ASIAN EDITION

2008

USP NF

The Official Compendia of Standards

Volume 2

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U.S. PHARMACOPEIA
The Standard of Quality™

2008

USP 31 THE UNITED STATES PHARMACOPEIA

NF 26 THE NATIONAL FORMULARY

Asian Edition

Volume 2

By authority of the United States Pharmacopeial Convention, meeting at Washington, D.C., March 9–13, 2005. Prepared by the Council of Experts and published by the Board of Trustees

Official from May 1, 2008

The designation on the cover of this publication, ''USP NF 2008,'' is for ease of identification only. The publication contains two separate compendia: *The United States Pharmacopeia*, Thirty-First Revision, and *The National Formulary*, Twenty-Sixth 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 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 2007 *USP30–NF25,* and the *Supplements* and *Interim Revision Announcements (IRAs)* to that edition, will be official until May 1, 2008, at which time the *USP31–NF26* becomes official.

Publication	Release Date	Official Date	Official Until
USP31–NF26	Nov. 1, 2007	May 1, 2008	May 1, 2009 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*)
First Supplement	Feb. 1, 2008	Aug. 1, 2008	May 1, 2009 (except as superceded by *Second Supplement, IRAs,* and *Revision Bulletins*)
Second Supplement	June 1, 2008	Dec. 1, 2008	May 1, 2009 (except as superceded by *IRAs* and *Revision Bulletins*)
USP32–NF27	Nov. 1, 2008	May 1, 2009	May 1, 2010 (except as superceded by *Supplements, IRAs,* and *Revision Bulletins*)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 *USP30–NF25* and *USP31–NF26.*

*IRA**	Release Date	Official Date	Revises
Jan. 1, 2008 *IRA, PF* 34(1)	Jan. 1, 2008	Feb. 1, 2008	*USP30–NF25* and its *Supplements*
Mar. 1, 2008 *IRA, PF* 34(2)	Mar. 1, 2008	April 1, 2008	*USP30–NF25* and its *Supplements*
May 1, 2008 *IRA, PF* 34(3)	May 1, 2008	June 1, 2008	*USP31–NF26*
July 1, 2008 *IRA, PF* 34(4)	July 1, 2008	Aug. 1, 2008	*USP31–NF26* and *First Supplement*
Sept. 1, 2008 *IRA, PF* 34(5)	Sept. 1, 2008	Oct. 1, 2008	*USP31–NF26* and *First Supplement*
Nov. 1, 2008 *IRA, PF* 34(6)	Nov. 1, 2008	Dec. 1, 2008	*USP31–NF26* and its *Supplements*
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*

*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.

List Price: U.S. $425

Asian Edition

This edition is intended for use in and is not for sale outside the following countries or regions: Afghanistan, Bangladesh, Bhutan, Cambodia, China (including Hong Kong), India, Indonesia, South Korea, Laos, Malaysia, Mongolia, Nepal, Pakistan, Philippines, Singapore, Sri Lanka, Taiwan, Thailand, Vietnam.

ISSN 0195-7996

ISBN 1-889788-54-6

Printed in the United States by Port City Press, Baltimore

The *General Notices and Requirements* (hereinafter referred to as the *General Notices*) and general requirements appearing in *General Chapters* provide in summary form the basic guidelines for the interpretation and application of the standards, tests, assays, and other specifications of the *United States Pharmacopeia*and eliminate the need to repeat throughout the book those requirements that are pertinent in numerous instances. Where no specific language is given to the contrary, the requirements under the *General Notices* and *General Chapters*apply.

Where exceptions to the *General Notices* or *General Chapters* are made, the wording in the individual monograph takes precedence and specifically indicates the directions or the intent. To emphasize that such exceptions do exist, the *General Notices* or *General Chapters* in some places employ where indicated a qualifying expression such as "unless otherwise specified." In the individual monographs, it is understood that the specific wording of standards, tests, assays, and other specifications is binding wherever deviations from the *General Notices*or *General Chapters* exist whether or not a statement of exception is made.

TITLE

The full title of this publication, including its supplements, is *The Pharmacopeia of the United States of America,* Thirtieth Revision. This title may be abbreviated to *United States Pharmacopeia,* Thirtieth Revision, or to *USP 30.* The *United States Pharmacopeia,* Thirtieth Revision, supersedes all earlier revisions. Where the term "USP" is used, without further qualification, during the period in which this Pharmacopeia is official, it refers only to *USP 30* and any supplement(s) thereto. The same titles, with no further distinction, apply equally to print or electronic presentation of these contents.

"OFFICIAL" AND "OFFICIAL ARTICLES"

The word "official", as used in this Pharmacopeia or with reference hereto, is synonymous with "Pharmacopeial", with "USP", and with "compendial".

The designation "USP" in conjunction with the official title or elsewhere on the label of an article indicates that a monograph is included in the *USP* and that the article purports to comply with all applicable USP standards. The designation "USP" on the label may not and does not constitute a representation, endorsement, or incorporation by the manufacturer's labeling of the informational material contained in the USP monograph, nor does it constitute assurance by USP that the article is known to comply with USP standards. An article may purport to comply with a USP standard or other requirements only when the article is recognized in the *USP.* The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, whether or not the added designation "USP" is used. Names considered to be synonyms of the official titles may not be used for official titles.

Although both compendia, the *United States Pharmacopeia* and the *National Formulary,* currently are published under one cover, they remain separate compendia. The designation *USP–NF* or similar combination may be used on the label of an article, provided the label also bears a statement such as "Meets *NF* standards as published by the USP," indicating the particular compendium to which the article purports to apply.

