The United States Pharmacopeia

TWENTY-FIRST REVISION

Official from January 1, 1985

The National Formulary

SIXTEENTH EDITION

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United States Pharmacopeial Convention, Inc.
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General Notices and Requirements

Applying to Standards, Tests, Assays, and Other Specifications of the United States Pharmacopeia

Guide to GENERAL NOTICES AND REQUIREMENTS

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The General Notices and Requirements (hereinafter referred to as the "General Notices") 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 obviate the need to repeat throughout the book those requirements that are pertinent in numerous instances.

Where, occasionally, exceptions to the General Notices are necessary, the wording in the individual monograph or general test chapter takes precedence and specifically indicates the directions or the intent. To emphasize that such exceptions do exist, the General Notices employ where indicated a qualifying expression such as "unless otherwise specified." Thus, it is understood that the specific wording of standards, tests, assays, and other specifications is binding wherever deviations from the General Notices exist. By the same token, where no language is given specifically to the contrary, the General Notices apply.

TITLE

The full title of this book, including its supplements, is The Pharmacopeia of the United States of America, Twenty-first Revision. This title may be abbreviated to United States Pharmacopeia, Twenty-first Revision, or to USP XXI. Where the term USP is used, without further qualification, during the period in which this Pharmacopeia is official, it refers to USP XXI and any supplement(s) thereto.

"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 on the label of an article is a reminder that the article purports to comply with USP standards; such specific designation on the label 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. 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.

Where a product 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 a product 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 product 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 or medical devices and when bought, sold, or dispensed for these purposes.

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 or a pharmaceutic ingredient or a component of a finished device for which the monograph title includes no indication of the nature of the finished form; a *dosage form* or a *finished device* 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; an *article* is an item for which a monograph is provided, whether an official substance, a dosage form, or a finished device.

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 1981 by the IUPAC Commission on Atomic Weights.

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 expression FDA refers to the U. S. Food and Drug Administration; NBS refers to the National Bureau of Standards. The expression FCC refers to the current edition of the Food Chemicals Codex, including its supplements. The term PhI refers to the International Pharmacopoeia, published as a recommendation on international standards of strength, quality, and purity for drugs by the World Health Organization. The expressions ACS, ANSI, AOAC, and ASTM refer, respectively, to the American Chemical Society, the American National Standards Institute, the Association of Official Analytical Chemists, and the American Society for Testing and Materials.

The term RS refers to Reference Standard as stated under *Reference Standards* in the General Notices.

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.

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) desig-

nate 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 are inclusive so that the range consists of 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, except where the monograph indicates that the article is intended for use in in-vitro diagnostic procedures or as a medical device. 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 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. Where the content of an ingredient is known to decrease with time, an amount in excess of that declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the monograph throughout the expiration period. The tolerances and limits stated in the definitions in the monographs for Pharmacopeial articles allow for such overages, and for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered insignificant under practical conditions.

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.

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. Where a process is given in the individual monograph, the preparation so made must be identical with that prepared by the given process.

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 standards set forth in the current edition of *Reagent Chemicals* published by the American Chemical Society. Where such ACS reagent standards 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 in their labeling shall include also the term "reagent" or "reagent grade."

REFERENCE STANDARDS

USP Reference Standards are authentic specimens that have been verified for suitability for use as comparison standards in compendial tests and assays. (See *USP Reference Standards* ⟨11⟩.)

Where first referred to in a monograph, the name of a USP Reference Standard is generally spelled out in full. However, where a USP Reference Standard is referred to thereafter in an assay or a test in this compendium, the words "Reference Standard" are abbreviated to "RS."

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.

UNITS OF POTENCY

For those products for which it is necessary to express the potency in terms of units by reference to a suitable working standard (usually a USP Reference Standard), the individual monographs refer to USP Units of activity. Unless otherwise indicated, USP Units are equivalent to the corresponding international units, where such exist or formerly existed, or to the units of activity established by the Food and Drug Administration in the case of antibiotics and biological products.

