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The designation on the cover of this publication, "USP NF 2009," is for ease of identification only. The publication contains two separate compendia: *The United States Pharmacopeia*, Thirty-Second Revision, and *The National Formulary*, Twenty-Seventh 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 change was adopted to give users more time to bring their methods and procedures into compliance with new and revised *USP–NF* requirements.

The table below describes the new official dates. The 2008 *USP31–NF26,* and the *Supplements* and *Interim Revision Announcements (IRAs)* to that edition, will be official until May 1, 2009, at which time the *USP32–NF27* becomes official.

Publication	Release Date	Official Date	Official Until
USP32–NF27	Nov. 1, 2008	May 1, 2009	May 1, 2010 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*)
First Supplement	Feb. 1, 2009	Aug. 1, 2009	May 1, 2010 (except as superceded by *Second Supplement, IRAs,* and *Revision Bulletins*)
Second Supplement	June 1, 2009	Dec. 1, 2009	May 1, 2010 (except as superceded by *IRAs* and *Revision Bulletins*)
USP33–NF28	Nov. 1, 2009	May 1, 2010	May 1, 2011 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*)

IRAs will continue to become official on the first day of the second month of the *Pharmacopeial Forum (PF)* issue in which they are published as final. For instance, *IRAs* published as final in the May-June *PF* (issue 3) will become official on June 1. This table gives the details of the *IRAs* that will apply to *USP31–NF26* and *USP32–NF27.*

*IRA**	Release Date	Official Date	Revises
Jan. 1, 2009 *IRA, PF* 35(1)	Jan. 1, 2009	Feb. 1, 2009	*USP31–NF26* and its *Supplements*
Mar. 1, 2009 *IRA, PF* 35(2)	Mar. 1, 2009	April 1, 2009	*USP31–NF26* and its *Supplements*
May 1, 2009 *IRA, PF* 35(3)	May 1, 2009	June 1, 2009	*USP32–NF27*
July 1, 2009 *IRA, PF* 35(4)	July 1, 2009	Aug. 1, 2009	*USP32–NF27* and *First Supplement*
Sept. 1, 2009 *IRA, PF* 35(5)	Sept. 1, 2009	Oct. 1, 2009	*USP32–NF27* and *First Supplement*
Nov. 1, 2009 *IRA, PF* 35(6)	Nov. 1, 2009	Dec. 1, 2009	*USP32–NF27* and its *Supplements*
Jan. 1, 2010 *IRA, PF* 36(1)	Jan. 1, 2010	Feb. 1, 2010	*USP32–NF27* and its *Supplements*
Mar. 1, 2010 *IRA, PF* 36(2)	Mar. 1, 2010	April 1, 2010	*USP32–NF27* and its *Supplements*

*NOTE—Beginning January 1, 2007, USP ceased identifying *IRAs* numerically (*First, Second,* etc.) and instead now designates them by the date on which they are published.

Revision Bulletins published on the USP website will continue to become official immediately upon publication, unless the *Revision Bulletin* specifies otherwise.

Revisions that contain a specific official date shall continue to become official upon such specified date, which supercedes the general official date for the publication.

For more information about the change in official dates, please visit the USP website at http://www.usp.org.

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Evaluation

For preparations supplied in containers with a nominal volume of more than 100 mL, apply the criteria of *Test 2.A*.

For preparations supplied in containers with a nominal volume of less than 100 mL, apply the criteria of *Test 2.B*.

For preparations supplied in containers with a nominal volume of 100 mL, apply the criteria of *Test 2.B*. [NOTE—*Test 2.A* is used in the *Japanese Pharmacopeia*.]

Test 2.A *(Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of more than 100 mL)*—The preparation complies with the test if the average number of particles present in the units tested does not exceed 12 per mL equal to or greater than 10 µm and does not exceed 2 per mL equal to or greater than 25 µm.

Test 2.B *(Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of less than 100 mL)*—The preparation complies with the test if the average number of particles present in the units tested does not exceed 3000 per container equal to or greater than 10 µm and does not exceed 300 per container equal to or greater than 25 µm.

⟨789⟩ PARTICULATE MATTER IN OPHTHALMIC SOLUTIONS

Particulate matter consists of mobile, randomly sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis because of the small amount of material they represent and because of their heterogeneous composition. Ophthalmic solutions should be essentially free from particles that can be observed on visual inspection. The tests described herein are physical tests performed for the purpose of enumerating extraneous particles within specific size ranges.

Every ophthalmic solution for which the monograph includes a test for *Particulate matter* is subject to the particulate matter limits set forth for the test being applied, unless otherwise specified in the individual monograph. When higher limits are appropriate, they will be specified in the individual monograph. Ophthalmic preparations that are suspensions, emulsions, or gels are exempt from these requirements, as are medical devices. Refer to the specific monograph when a question of test applicability occurs.