Where an article differs from the standards of strength, quality, and purity, as determined by the application of the assays and tests set forth for it in the Pharmacopeia, its difference shall be plainly stated on its label. Where an article fails to comply in identity with the identity prescribed in the *USP,* or contains an added substance that interferes with the prescribed assays and tests, such article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in the Pharmacopeia.

Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for use as drugs, as nutritional or dietary supplements, or as medical devices and when bought, sold, or dispensed for these purposes or when labeled as conforming to this Pharmacopeia.

An article is deemed to be recognized in this Pharmacopeia when a monograph for the article is published in it, including its supplements, addenda, or other interim revisions, and an official date is generally or specifically assigned to it.

The following terminology is used for distinguishing the articles for which monographs are provided: an *official substance* is an active drug entity, a recognized nutrient, a dietary supplement ingredient, or a pharmaceutic ingredient (see also *NF 26*) or a component of a finished device for which the monograph title includes no indication of the nature of the finished form; an *official preparation* is a *drug product,* a *nutritional supplement, dietary supplement,* or a *finished device.* It is the finished or partially finished (e.g., as in the case of a sterile solid to be constituted into a solution for administration) preparation or product of one or more official substances formulated for use on or for the patient or consumer; an *article* is an item for which a monograph is provided, whether an official substance or an official preparation.

Designating Conformance with Official Standards—When the letters "USP" or "NF" or "USP–NF" are used on the label of an article to indicate compliance with compendial standards, the letters shall appear in conjunction with the official title of the article or when appropriate, with the ingredients contained therein. The letters are not to be enclosed in any symbol such as a circle, square, etc., and must appear in block capital letters.

If a dietary supplement purports to be or is represented as an official product and such claim is determined by the USP not to be made in good faith, it is the policy of the USP to seek appropriate legal redress.

Products Not Marketed in the United States—Interest in the USP outside the United States has always existed. From time to time, monographs may be adopted for articles not legally marketed in the United States as a service to authorities in other countries where USP standards are recognized and applied. Appearance of any such monograph does not grant any marketing rights whatsoever, and the status of the article in the United States must be checked with the U.S. Food and Drug Administration in the event of any question.

Nutritional and Other Dietary Supplements—The designation of an official preparation containing one or more recognized nutrients or dietary supplement ingredients as "USP" or the use of the designation "USP" in conjunction with the title of such nutritional or dietary supplement preparation may be made only if the preparation meets all the applicable requirements contained in the individual monograph and general chapters. Any language modifying or limiting this representation shall be accompanied by a statement indicating that the article is "not USP", and indicating how the article differs from the standards of strength, quality, or purity as determined by the application of the tests and assays set forth in the compendia. Any additional ingredient in such article that is not recognized in the Pharmacopeia and for which nutritional value is claimed shall not be represented nor imply that such ingredient is of USP quality or recognized by USP. If a preparation does not comply with all applicable requirements but contains nutrients or dietary supplement ingredients that are recognized in the *USP,* the article may not designate the individual nutrients or ingredients as complying with USP standards or being of USP quality without designating on the label that the article itself does not comply with USP standards.

ATOMIC WEIGHTS AND CHEMICAL FORMULAS

The atomic weights used in computing molecular weights and the factors in the assays and elsewhere are those recommended in 1997 by the IUPAC Commission on Atomic Weights and Isotopic Abundances. Chemical formulas, other than those in the Definitions, tests, and assays, are given for purposes of information and calculation. The format within a given monograph is such that after the official title, the primarily informational portions of the text appear first, followed by the text comprising requirements, the latter section of the monograph being introduced by a boldface double-arrow symbol ». (Graphic formulas and chemical nomenclature provided as information in the individual monographs are discussed in the *Preface.*)

ABBREVIATIONS

The term RS refers to a USP Reference Standard as stated under *Reference Standards* in these *General Notices* (see also *USP Reference Standards* ⟨11⟩ for a comprehensive discussion of reference materials).

The terms CS and TS refer to Colorimetric Solution and Test Solution, respectively (see under *Reagents, Indicators, and Solutions*). The term VS refers to Volumetric Solution as stated under *Solutions* in the *General Notices*.

The term *PF* refers to *Pharmacopeial Forum*, the journal of standards development and official compendia revision (see *Pharmacopeial Forum* in these *General Notices*).

Abbreviations for the names of many institutions, organizations, and publications are used for convenience throughout *USP* and *NF*. An alphabetized tabulation follows.

Abbreviation	Institution, Organization, or Publication
AAMI	Association for the Advancement of Medical Instrumentation
ACS	American Chemical Society
ANSI	American National Standards Institute
AOAC	AOAC International (formerly Association of Official Analytical Chemists)
ASTM	American Society for Testing and Materials
ATCC	American Type Culture Collection
CAS	Chemical Abstracts Service
CFR	U.S. Code of Federal Regulations
EP	European Pharmacopoeia
EPA	U.S. Environmental Protection Agency
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
HIMA	Health Industry Manufacturers Association
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JP	Japanese Pharmacopoeia
NIST	National Institute of Standards and Technology
USAN	United States Adopted Names
WHO	World Health Organization

Abbreviated Statements in Monographs—Incomplete sentences are employed in various portions of the monographs for directness and brevity. Where the limit tests are so abbreviated, it is to be understood that the chapter numbers (shown in angle brackets) designate the respective procedures to be followed, and that the values specified after the colon are the required limits.

SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures—The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see *Titrimetry* ⟨541⟩).

Tolerances—The limits specified in the monographs for Pharmacopeial articles are established with a view to the use of these articles as drugs, nutritional or dietary supplements, or devices, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

A dosage form shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. The tolerances and limits stated in the Definitions in the monographs for Pharmacopeial articles allow for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. Where the minimum amount of a substance present in a nutritional or dietary supplement is required to be higher than the lower tolerance limit allowed for in the monograph because of applicable legal requirements, then the upper tolerance limit contained in the monograph shall be increased by a corresponding amount.

The specified tolerances are based upon such attributes of quality as might be expected to characterize an article produced from suitable raw materials under recognized principles of good manufacturing practice.

The existence of compendial limits or tolerances does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" the Pharmacopeial quality. Similarly, the fact that an article has been prepared to closer tolerances than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the Pharmacopeial requirements.

Interpretation of Requirements—Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated limits to determine whether there is conformance with compendial assay or test requirements. The observed or calculated values usually will contain more significant figures than there are in the stated limit, and a reportable result is to be rounded off to the number of places that is in agreement with the limit expression by the following procedure. Intermediate calculations (e.g., slope for linearity in *Validation of Compendial Procedures* ⟨1225⟩) may be rounded for reporting purposes, but the original value (not rounded) should be used for any additional required calculations. Rounding off should not be done until the final calculations for the reportable value have been completed. [NOTE—Limits, which are fixed numbers, are not rounded off.]

A reportable value is often a summary value for several individual determinations. It is the end result of a completed measurement method, as documented. It is the value compared with the acceptance criterion. In most cases, the reportable value is used as documentation for internal or external users.

When rounding off is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is greater than 5, it is eliminated and the preceding digit is increased by one. If this digit equals 5, the 5 is eliminated and the preceding digit is increased by one.

Illustration of Rounding Numerical Values for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit ≥98.0%	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit ≤101.5%	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes
Limit test ≤0.02%	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤3ppm	0.00035%	0.0004%	No
	0.00025%	0.0003%	Yes
	0.00028%	0.0003%	Yes

GENERAL CHAPTERS

Each general chapter is assigned a number that appears in brackets adjacent to the chapter name (e.g., ⟨621⟩ *Chromatography*). Articles recognized in these compendia must comply with the official standards and tests and assays in the *General Notices*, relevant monographs, and General Chapters numbered below 1000. General Chapters numbered above 1000 are considered interpretive and are intended to provide information on, give definition to, or describe a particular subject. They contain no official standards, tests, assays, or other mandatory requirements applicable to any Pharmacopeial article unless specifically referenced in a monograph or elsewhere in the Pharmacopeia.

The use of the general chapter numbers is encouraged for identification of and rapid access to general tests and information. It is especially helpful where monograph section headings and chapter names are not the same (e.g., *Ultraviolet Absorption* ⟨197U⟩ in a monograph refers to method ⟨197U⟩ under general tests chapter ⟨197⟩ *Spectrophotometric Identification Tests; Specific rotation* ⟨781S⟩ in a monograph refers to method ⟨781S⟩ under general tests chapter ⟨781⟩ *Optical Rotation;* and *Calcium* ⟨191⟩ in a monograph refers to the tests for *Calcium* under general tests chapter ⟨191⟩ *Identification Tests—General*).

PHARMACOPEIAL FORUM

Pharmacopeial Forum (PF) is the USP journal of standards development and official compendia revision. *Pharmacopeial Forum* is the working document of the USP Council of Experts. It is intended to provide public portions of communications within the General Committee of Revision and public notice of proposed new and revised standards of the *USP* and *NF* and to afford opportunity for comment thereon. The organization of *PF* includes, but is not limited to, the following sections. Subsections occur where needed for Drugs and Pharmaceutic Ingredients (Excipients) and for Dietary Supplements.

Interim Revision Announcement (if present)—Official revisions and their effective dates, announcement of the availability of new USP Reference Standards, and announcement of assays or tests that are held in abeyance pending availability of required USP Reference Standards.

In-Process Revision—New or revised monographs or chapters that are proposed for adoption as official *USP* or *NF* standards.

Pharmacopeial Previews—Possible revisions or new monographs or chapters that are considered to be in a preliminary stage of development.

Stimuli to the Revision Process—Reports, statements, articles, or commentaries relating to compendial issues.

Nomenclature—Articles and announcements relevant to compendial nomenclature issues and listings of suggested and new United States Adopted Names (USAN) and International Nonproprietary Names (INN).

Official Reference Standards—Catalog of current lots of USP Reference Standards with ordering information and names and addresses of worldwide suppliers.

SUPPLEMENTS

Supplements to official text are published periodically and include text previously published in *PF*,which is ready to be made official.

REAGENT STANDARDS

The proper conduct of the Pharmacopeial tests and assays and the reliability of the results depend, in part, upon the quality of the reagents used in the performance of the procedures. Unless otherwise specified, reagents are to be used that conform to the specifications set forth in the current edition of *Reagent Chemicals* published by the American Chemical Society. Where such ACS reagent specifications are not available or where for various reasons the required purity differs, compendial specifications for reagents of acceptable quality are provided (see *Reagents, Indicators, and Solutions*). Listing of these reagents, including the indicators and solutions employed as reagents, in no way implies that they have therapeutic utility; furthermore, any reference to USP or NF in their labeling shall include also the term "reagent" or "reagent grade."