INGREDIENTS AND PROCESSES

Pharmacopeial dosage forms and finished devices are prepared from ingredients that meet the requirements of the compendial monographs for those individual ingredients for which monographs are provided. Water used as an ingredient of compendial dosage forms 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 federal Environmental Protection Agency may be used in the preparation of official substances.

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

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*.

Uniformity of Composition—While a demonstration of homogeneity in individual units of a given lot of a Pharmacopeial dosage form or finished device may not always be practicable, variations in composition are undesirable and substantial differences in the content of active ingredient(s) among individual capsules, tablets, and other finished forms are to be avoided. A test for *Uniformity of Dosage Units* ⟨905⟩ is applied wherever practicable.

Added Substances—An official substance, as distinguished from a dosage form, 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 bases, carriers, coatings, colors, flavors, preservatives, stabilizers, and vehicles may be added to a Pharmacopeial dosage form or finished device 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 to provide their intended effect, (c) their presence does not impair the bioavailability or the therapeutic efficacy or safety of the dosage form, and (d) they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.

Colors—Added substances employed solely to impart color may be incorporated into Pharmacopeial articles that are dosage forms or finished devices, except those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors in drugs issued by the Food and Drug Administration, provided such added substances are otherwise appropriate in all respects. (See also *Added Substances* under *Injections* ⟨1⟩.)

Capsules and Tablets—Capsules and tablets may be made with suitable diluents, colors, lubricants, disintegrants, and adhesives, such as starches, lactose, sucrose, and other innocuous materials. Tablets and the contents of capsules that are intended to be homogeneous are uniform in appearance within a given lot. Coatings may be applied to Pharmacopeial dosage forms. Coatings and excessive amounts of substances or inappropriate processing procedures that may impair bioavailability of the active ingredients are to be avoided.

Parenteral and Topical Preparations—For the preservation of preparations intended for parenteral administration or topical application, suitable antioxidants, antimicrobial agents, buffers, and/or stabilizers may be added unless interdicted in the monograph.

For requirements concerning the presence and proportions of added substances in parenteral preparations and for the pertinent labeling requirements, see *Added Substances* and *Labeling* under *Injections* ⟨1⟩.

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 on the label unless otherwise specified in the individual monograph.

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.

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 *Volumetric Apparatus* ⟨31⟩.) 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 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.

Where the use of a centrifuge is 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—Tests for the presence of foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the medicinal agent is customarily employed.

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 or adulterant that might be present, including microbial contamination. Tests suitable for detecting impurities the presence of which is inconsistent with good pharmaceutical practice, such as may arise from a change in the source of material or from changes in the processing, should be employed in addition to the tests provided in the individual monograph.

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

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of 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 assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls sometimes 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, one or more of 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. 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 less 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.

Where it is directed in an assay or a test that a counted number of dosage units is to be examined, the specified number is a minimal figure chosen only for convenience of analytical manipulation; it is not intended to restrict the total 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 less 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.

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. 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 section, *Reference Standard(s)*. Where instructions are given in the test or assay to dry, or not to dry, the USP Reference Standard, such instructions are to be followed in the particular procedure involved.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within 10 percent 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.

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 filtered 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 substances 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 a substance taken from a labeled container to meet the requirements of a prescribed identification test indicates that the substance may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the substance 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 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms—Logarithms used in the assays are to the base 10.

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

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, of either 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 about 100-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 in terms 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 may be 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 "controlled room temperature" is specified, a temperature range between 15° and 30° is intended.

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. For special kinds of water such as "carbon dioxide-free water," see the introduction to the section, *Reagents, Indicators, and Solutions.*

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.* Where the determination is made by drying under specified conditions, the test is generally 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.

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 the integrity 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 special, 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	10,000 and over

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.

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 its 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-resistant Packaging—The container or individual carton of a sterile article intended for ophthalmic 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 required to comply with the tamper-resistant packaging and labeling requirements of the Food and Drug Administration where applicable.

Preferably, the immediate container and/or the outer container or protective packaging utilized 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 have been used. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

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 tight 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 utilized 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 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 pre-filled 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.

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.

Storage Temperature—Specific directions are stated in some monographs with respect to the temperatures at which Pharmacopeial articles shall be stored, where it is considered that storage at a lower or a higher temperature may 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. The conditions are defined by the following terms.