Light obscuration and microscopic procedures for the determination of particulate matter in ophthalmic solutions are identical to those for injections; therefore, where appropriate, *Particulate Matter in Injections* ⟨788⟩ is cross-referenced. This chapter provides a test approach in two stages. The ophthalmic solution is first tested by the light obscuration procedure (stage 1). If it fails to meet the prescribed limits, it must pass the microscopic procedure (stage 2) with its own set of test limits. Where for technical reasons the ophthalmic solution cannot be tested by light obscuration, microscopic testing may be used exclusively. Documentation is required, demonstrating that the light obscuration procedure is incapable of testing the ophthalmic solution or that it produces invalid results.

It is expected that most articles will meet the requirements on the basis of the light obscuration test alone; however, it may be necessary to test some articles by the light obscuration test followed by the microscopic test to reach a conclusion on conformance to requirements. Any product that is not a pure solution having a clarity and a viscosity approximating those of water may provide erroneous data when analyzed by the light obscuration counting method. Such materials may be analyzed by the microscopic counting method. In some instances, the viscosity of a material to be tested may be sufficiently high so as to preclude its analysis by either test method. In this event, a quantitative dilution with an appropriate diluent may be made to decrease viscosity, as necessary, to allow the analysis to be performed.

In the tests described below, the results obtained by examining a discrete unit or group of units for particulate matter cannot be extrapolated with certainty to other units that remain untested. Thus, sampling plans based on known operational factors must be developed if valid inferences are to be drawn from observed data to characterize the level of particulate matter in a large group of units. Sampling plans need to be based on consideration of product volume, particle numbers historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units.

LIGHT OBSCURATION PARTICLE COUNT TEST

This test applies to ophthalmic solutions, including solutions constituted from sterile solids, for which a test for *Particulate matter* is specified in the individual monograph. The test counts suspended particles that are solid or liquid.

Test Apparatus, Instrument Standardization, Test Environment, Test Procedure, and Calculations—Proceed as directed for *Light Obscuration Particle Count Test* under *Particulate Matter in Injections* ⟨788⟩.

Interpretation—The ophthalmic solution meets the requirements of the test if the average number of particles present in the units tested does not exceed the appropriate value listed in *Table 1*. If the average number of particles exceeds the limit, test the article by the *Microscopic Particle Count Test*.

Table 1. Light Obscuration Test Particle Count

	Diameter	
	≥ 10 µm	≥ 25 µm
Number of particles	50 per mL	5 per mL

MICROSCOPIC PARTICLE COUNT TEST

Some articles cannot be tested meaningfully by light obscuration. In such cases, individual monographs clearly specify that only a microscopic particle count is to be performed. The microscopic particle count test enumerates subvisible, essentially solid, particulate matter in ophthalmic solutions, after collection on a microporous membrane filter. Some ophthalmic solutions, such as solutions that do not filter readily because of their high viscosity, may be exempted from analysis using the microscopic test.

When performing the microscopic test, do not attempt to size or enumerate amorphous, semiliquid, or otherwise morphologically indistinct materials that have the appearance of a stain or discoloration on the membrane surface. These materials show little or no surface relief and present a gelatinous or film-like appearance. Because in solution this material consists of units on the order of 1 µm or less, which may be counted only after aggregation or deformation on an analytical membrane, interpretation of enumeration may be aided by testing a sample of the solution by the light obscuration particle count method.

Test Apparatus, Test Environment, Test Procedure, and Enumeration of Particles—Proceed as directed for *Microscopic Particle Count Test* under *Particulate Matter in Injections* ⟨788⟩.

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Interpretation—The ophthalmic solution meets the requirements of the test if the average number of particles present in the units tested does not exceed the appropriate value listed in *Table 2.*

Table 2. Microscopic Method Particle Count

	Diameter		
	≥ 10 µm	≥ 25 µm	≥ 50 µm
Number of particles	50 per mL	5 per mL	2 per mL

〈791〉 pH

For compendial purposes, pH is defined as the value given by a suitable, properly standardized, potentiometric instrument (pH meter) capable of reproducing pH values to 0.02 pH unit using an indicator electrode sensitive to hydrogen-ion activity, the glass electrode, and a suitable reference electrode. The instrument should be capable of sensing the potential across the electrode pair and, for pH standardization purposes, applying an adjustable potential to the circuit by manipulation of "standardization," "zero," "asymmetry," or "calibration" control, and should be able to control the change in millivolts per unit change in pH reading through a "temperature" and/or "slope" control. Measurements are made at 25 ± 2°, unless otherwise specified in the individual monograph or herein.