REFERENCE REAGENTS

Some compendial tests or assays require the use of specific reagents. These are supplied by USP when they might not be generally commercially available or because they are necessary for the testing and are available only to the originator of the tests or assay.

USP REFERENCE STANDARDS

USP Reference Standards are authentic specimens that have been approved by the USP Reference Standards Committee as suitable for use as comparison standards in *USP* or *NF* tests and assays. (see *USP Reference Standards* ⟨11⟩.) Currently official lots of USP Reference Standards are published in *Pharmacopeial Forum.*

Where a USP Reference Standard is referred to in a monograph or chapter, the words "Reference Standard" are abbreviated to "RS" (see *USP Reference Standards* ⟨11⟩).

Where a test or an assay calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article is to be used.

The requirements for any new *USP* or *NF* standards, tests, or assays for which a new USP Reference Standard is specified are not in effect until the specified USP Reference Standard is available. The availability of new USP Reference Standards and the official dates of the *USP* or *NF* standards, tests, or assays requiring their use are announced via *Supplements* or *Interim Revision Announcements.*

UNITS OF POTENCY

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Units defined by USP Reference Standards are USP Units, and the individual monographs refer to these. Unless otherwise indicated, USP Units are equivalent to the corresponding International Units, where such exist. Such equivalence is usually established on the basis solely of the compendial assay for the substance.

For biological products, whether or not International Units or USP Units do exist (see *Biologics* ⟨1041⟩), units of potency are defined by the corresponding U.S. Standard established by the FDA.

INGREDIENTS AND PROCESSES

Official drug products and finished devices are prepared from ingredients that meet the requirements of the compendial monographs for those individual ingredients for which monographs are provided (see also *NF 26*). Generally, nutritional and dietary supplements are prepared from ingredients that meet requirements of the compendial monographs for those ingredients for which monographs are provided, except that substances of acceptable food grade quality may be used in the event of a difference.

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs (see also *Foreign Substances and Impurities* under *Tests and Assays*).

Preparations for which a complete composition is given in this Pharmacopeia, unless specifically exempted herein or in the individual monograph, are to contain only the ingredients named in the formulas. However, there may be deviation from the specified

processes or methods of compounding, though not from the ingredients or proportions thereof, provided the finished preparation conforms to the relevant standards laid down herein and to preparations produced by following the specified process.

The tolerances specified in individual monographs and in the general chapters for compounded preparations are based on attributes of quality such as might be expected to characterize an article compounded from suitable bulk drug substances and ingredients in accordance with the procedures provided or under recognized principles of good pharmaceutical practice as described in this Pharmacopeia (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩) and elsewhere.

Monographs for preparations intended to be compounded pursuant to prescription may contain assay methods. Assay methods are not intended for evaluating a compounded preparation prior to dispensing. Assay methods are intended to serve as the official test methods in the event of a question or dispute as to whether the compounded preparation complies with official standards.

Where a monograph on a preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried prior to use if due allowance is made for the water or other volatile substances present in the quantity taken.

Unless specifically exempted elsewhere in this Pharmacopeia, the identity, strength, quality, and purity of an official article are determined by the definition, physical properties, tests, assays, and other specifications relating to the article, whether incorporated in the monograph itself, in the *General Notices,* or in the section *General Chapters.*

Water—Water used as an ingredient of official preparations meets the requirements for *Purified Water,* for *Water for Injection,* or for one of the sterile forms of water covered by a monograph in this Pharmacopeia.

Potable water meeting the requirements for drinking water as set forth in the regulations of the U.S. Environmental Protection Agency may be used in the preparation of official substances.

Alcohol—All statements of percentages of alcohol, such as under the heading *Alcohol content,* refer to percentage, by volume, of C_2H_5OH at 15.56°. Where reference is made to "C_2H_5OH," the chemical entity possessing absolute (100 percent) strength is intended.

Alcohol—Where "alcohol" is called for in formulas, tests, and assays, the monograph article *Alcohol* is to be used.

Dehydrated Alcohol—Where "dehydrated alcohol" (absolute alcohol) is called for in tests and assays, the monograph article *Dehydrated Alcohol* is to be used.

Denatured Alcohol—Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of Pharmacopeial preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A finished product that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a normal ingredient or a permissible added substance; in either case the denaturant must be identified on the label of the topical preparation. Where a process is given in the individual monograph, the preparation so made must be identical with that prepared by the given process.

Added Substances—An official substance, as distinguished from an official preparation, contains no added substances except where specifically permitted in the individual monograph. Where such addition is permitted, the label indicates the name(s) and amount(s) of any added substance(s).

Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices,* suitable substances such as antimicrobial agents, bases, carriers, coatings, colors, flavors, preservatives, stabilizers, and vehicles may be added to an official preparation to enhance its stability, usefulness, or elegance or to facilitate its preparation. Such substances are regarded as unsuitable and are prohibited unless (a) they are harmless in the amounts used, (b) they do not exceed the minimum quantity required for providing their intended effect, (c) their presence does not impair the bioavailability or the therapeutic efficacy or safety of the official preparation, and (d) they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.

Nutritional and Dietary Supplements—Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices,* consistent with applicable regulatory requirements, suitable added substances such as bases, carriers, coatings, colors, flavors, preservatives, and stabilizers may be added to a nutritional supplement preparation to enhance its stability, usefulness, or elegance, or to facilitate its preparation. Such added substances shall be regarded as suitable and shall be permitted unless they interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards.