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). A *freezer* is a cold place in which the temperature is maintained thermostatically between −20° and −10° (−4° and 14°F).

Cool—Any temperature between 8° and 15° (46° and 59°F). An article for which storage in a cool place is directed may, alternatively, be stored in a *refrigerator*, unless otherwise specified in the individual monograph.

Room Temperature—The temperature prevailing in a working area. *Controlled room temperature* is a temperature maintained thermostatically between 15° and 30° (59° and 86°F).

Warm—Any temperature between 30° and 40° (86° and 104°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 a product to loss of strength or potency, or to destructive alteration of the dosage form, the container label bears an appropriate instruction to protect the product from freezing.

Storage in Bulk—Bulk packages are exempt from the storage requirements when the products are intended

for manufacture or for subsequent repackaging for the dispenser or distributor.

Storage under Non-specific Conditions—Where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that the storage conditions include protection from moisture, freezing, and excessive heat.

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, unless such container is also essentially the immediate container or the outside of the consumer package, is exempt from the labeling requirements of this Pharmacopeia.

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.

The potency of some antibiotics, as well as of relatively new drugs generally, is defined in terms of μg or mg of the active moiety (i.e., that portion of the compound which conveys the qualitative pharmacologic activity), even though the antibiotic or other drug used in the dosage form may be in the form of a salt, ester, or other chemical combination. The full name of the chemical combination is used in the content declaration.

Amount of Ingredient per Dosage Unit—Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each therapeutically active ingredient contained in each such unit. Pharmacopeial articles not in unit dosage form shall be labeled to express the quantity of each therapeutically active ingredient in each mL or in each g, 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.

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 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 Vitamin-containing Products—The vitamin content of Pharmacopeial preparations shall be stated on the label in metric units. 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).

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.

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. Where a tablet is enteric-coated, the label so states.

Expiration Date—The labels of all Pharmacopeial dosage forms shall bear an expiration date. The monographs for some dosage forms specify the expiration date that shall appear on the label. In the absence of a specific requirement in the individual monograph for a dosage form, 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 dosage form 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 a dosage form is required to bear an expiration date, such dosage form 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 product 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. For articles requiring constitution prior to use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

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; and the expected length of time of the course of therapy. Unless otherwise required, the dispenser may, 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 drug. Unless otherwise specified in the individual monograph, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier.

VEGETABLE AND ANIMAL DRUGS

The requirements for vegetable and animal drugs apply to the articles as they enter commerce; however, lots of such drugs 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 drugs 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 drugs are to be free from pathogenic organisms (see *Microbiological Attributes of Non-sterile 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 drugs, estimated as *Acid-insoluble ash*, shall not exceed 2 percent of the weight of the drug, unless otherwise specified in the individual monograph.

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

In commerce it is seldom possible to obtain vegetable drugs 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 drug.

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 metric system of weights and measures is used in this Pharmacopeia. The metric and other units, and the abbreviations commonly employed, are as follows:

Ci = curie
mCi = millicurie
μCi = microcurie
nCi = nanocurie
Mrad = megarad
m = meter
dm = decimeter
cm = centimeter
mm = millimeter
μm = micrometer (0.001 mm)
nm = nanometer*
kg = kilogram
g = gram
mg = milligram
μg; mcg = microgram†
ng = nanogram
pg = picogram
dL = deciliter
L = liter
mL = milliliter‡
μL = microliter
Eq = gram-equivalent weight (equivalent)
mEq = milliequivalent
mol = gram-molecular weight (mole)
mmol = millimole
Osmol = osmole
mOsmol = milliosmole
Hz = hertz
kHz = kilohertz
MHz = megahertz
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 abbreviation mμ (for millimicron) was used.

† 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 one 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 one liter 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 one liter 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 100 g of solution or mixture.

Percent weight in volume—(w/v) expresses the number of g of a constituent in 100 mL 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 100 mL 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, in sufficient 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.