The pH scale is defined by the equation:

$$pH = pHs + (E - E_S) / k$$

in which E and E_S are the measured potentials where the galvanic cell contains the solution under test, represented by pH, and the appropriate *Buffer Solution for Standardization,* represented by pHs, respectively. The value of k is the change in potential per unit change in pH and is theoretically $[0.05916 + 0.000198(t - 25°)]$ volts at any temperature t.

It should be emphasized that the definitions of pH, the pH scale, and the values assigned to the *Buffer Solutions for Standardization* are for the purpose of establishing a practical, operational system so that results may be compared between laboratories. The pH values thus measured do not correspond exactly to those obtained by the definition, $pH = -\log a_{H^+}$. So long as the solution being measured is sufficiently similar in composition to the buffer used for standardization, the operational pH corresponds fairly closely to the theoretical pH. Although no claim is made with respect to the suitability of the system for measuring hydrogen-ion activity or concentration, the values obtained are closely related to the activity of the hydrogen-ion in aqueous solutions.

Where a pH meter is standardized by use of an aqueous buffer and then used to measure the "pH" of a nonaqueous solution or suspension, the ionization constant of the acid or base, the dielectric constant of the medium, the liquid-junction potential (which may give rise to errors of approximately 1 pH unit), and the hydrogen-ion response of the glass electrode are all changed. For these reasons, the values so obtained with solutions that are only partially aqueous in character can be regarded only as apparent pH values.

BUFFER SOLUTIONS FOR STANDARDIZATION OF THE pH METER

Buffer Solutions for Standardization are to be prepared as directed in the accompanying table.* Buffer salts of requisite purity can be obtained from the National Institute of Science and Technology. Solutions may be stored in hard glass or polyethylene bottles fitted with a tight closure or carbon dioxide-absorbing tube (soda lime). Fresh solutions should be prepared at intervals not to exceed 3 months using carbon dioxide-free water. The table indicates the pH of the buffer solutions as a function of temperature. The instructions presented here are for the preparation of solutions having the designated molal *(m)* concentrations. For convenience, and to facilitate their preparation, however, instructions are given in terms of dilution to a 1000-mL volume rather than specifying the use of 1000 g of solvent, which is the basis of the molality system of solution concentration. The indicated quantities cannot be computed simply without additional information.

Potassium Tetraoxalate, 0.05 m—Dissolve 12.61 g of $KH_3(C_2O_4)_2 \cdot 2H_2O$ in water to make 1000 mL.

Potassium Biphthalate, 0.05 m—Dissolve 10.12 g of $KHC_8H_4O_4$, previously dried at 110° for 1 hour, in water to make 1000 mL.

Equimolal Phosphate, 0.05 m—Dissolve 3.53 g of Na_2HPO_4 and 3.39 g of KH_2PO_4, each previously dried at 120° for 2 hours, in water to make 1000 mL.

Sodium Tetraborate, 0.01 m—Dissolve 3.80 g of $Na_2B_4O_7 \cdot 10H_2O$ in water to make 1000 mL. Protect from absorption of carbon dioxide.

Calcium Hydroxide, saturated at 25°—Shake an excess of calcium hydroxide with water, and decant at 25° before use. Protect from absorption of carbon dioxide.

Because of variations in the nature and operation of the available pH meters, it is not practicable to give universally applicable directions for the potentiometric determinations of pH. The general principles to be followed in carrying out the instructions provided for each instrument by its manufacturer are set forth in the following paragraphs. Examine the electrodes and, if present, the salt bridge prior to use. If necessary, replenish the salt bridge solution, and observe other precautions indicated by the instrument or electrode manufacturer.

* Commercially available buffer solutions for pH meter standardization, standardized by methods traceable to the National Institute of Standards and Technology (NIST), labeled with a pH value accurate to 0.01 pH unit may be used. For standardization solutions having a pH lower than 4, a labeled accuracy of 0.02 is acceptable. Solutions prepared from ACS reagent grade materials or other suitable materials, in the stated quantities, may be used provided the pH of the resultant solution is the same as that of the solution prepared from the NIST certified material.

pH Values of Buffer Solutions for Standardization

Temperature, °C	Potassium Tetraoxalate, 0.05 *m*	Potassium Biphthalate, 0.05 *m*	Equimolal Phosphate, 0.05 *m*	Sodium Tetraborate, 0.01 *m*	Calcium Hydroxide, Saturated at 25°
10	1.67	4.00	6.92	9.33	13.00
15	1.67	4.00	6.90	9.28	12.81
20	1.68	4.00	6.88	9.23	12.63
25	1.68	4.01	6.86	9.18	12.45
30	1.68	4.02	6.85	9.14	12.29
35	1.69	4.02	6.84	9.10	12.13
40	1.69	4.04	6.84	9.07	11.98
45	1.70	4.05	6.83	9.04	11.84
50	1.71	4.06	6.83	9.01	11.71

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