Additional Ingredients—Additional ingredients, including excipients, may be added to nutritional supplement preparations containing recognized nutrients, consistent with applicable regulatory requirements, provided that they do not interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards.

Inert Headspace Gases—The air in a container of an article for parenteral use may be evacuated or be replaced by carbon dioxide, helium, or nitrogen, or by a mixture of these gases, which fact need not be declared in the labeling.

Colors—Added substances employed solely to impart color may be incorporated into official preparations, except those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the FDA, provided such added substances are otherwise appropriate in all respects. (See also *Added Substances* under *Injections* ⟨1⟩.)

Ointments and Suppositories—In the preparation of ointments and suppositories, the proportions of the substances constituting the base may be varied to maintain a suitable consistency under different climatic conditions, provided the concentrations of active ingredients are not varied and the bioavailability, therapeutic efficacy, or safety of the preparation is not impaired.

Change to read:

TESTS AND ASSAYS

Apparatus—A specification for a definite size or type of container or apparatus in a test or assay is given solely as a recommendation. Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed. (See also *Thermometers* ⟨21⟩, *Volumetric Apparatus* ⟨31⟩, and *Weights and Balances* ⟨41⟩.) Where low-actinic or light-resistant containers are specified, clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

Where an instrument for physical measurement, such as a spectrophotometer, is specified in a test or assay by its distinctive name, another instrument of equivalent or greater sensitivity and accuracy may be used. In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used, solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure.

Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification. Items capable of equal or better performance may be used if these characteristics have been validated.

Where the use of a centrifuge is indicated, unless otherwise specified, the directions are predicated upon the use of apparatus having an effective radius of about 20 cm (8 inches) and driven at a speed sufficient to clarify the supernatant layer within 15 minutes.

Unless otherwise specified, for chromatographic tubes and columns the diameter specified refers to internal diameter (ID); for other types of tubes and tubing the diameter specified refers to outside diameter (OD).

Steam Bath—Where the use of a steam bath is directed, exposure to actively flowing steam or to another form of regulated heat, corresponding in temperature to that of flowing steam, may be used.

Water Bath—Where the use of a water bath is directed without qualification with respect to temperature, a bath of vigorously boiling water is intended.

Foreign Substances and Impurities—Tests for the presence of foreign substances and impurities are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* ⟨1086⟩).

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the source of material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.

Other Impurities—Official substances may be obtained from more than one process, and thus may contain impurities not considered during preparation of monograph assays or tests. Wherever a monograph includes a chromatographic assay or purity test based on chromatography, other than a test for organic volatile impurities, and that monograph does not detect such an impurity, solvents excepted, the impurity shall have its amount and identity, where both are known, stated under the heading *Other Impurity(ies)* by the labeling (certificate of analysis) of the official substance.

The presence of any unlabeled impurity in an official substance is a variance from the standard if the content is 0.1% or greater. Tests suitable for detecting and quantitating unlabeled impurities, when present as the result of process change or other identifiable, consistent occurrence, shall be submitted to the USP for inclusion in the individual monograph. Otherwise, the impurity shall be identified, preferably by name, and the amount listed under the heading *Other Impurity(ies)* in the labeling (certificate of analysis) of the official substance. The sum of all *Other Impurities* combined with the monograph-detected impurities does not exceed 2.0% (see *Ordinary Impurities* ⟨466⟩), unless otherwise stated in the monograph.

Categories of drug substances excluded from *Other Impurities* requirements are fermentation products and semi-synthetics derived therefrom, radio pharmaceuticals, biologics, biotechnology-derived products, peptides, herbals, and crude products of animal or plant origin. Any substance known to be toxic must not be listed under *Other Impurities.*

Residual Solvents—The requirements are stated in *Residual Solvents* ⟨467⟩ together with information in *Impurities in Official Articles* ⟨1086⟩. Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in *Residual Solvents* ⟨467⟩, using the general methods presented therein or other suitable methods. (Official July 1, 2008•5)

Procedures—Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the use of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures used. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for ensuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing *process validation* studies and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not fewer than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy. To minimize environmental impact or contact with hazardous materials, apparatus and chemicals specified in Pharmacopeial procedures also may be proportionally changed.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not fewer than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.

Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not fewer than a given number, usually 20, of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.

Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the *Assay* procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on drying,* or *Water,* or *Loss on ignition,* respectively, is given in the monograph. Results are calculated on an "as-is" basis unless otherwise specified in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for *Loss on drying* or *Water,* the expression "previously dried" without qualification

signifies that the substance is to be dried as directed under *Loss on drying* or *Water* (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter *USP Reference Standards* ⟨11⟩, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within 10% of the specified weight or volume. However, the weight or volume taken is accurately determined, and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under *Volumetric Apparatus* ⟨31⟩, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under *Volumetric Apparatus* ⟨31⟩, may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as "25.0 mL" and "25.0 mg," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under *Volumetric Apparatus* ⟨31⟩ or under *Weights and Balances* ⟨41⟩.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also *Use of Reference Standards* under *Spectrophotometry and Light-Scattering* ⟨851⟩.

Blank Determination—Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

Desiccator—The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution—Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see *Volumetric Apparatus* ⟨31⟩).

Drying to Constant Weight—The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration—Where it is directed to "filter," without further qualification, the intent is that the liquid be passed through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests—The Pharmacopeial tests headed *Identification* are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight—The specification "ignite to constant weight" means that the ignition shall be continued, at 800 ±25° unless otherwise indicated, until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators—Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL, or 3drops, of the solution shall be added, unless otherwise directed.

