30, 2014	November 26, 2014	January 1, 2015
40(5)	September 2, 2014	November 30, 2014	January 30, 2015	March 1, 2015
40(6)	November 3, 2014	January 31, 2015	March 27, 2015	May 1, 2015

Revision Bulletins published on the USP website become official on the date specified in the *Revision Bulletin*.

NOTICE AND WARNING

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Anhydrous

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Burets *(Continued)*

Subdivisions, mL	0.02	0.1	0.1
Limit of error, mL	0.02	0.03	0.05

⟨41⟩ BALANCES

This chapter states the requirements for balances used for materials that must be accurately weighed (see *General Notices, 8.20*). Unless otherwise specified, when substances must be "accurately weighed", the weighing shall be performed using a balance that is calibrated over the operating range and meets the requirements defined for repeatability and accuracy. For balances used for other applications, the balance repeatability and accuracy should be commensurate with the requirements for its use.

For discussion of the theoretical basis of these requirements, see general information chapter *Weighing on an Analytical Balance* ⟨1251⟩, which may be a helpful—but not mandatory—resource.

REPEATABILITY

Repeatability is assessed by weighing one test weight NLT 10 times. [NOTE—The test weight must be within the balance's operating range, but the weight need not be calibrated. Because repeatability is virtually independent of sample mass within the balance's capacity, use of a small test weight, which may be difficult to handle, is not required.]

Repeatability is satisfactory if two times the standard deviation of the weighed value, divided by the nominal value of the weight used, does not exceed 0.10%. If the standard deviation obtained is less than $0.41d$, where d is the scale interval, replace this standard deviation with $0.41d$. In this case, repeatability is satisfactory if two times $0.41d$, divided by the nominal value of the weight used, does not exceed 0.10%.

ACCURACY

The accuracy of a balance is satisfactory if its weighing value, when tested with a suitable weight(s), is within 0.10% of the test weight value.

A test weight is suitable if it has a mass between 5% and 100% of the balance's capacity. The test weight's maximum permissible error (mpe), or alternatively its calibration uncertainty, shall be NMT one-third of the applied test limit of the accuracy test. [NOTE—Applicable standards are the following: ASTM E617 (available from http://www.astm.org) and OIML R 111 (available from http://www.oiml.org).]

Microbiological Tests

⟨51⟩ ANTIMICROBIAL EFFECTIVENESS TESTING

Antimicrobial preservatives are substances added to nonsterile dosage forms to protect them from microbiological growth or from microorganisms that are introduced inadvertently during or subsequent to the manufacturing process. In the case of sterile articles packaged in multiple-dose containers, antimicrobial preservatives are added to inhibit the growth of microorganisms that may be introduced from repeatedly withdrawing individual doses.

Antimicrobial preservatives should not be used as a substitute for good manufacturing practices or solely to reduce the viable microbial population of a nonsterile product or control the presterilization bioburden of multidose formulations during manufacturing. Antimicrobial preservatives in compendial dosage forms meet the requirements for *Added Substances* under *Ingredients and Processes* in the *General Notices*.

All useful antimicrobial agents are toxic substances. For maximum protection of patients, the concentration of the preservative shown to be effective in the final packaged product should be below a level that may be toxic to human beings.

The concentration of an added antimicrobial preservative can be kept at a minimum if the active ingredients of the formulation possess an intrinsic antimicrobial activity. Antimicrobial effectiveness, whether inherent in the product or whether produced because of the addition of an antimicrobial preservative, must be demonstrated for all injections packaged in multiple-dose containers or for other products containing antimicrobial preservatives. Antimicrobial effectiveness must be demonstrated for multiple-dose topical and oral dosage forms and for other dosage forms such as ophthalmic, otic, nasal, irrigation, and dialysis fluids (see *Pharmaceutical Dosage Forms* ⟨1151⟩).

This chapter provides tests to demonstrate the effectiveness of antimicrobial protection. Added antimicrobial preservatives must be declared on the label. The tests and criteria for effectiveness apply to a product in the original, unopened container in which it was distributed by the manufacturer.

PRODUCT CATEGORIES

For the purpose of testing, compendial articles have been divided into four categories (see *Table 1*). The criteria of antimicrobial effectiveness for these products are a function of the route of administration.

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.

