

2014

USP 37

**THE UNITED STATES PHARMACOPEIA**

NF 32

**THE NATIONAL FORMULARY**

Volume 1

*By authority of the United States Pharmacopeial Convention  
Prepared by the Council of Experts and its Expert Committees*

*Official from May 1, 2014*

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  
12601 Twinbrook Parkway, Rockville, MD 20852

## 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
<i>USP 37–NF 32</i>	November 1, 2013	May 1, 2014	May 1, 2015 (except as superseded by supplements, <i>IRAs</i> , and <i>Revision Bulletins</i> )
<i>First Supplement to the USP 37–NF 32</i>	February 1, 2014	August 1, 2014	May 1, 2015 (except as superseded by <i>Second Supplement</i> , <i>IRAs</i> , and <i>Revision Bulletins</i> )
<i>Second Supplement to the USP 37–NF 32</i>	June 1, 2014	December 1, 2014	May 1, 2015 (except as superseded by <i>IRAs</i> and <i>Revision Bulletins</i> )
<i>USP 38–NF 33</i>	November 1, 2014	May 1, 2015	May 1, 2016 (except as superseded by supplements, <i>IRAs</i> , and <i>Revision Bulletins</i> )

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

**Concerning U.S. Patent or Trademark Rights**—The inclusion in *The United States Pharmacopeia* or in the *National Formulary* of a monograph on any drug in respect to which patent or trademark rights may exist shall not be deemed, and is not intended as, a grant of, or authority to exercise, any right or privilege protected by such patent or trademark. All such rights and privileges are vested in the patent or trademark owner, and no other person may exercise the same without express permission, authority, or license secured from such patent or trademark owner.

**Concerning Use of USP or NF Text**—Attention is called to the fact that *USP* and *NF* text is fully copyrighted. Authors and others wishing to use portions of the text should request permission to do so from the Secretary of the USPC Board of Trustees.

Copyright © 2013 The United States Pharmacopeial Convention  
12601 Twinbrook Parkway, Rockville, MD 20852

All rights reserved.

ISSN: 0195-7996

ISBN: 978-1-936424-22-1

Printed in the United States by United Book Press, Inc., Baltimore, MD

Ammonium (continued)  
 formate, 1376  
 glycyrrhizate, 5852  
 hydroxide, 1376  
 hydroxide 6 N, 1376  
 molybdate, 1376, 1765  
 molybdate injection, 1766  
 molybdate TS, 1446  
 nitrate, 1376  
 nitrate, ceric TS, 1447  
 nitrate TS, silver, 1451  
 oxalate, 1376  
 oxalate TS, 1446  
 persulfate, 1376  
 phosphate, 5853  
 phosphate, dibasic, 1376  
 phosphate, dibasic TS, 1446  
 phosphate, monobasic, 1376  
 polysulfide TS, 1446  
 pyrrolidinedithiocarbamate, 1376  
 pyrrolidinedithiocarbamate, saturated TS, 1446  
 reineckate, 1376  
 reineckate TS, 1446  
 sulfamate, 1376  
 sulfate, 1376, 5854  
 sulfate, cupric TS, 1447  
 sulfate, ferric TS, 1448  
 sulfide TS, 1446  
 thiocyanate, 1376  
 thiocyanate, tenth-normal (0.1 N), 1454  
 thiocyanate TS, 1446  
 vanadate, 1376  
 vanadate TS, 1446

Amobarbital sodium, 1767  
 for injection, 1767  
 and secobarbital sodium capsules, 4667

Amodiaquine, 1767  
 hydrochloride, 1768  
 hydrochloride tablets, 1769

Amoxapine, 1770  
 tablets, 1770

Amoxicillin, 1771  
 boluses, 1773  
 capsules, 1774  
 and clavulanate potassium for oral suspension, 1778  
 and clavulanate potassium tablets, 1779  
 and clavulanic acid extended-release tablets, 1780  
 for injectable suspension, 1775  
 intramammary infusion, 1774  
 oral suspension, 1775  
 for oral suspension, 1775  
 tablets, 1776  
 tablets for oral suspension, 1777

Amphetamine  
 sulfate, 1783  
 sulfate tablets, 1784

Amphotericin B, 1785  
 cream, 1785  
 for injection, 1786  
 lotion, 1786  
 ointment, 1786

Ampicillin, 1786  
 boluses, 1792  
 capsules, 1792  
 for injectable suspension, 1795  
 for injection, 1794  
 and probenecid for oral suspension, 1797  
 sodium, 1798  
 soluble powder, 1794

and sulbactam for injection, 1799  
 for oral suspension, 1795  
 tablets, 1796

Amprolium, 1800  
 soluble powder, 1801  
 oral solution, 1801

Amyl  
 acetate, 1377  
 alcohol, 1377  
 nitrite, 1802  
 nitrite inhalant, 1802