Logarithms—Logarithms used in the assays are to the base10.

Microbial Strains—Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible—This term indicates a quantity not exceeding 0.50mg.

Odor—Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, either of a freshly opened package of the article (for packages containing not more than 25 g) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about100-mL capacity. An odor designation is descriptive only and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements—The term "mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated interns of the pressure exerted by a column of mercury of the stated height.

Solutions—Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with *Purified Water.*

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid is to be diluted with, or 1 part *by weight* of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts *by volume.*

An expression such as "(20 : 5 : 2)" means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under *Volumetric Solutions* in the section *Reagents, Indicators, and Solutions,* and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity maybe used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity—Unless otherwise stated, the specific gravity basis is 25°/25°, i.e., the ratio of the weight of a substance in air at 25°to the weight of an equal volume of water at the same temperature.

Temperatures—Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at 25°. Where moderate heat is specified, any temperature not higher than 45° (113° F) is indicated. See *Storage Temperature* under *Preservation, Packaging, Storage, and Labeling* for other definitions.

Time Limit—In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum—The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water—Where water is called for in tests and assays, *Purified Water* is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide–free water," see the introduction to the section *Reagents, Indicators, and Solutions.* For *High-Purity Water* see *Containers* ⟨661⟩.

Water and Loss on Drying—Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading *Water.* Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the testis gen-

erally given under the heading *Loss on drying*. However,*Loss on drying* is most often given as the heading where the loss in weight is known to represent residual volatile constituents, including organic solvents as well as water.

Test Results, Statistics, and Standards—Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to ensure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply.

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for *Dissolution*and *Uniformity of dosage units*, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.

Where the *Content Uniformity* determinations have been made using the same procedure specified in the *Assay*, the average of all of the individual *Content Uniformity* determinations may be used as the *Assay* value.

Description—Information on the "description" pertaining to an article, which is relatively general in nature, is provided in the reference table *Description and Relative Solubility of USP and NF Articles* in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility—The statements concerning solubilities given in the reference table *Description and Relative Solubility of USP and NF Articles* for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	Greater than or equal to 10,000

Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

Interchangeable Methods—Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the *European Pharmacopoeia*and/or the *Japanese Pharmacopoeia* and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method from one of these pharmacopeias, it should comply with the requirements of the *United States Pharmacopeia*. However, where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

PRESCRIBING AND DISPENSING

Prescriptions for compendial articles shall be written to state the quantity and/or strength desired in metric units unless otherwise indicated in the individual monograph (see also *Units of Potency* in these *General Notices*). If an amount is prescribed by any other system of measurement, only an amount that is the metric equivalent of the prescribed amount shall be dispensed.

PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers—The *container* is that which holds the article and is or may be in direct contact with the article. The *immediate container* is that which is in direct contact with the article at all times. The *closure* is a part of the container.

Prior to being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

Tamper-Evident Packaging —The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-evident packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging used by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-Resistant Container (see *Light Transmission* under *Containers* ⟨661⟩)—A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in alight-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-Closed Container—A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container—A tight container protects the contents from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution; and is capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-Index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE—Where packaging and storage in a *tight container*or a *well-closed container* is specified in the individual monograph, the container used for an article when dispensed on prescription meets the requirements under *Containers—Permeation* ⟨671⟩.

Hermetic Container—A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-Unit Container—A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-Dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-Dose Container—A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Unit-of-Use Container—A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

Multiple-Unit Container—A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-Dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

Poison Prevention Packaging Act—This act (see the Website, www.cpsc.gov/businfo/pppa.html) requires special packaging of most human oral prescription drugs, oral controlled drugs, certain nonoral prescription drugs, certain dietary supplements, and many over-the-counter (OTC) drug preparations in order to protect the public from personal injury or illness from misuse of these preparations (16 CFR § 1700.14).

The immediate packaging of substances regulated under the PPPA must comply with the special packaging standards (16 CFR § 1700.15 and 16 CFR § 1700.20). The PPPA regulations for special packaging apply to all packaging types including reclosable, nonclosable, and unit-dose types.

Special packaging is not required for drugs dispensed within a hospital setting for inpatient administration. Manufacturers and packagers of bulk-packaged prescription drugs do not have to use special packaging if the drug will be repackaged by the pharmacist. PPPA-regulated prescription drugs may be dispensed in nonchild-resistant packaging upon the request of the purchaser or when directed in a legitimate prescription (15 U.S.C. § 1473).

Manufacturers or packagers of PPPA-regulated OTC preparations are allowed to package one size in nonchild-resistant packaging as long as popular-size, special packages are also supplied. The nonchild-resistant package requires special labeling (18 CFR § 1700.5).

Various types of child-resistant packages are covered in ASTM International Standard D-3475, Standard Classification of Child-Resistant Packaging. Examples are included as an aid in the understanding and comprehension of each type of classification.

Storage Temperature and Humidity—Specific directions are stated in some monographs with respect to the temperatures and humidity at which Pharmacopeial articles shall be stored and distributed (including the shipment of articles to the consumer) when stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply (see also *Pharmaceutical Stability* ⟨1150⟩). The conditions are defined by the following terms.

Freezer—A place in which the temperature is maintained thermostatically between −25° and −10° (−13° and14 °F).

Cold—Any temperature not exceeding 8° (46 °F). A *refrigerator* is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46°F).

Cool—Any temperature between 8° and 15° (46° and59 °F). An article for which storage in a *cool place*is directed may, alternatively, be stored and distributed in a *refrigerator,* unless otherwise specified by the individual monograph.