TEST ORGANISMS

Use cultures of the following microorganisms[1]: *Candida albicans* (ATCC No. 10231), *Aspergillus niger* (ATCC No. 16404), *Escherichia coli* (ATCC No. 8739), *Pseudomonas aeruginosa* (ATCC No. 9027), and *Staphylococcus aureus* (ATCC No. 6538). The viable microorganisms used in the test must not be more than five passages removed from the original ATCC culture. For purposes of the test, one passage is defined as the transfer of organisms from an established culture to fresh medium. All transfers are counted. In the case of organisms maintained by seed-lot techniques, each cycle of freezing, thawing, and revival in fresh medium is taken as one transfer. A seed-stock technique should be used for long-term storage of cultures. Cultures received from the ATCC should be resuscitated according to directions. If grown in broth, the cells are pelleted by centrifugation. Resuspend in 1/20th the volume of fresh maintenance broth, and add an equal volume of 20% (v/v in water) sterile glycerol. Cells grown on agar may be scraped from the surface into the 10% glycerol broth. Dispense small aliquots of the suspension into sterile vials. Store the vials in liquid nitrogen or in a mechanical freezer at no more than −50°. When a fresh seed-stock vial is required, it may be removed and used to inoculate a series of working cultures. These working cultures may then be used periodically (each day in the case of bacteria and yeast) to start the inoculum culture.

MEDIA

All media used in the test must be tested for growth promotion. Use the microorganisms indicated above under *Test Organisms*.

PREPARATION OF INOCULUM

Preparatory to the test, inoculate the surface of a suitable volume of solid agar medium from a recently revived stock culture of each of the specified microorganisms. The culture conditions for the inoculum culture are described in *Table 2* in which the suitable media are Soybean–Casein Digest or Sabouraud Dextrose Agar Medium (see *Microbial Enumeration Tests* ⟨61⟩ and *Tests for Specified Microorganisms* ⟨62⟩).

To harvest the bacterial and *C. albicans* cultures, use sterile saline TS, washing the surface growth, collecting it in a suitable vessel, and adding sufficient sterile saline TS to obtain a microbial count of about 1×10^8 colony-forming units (cfu) per mL. To harvest the cells of *A. niger*, use sterile saline TS containing 0.05% of polysorbate 80, and add sufficient sterile saline TS to obtain a count of about 1×10^8 cfu per mL.

Alternatively, the stock culture organisms may be grown in a suitable liquid medium (i.e., Soybean–Casein Digest Broth or Sabouraud Dextrose Broth) and the cells harvested by centrifugation, then washed and resuspended in sterile saline TS to obtain a microbial count of about 1×10^8 cfu per mL. [NOTE—The estimate of inoculum concentration may be performed by turbidimetric measurements for the challenge microorganisms. Refrigerate the suspension if it is not used within 2 hours.]

Determine the number of cfu per mL in each suspension, using the conditions of media and microbial recovery incubation times listed in *Table 2* to confirm the initial cfu per mL estimate. This value serves to calibrate the size of inoculum used in the test. The bacterial and yeast suspensions are to be used within 24 hours of harvest, but the fungal preparation may be stored under refrigeration for up to 7 days.

PROCEDURE

The test can be conducted either in five original containers if sufficient volume of product is available in each container and the product container can be entered aseptically (i.e., needle and syringe through an elastomeric rubber stopper), or in five sterile, capped bacteriological containers of suitable size into which a sufficient volume of product has been transferred. Inoculate each container with one of the prepared and standardized inoculum, and mix. The volume of the suspension inoculum used is between 0.5% and 1.0% of the volume of the product. The concentration of test microorganisms that is added to the product (*Categories 1, 2,* and *3*) are such that the final concentration of the test preparation after inoculation is between 1×10^3 and 1×10^5 cfu per mL of the product. For *Category 4* products (antacids) the final concentration of the test preparation after inoculation is between 1×10^2 and 1×10^4 cfu per mL of the product.

The initial concentration of viable microorganisms in each test preparation is estimated based on the concentration of microorganisms in each of the standardized inoculum as determined by the plate-count method.

Incubate the inoculated containers at 22.5 ± 2.5°. Sample each container at the appropriate intervals specified in *Table 3*. Record any changes observed in appearance at these intervals. Determine by the plate-count procedure the number of cfu present in each test preparation for the applicable intervals (see *Procedure* under *Microbial Enumeration Tests* ⟨61⟩ and *Tests for Specified Microorganisms* ⟨62⟩). Incorporate an inactivator (neutralizer) of the specific antimicrobial in the plate count or in the appropriate dilution prepared for plating. These conditions are determined in the validation study for that sample based upon the conditions of media and microbial recovery incubation times listed in *Table 2*. Using the calculated concentrations of cfu per mL present at the start of the test, calculate the change in log$_{10}$ values of

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