$\alpha$ -Amylase, 1377

Amylene hydrate, 5855

tert-Amyl alcohol, 1377

Anagrelide  
 capsules, 1804  
 hydrochloride, 1803

Analysis of Biological Assays (1034), 603

Analytical data—interpretation and treatment (1010), 515

Analytical instrument qualification (1058), 747

Anastrozole, 1806

Ancillary materials for cell, gene, and tissue-engineered products (1043), 619

Andrographis, 5245  
 extract, powdered, 5248  
 powdered, 5247

Anethole, 5855

(*E*)-Anethole, 1377

Angustifolia  
 extract, powdered echinacea, 5350  
 powdered echinacea, 5346

## Anhydrous

acetone, 1372  
 alumina, 1377  
 barium chloride, 1377  
 calcium chloride, 1377  
 calcium phosphate, dibasic, 2098  
 citric acid, 2367  
 cupric sulfate, 1377  
 dibasic sodium phosphate, 1377  
 magnesium perchlorate, 1377  
 magnesium sulfate, 1377  
 methanol, 1377  
 potassium carbonate, 1377  
 sodium acetate, 1377  
 sodium carbonate, 1377  
 sodium phosphate, monobasic, 1429  
 sodium sulfate, 1377  
 sodium sulfite, 1377

Anileridine, 1807  
 hydrochloride, 1808  
 hydrochloride tablets, 1809  
 injection, 1808

Aniline, 1377  
 blue, 1377  
 sulfate, 1377

Anion-exchange resin  
 50- to 100-mesh, styrene-divinylbenzene, 1377  
 strong, lightly cross-linked, in the chloride form, 1377  
 styrene-divinylbenzene, 1377  
*p*-Anisaldehyde, 1378

Anise oil, 5856

*p*-Anisidine, 1378

Anisole, 1378

Annotations  
 to NF 32, 5820  
 to USP 32, xi

Antazoline phosphate, 1810

Anthracene, 1378

Anthrallin, 1810  
 cream, 1811  
 ointment, 1812

Anthrax vaccine adsorbed, 1813

Anthrone, 1378  
 TS, 1446

Antibiotics—microbial assays (81), 77

Anticoagulant  
 citrate dextrose solution, 1815  
 citrate phosphate dextrose solution, 1816  
 citrate phosphate dextrose adenine solution, 1817  
 heparin solution, 3228  
 sodium citrate solution, 1819

Anti-D reagent, 1378

Anti-D (Rh<sub>0</sub>) reagent, 1378

Anti-factor Xa and anti-factor IIa assays for unfractionated and low molecular weight heparins (208), 152

Antifoam reagent, 1378

Antihuman globulin reagent, 1378

Antimicrobial  
 agents—content (341), 179  
 effectiveness testing (51), 52

Antimony  
 pentachloride, 1378  
 potassium tartrate, 1819  
 sodium tartrate, 1820  
 trichloride, 1379  
 trichloride TS, 1446

Antipyrine, 1820  
 and benzocaine otic solution, 1821  
 benzocaine, and phenylephrine hydrochloride otic solution, 1822

Antithrombin III, 1379  
 human, 1822

Apomorphine hydrochloride, 1824  
 tablets, 1825

Apparent intrinsic dissolution—dissolution testing procedures for rotating disk and stationary disk (1087), 831

Applications of nuclear magnetic resonance spectroscopy (1761), 1284

Application of water activity determination to nonsterile pharmaceutical products (1112), 925

Apraclonidine  
 hydrochloride, 1825  
 ophthalmic solution, 1826

Aprobarbital, 1379

Aprotinin, 1827  
 injection, 1829

Arctimomab injection, technetium Tc 99m, 4844

Arginine, 1829  
 capsules, 5250  
 hydrochloride, 1830  
 hydrochloride injection, 1831  
 tablets, 5250

Aripiprazole, 1831

Aromatic  
 castor oil, 2175  
 elixir, 5856

Arsanilic acid, 1832



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 non-sterile 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 I*). 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<sup>1</sup>: *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  $-50^{\circ}$ . 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  $1 \times 10^6$  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  $1 \times 10^6$  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  $1 \times 10^6$  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  $1 \times 10^5$  and  $1 \times 10^6$  cfu per mL of the product. For *Category 4* products (antacids) the final concentration of the test preparation after inoculation is between  $1 \times 10^5$  and  $1 \times 10^6$  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  $22.5 \pm 2.5^{\circ}$ . 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



# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.