Controlled Cold Temperature—This temperature is defined as the temperature maintained thermostatically between 2° and 8° (36° and 46 °F),that allows for excursions in temperature between 0° and 15° (32°and 59 °F) that may be experienced during storage, shipping, and distribution such that the allowable calculated MKT is not more than 8° (46°F). Transient spikes up to 25° (77 °F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise.

Room Temperature—The temperature prevailing in a working area.

Controlled Room Temperature—A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°(68° to 77 °F); that results in a mean kinetic temperature calculated to be not more than 25°; and that allows for excursions between 15° and30° (59° and 86 °F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40° are permitted as long as they do not exceed 24 hours. Spikes above 40° may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also *Pharmaceutical Stability* ⟨1150⟩.)

An article for which storage at *Controlled Room Temperature* is directed may, alternatively, be stored and distributed in a *cool place,* unless otherwise specified in the individual monograph or on the label.

Warm—Any temperature between 30° and 40° (86° and104 °F).

Excessive Heat—Any temperature above 40° (104°F).

Protection from Freezing—Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Dry Place—The term "dry place" denotes a place that does not exceed 40% average relative humidity at *Controlled Room Temperature* or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value is 40% relative humidity.

Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered a dry place.

Storage under Nonspecific Conditions—Where no specific directions or limitations are provided in the *Packaging and storage* section of individual monographs or in the article's labeling, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Articles shall be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Active pharmaceutical ingredients are exempt from this requirement.

Labeling—The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.

Amount of Ingredient per Dosage Unit—The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in *Deliverable Volume* ⟨698⟩. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see *Percentage Measurements*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also *Units of Potency* in these *General Notices*).

Use of Leading and Terminal Zeros—In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than 1 shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2mg]).

Labeling of Salts of Drugs—It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g.,Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-Containing Products—The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol).The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

Labeling Botanical-Containing Products—The label of an herb or other botanical intended for use as a dietary supplement bears the statement, "If you are pregnant or nursing a baby, seek the advice of a health professional before using this product."

Labeling Parenteral and Topical Preparations—The label of a preparation intended for parenteral or topical use states the names of all added substances (see *Added Substances* in these *General Notices and Requirements*, and see *Labeling* under *Injections* ⟨1⟩), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes—The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol—The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C_2H_5OH.

Special Capsules and Tablets—The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.

Expiration Date and Beyond-Use Date—The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," or "Expires 6/89"). [NOTE—For additional information and guidance, refer to the Nonprescription Drug Manufacturers Association's *Voluntary Codes and Guidelines of the OTC Medicines Industry.*]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article must not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the *General Notices and Requirements* of this Pharmacopeia. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution prior to use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall,

on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) 1 year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be 1 year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser must maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than 25°. The plastic material used in packaging the dosage forms must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records must be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

Pharmaceutical Compounding—The label on the container or package of an official compounded preparation shall bear a beyond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, is to be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see *Stability Criteria and Beyond-Use Dating* under *Stability of Compounded Preparations* in the general tests chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Guidelines for Packaging and Storage Statements in *USP–NF* Monographs—In order to provide users of the *USP–NF* with proper guidance on how to package and store compendial articles, every monograph in the *USP–NF* is required to have a packaging and storage specification.

For those instances where, for some reason, storage information is not yet found in the *Packaging and storage* specification of a monograph, the section *Storage Under Nonspecific Conditions* is included in the *General Notices* as interim guidance. The *Storage Under Nonspecific Conditions* statement is not meant to substitute for the inclusion of proper, specific storage information in the *Packaging and storage* statement of any monograph.

For the packaging portion of the statement, the choice of containers is given in the *General Notices* and includes *Light-Resistant Container, Well-Closed Container, Tight Container, Hermetic Container, Single-Unit Container, Single-Dose Container, Unit-Dose Container,* and *Unit-of-Use Container.* For most preparations, the choice is determined by the container in which it is to be dispensed (e.g., tight, well-closed, hermetic, unit-of-use, etc). For active pharmaceutical ingredients (APIs), the choice would appear to be tight, well-closed, or, where needed, a light-resistant container. For excipients, given their typical nature as large-volume commodity items, with containers ranging from drums to tank cars, a well-closed container is an appropriate default. Therefore, in the absence of data indicating a need for a more protective class of container, the phrase "Preserve in well-closed containers" should be used as a default for excipients.

For the storage portion of the statement, the choice of storage temperatures presented in the *General Notices* includes *Freezer, Cold, Cool, Controlled Cold Temperature, Room Temperature, Controlled Room Temperature, Warm, Excessive Heat,* and *Protection from Freezing.* The definition of a dry place is provided if protection from humidity is important.

For most preparations, the choice is determined by the experimentally determined stability of the preparation and may include any of the previously stated storage conditions as determined by the manufacturer. For APIs that are expected to be retested before incorporation into a preparation, a more general and nonrestrictive condition may be desired. In this case, the specification "room temperature" (the temperature prevailing in a working area) should suffice. The use of the permissive room temperature condition reflects the stability of an article over a wide temperature range. For excipients, the phrase "No storage requirements specified" in the *Packaging and storage* statement of the monograph would be appropriate.

Because most APIs in the *USP–NF* have associated Reference Standards, special efforts should be considered to ensure that the Reference Standards' storage conditions correspond to the conditions indicated in the *USP–NF* monographs.

The Packaging and Storage Expert Committee may review questionable *Packaging and storage* statements on a case-by-case basis. In cases where the *Packaging and storage* statements are incomplete, the monographs would move forward to publication while the *Packaging and storage* statements are temporarily deferred.

VEGETABLE AND ANIMAL SUBSTANCES

The requirements for vegetable and animal substances apply to the articles as they enter commerce; however, lots of such substances intended solely for the manufacture or isolation of volatile oils, alkaloids, glycosides, or other active principles may depart from such requirements.

Statements of the distinctive microscopic structural elements in powdered substances of animal or vegetable origin may be included in the individual monograph as a means of determining identity, quality, or purity.

Foreign Matter—Vegetable and animal substances are to be free from pathogenic organisms (see *Microbiological Attributes of Nonsterile Pharmaceutical Products* ⟨1111⟩), and are to be as free as reasonably practicable from microorganisms, insects, and other animal contamination, including animal excreta. They shall show no abnormal discoloration, abnormal odor, sliminess, or other evidence of deterioration.

The amount of foreign inorganic matter in vegetable or animal substances, estimated as *Acid-insoluble ash,* shall not exceed 2 percent of the weight of the substance, unless otherwise specified in the individual monograph.

Before vegetable substances are ground or powdered, stones, dust, lumps of soil, and other foreign inorganic matter are to be removed by mechanical or other suitable means.

In commerce it is seldom possible to obtain vegetable substances that are without some adherent or admixed, innocuous, foreign matter, which usually is not detrimental. No poisonous, dangerous, or otherwise noxious foreign matter or residues may be present. Foreign matter includes any part of the plant not specified as constituting the substance.

Preservation—Vegetable or animal substances may be protected from insect infestation or microbiological contamination by means of suitable agents or processes that leave no harmful residues.

WEIGHTS AND MEASURES

The International System of Units (SI) is used in this Pharmacopeia. The SI metric and other units, and the symbols commonly employed, are as follows.

Bq = becquerel
kBq = kilobecquerel
MBq = megabecquerel
GBq = gigabecquerel
Ci = curie
mCi = millicurie
μCi = microcurie
nCi = nanocurie
Gy = gray
mGy = milligray
m = meter
dm = decimeter
cm = centimeter
mm = millimeter
μm = micrometer (0.001mm)
nm = nanometer *
kg = kilogram
g = gram**
mg = milligram
μg; mcg = microgram†
ng = nanogram
pg = picogram
fg = femtogram
dL = deciliter
L = liter
mL = milliliter,‡
μL = microliter
Eq = gram-equivalent weight
mEq = milliequivalent
mol = gram-molecular weight (mole)
Da = dalton (relative molecular mass)
mmol = millimole
Osmol = osmole
mOsmol = milliosmole
Hz = hertz
kHz = kilohertz
MHz = megahertz
V = volts
MeV = million electron volts
keV = kilo-electron volt
mV = millivolt
psi = pounds per square inch
Pa = pascal
kPa = kilopascal
g = gravity (in centrifugation)

*Formerly the symbol mμ (for millimicron) was used.

**The gram is the unit of mass that is used to measure quantities of materials. Weight, which is a measure of the gravitational force acting on the mass of a material, is proportional to, and may differ slightly from, its mass because of the effects of factors such as gravity, temperature, latitude, and altitude. The difference between mass and weight is considered to be insignificant for compendial assays and tests, and the term "weight" is used throughout *USP* and *NF*.

†Formerly the abbreviation mcg was used in the Pharmacopeial monographs; however, the symbol μg now is more widely accepted and thus is used in this Pharmacopeia. The term "gamma," symbolized by γ, is frequently used for microgram in biochemical literature. [NOTE—The abbreviation mcg is still commonly employed to denote microgram(s) in labeling and in prescription writing. Therefore, for purposes of labeling,"mcg" may be used to denote microgram(s).]

‡One milliliter (mL) is used herein as the equivalent of 1 cubic centimeter (cc).

CONCENTRATIONS

Molal, molar, and normal solution concentrations are indicated throughout this Pharmacopeia for most chemical assay and test procedures (see also *Volumetric Solutions* in the section *Reagents, Indicators, and Solutions*). Molality is designated by the symbol *m* preceded by a number that is the number of moles of the designated solute contained in 1 kilogram of the designated solvent. Molarity is designated by the symbol M preceded by a number that is the number of moles of the designated solute contained in an amount of the designated solvent that is sufficient to prepare 1 L of solution. Normality is designated by the symbol N preceded by a number that is the number of equivalents of the designated solute contained in an amount of the designated solvent that is sufficient to prepare 1 L of solution.

Percentage Measurements—Percentage concentrations are expressed as follows:

Percent Weight in Weight—(w/w) expresses the number of g of a constituent in 100g of solution or mixture.

Percent Weight in Volume—(w/v) expresses the number of g of a constituent in 100mL of solution, and is used regardless of whether water or another liquid is the solvent.

Percent Volume in Volume—(v/v) expresses the number of mL of a constituent in 100mL of solution.

The term *percent* used without qualification means, for mixtures of solids and semisolids, percent weight in weight; for solutions or suspensions of solids in liquids, percent weight in volume; for solutions of liquids in liquids, percent volume in volume; and for solutions of gases in liquids, percent weight in volume. For example, a 1 percent solution is prepared by dissolving 1 g of a solid or semisolid, or 1 mL of a liquid, insufficient solvent to make 100 mL of the solution.

In the dispensing of prescription medications, slight changes in volume owing to variations in room temperatures may be disregarded.

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