Official Monographs for USP XXI

Absorbable Dusting Powder—*see* Dusting Powder, Absorbable

Absorbable Gelatin Film—*see* Gelatin Film, Absorbable

Absorbable Gelatin Sponge—*see* Gelatin Sponge, Absorbable

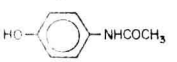
Absorbable Surgical Suture—*see* Suture, Absorbable Surgical

Absorbent Gauze—*see* Gauze, Absorbent

Acacia—*see* Acacia NF

Acacia Syrup—*see* Acacia Syrup NF

Acetaminophen



$C_8H_9NO_2$ 151.16
Acetamide, *N*-(4-hydroxyphenyl)-.
4′-Hydroxyacetanilide [*103-90-2*].

» Acetaminophen contains not less than 98.0 percent and not more than 101.0 percent of $C_8H_9NO_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Acetaminophen Reference Standard*—Dry over silica gel for 18 hours before using.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, previously dried over a suitable desiccant, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Acetaminophen RS.

B: The ultraviolet absorption spectrum of a 1 in 200,000 solution of it in a 1 in 100 solution of 0.1 *N* hydrochloric acid in methanol exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Acetaminophen RS, concomitantly measured.

C: To 10 mL of a 1 in 100 solution add 1 drop of ferric chloride TS: a violet-blue color is produced.

Melting range ⟨741⟩: between 168° and 172°.

pH ⟨791⟩—Add 4.0 g to 40 mL of carbon dioxide-free water, stir for 5 minutes, allow the solids to settle, and determine the pH of the supernatant liquid: the pH is between 5.1 and 6.5.

Water, *Method I* ⟨921⟩: not more than 0.5%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Chloride ⟨221⟩—Shake 1.0 g with 25 mL of water, filter, and add 1 mL of 2 *N* nitric acid: the filtrate shows no more chloride than corresponds to 0.20 mL of 0.020 *N* hydrochloric acid (0.014%).

Sulfate ⟨221⟩—Shake 1.0 g with 25 mL of water, filter, add 2 mL of 1 *N* acetic acid, then add 2 mL of barium chloride TS: the mixture shows no more sulfate than corresponds to 0.20 mL of 0.020 *N* sulfuric acid (0.02%).

Sulfide—Place about 2.5 g in a 50-mL beaker. Add 5 mL of alcohol and 1 mL of 3 *N* hydrochloric acid. Moisten a piece of lead acetate test paper with water, and fix to the underside of a watch glass. Cover the beaker with the watch glass so that part of the lead acetate paper hangs down near the pouring spout of the beaker. Heat the contents of the beaker on a hot plate just to boiling: no coloration or spotting of the test paper occurs.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Readily carbonizable substances ⟨271⟩—Dissolve 0.50 g in 5 mL of sulfuric acid TS: the solution has no more color than Matching Fluid A.

Free *p*-aminophenol—Transfer 5.0 g to a 100-mL volumetric flask, and dissolve in about 75 mL of a mixture of equal volumes of methanol and water. Add 5.0 mL of alkaline nitroferricyanide solution (prepared by dissolving 1 g of sodium nitroferricyanide and 1 g of anhydrous sodium carbonate in 100 mL of water), dilute with a mixture of equal volumes of methanol and water to volume, mix, and allow to stand for 30 minutes. Concomitantly determine the absorbances of this solution and of a freshly prepared solution of *p*-aminophenol, similarly prepared at a concentration of 2.5 μg per mL, using the same quantities of the same reagents, in 1-cm cells, at the maximum at about 710 nm, with a suitable spectrophotometer, using 5.0 mL of alkaline nitroferricyanide solution diluted with a mixture of equal volumes of methanol and water to 100 mL as the

blank: the absorbance of the test solution does not exceed that of the standard solution, corresponding to not more than 0.005% of *p*-aminophenol.

***p*-Chloroacetanilide**—Transfer 1.0 g to a glass-stoppered, 15-mL centrifuge tube, add 5.0 mL of ether, shake by mechanical means for 30 minutes, and centrifuge at 1000 rpm for 15 minutes or until a clean separation is obtained. On a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩), coated with a 0.25-mm layer of chromatographic silica gel mixture, apply 200 µL of the supernatant liquid, in 40-µL portions, to obtain a single spot not more than 10 mm in diameter. Similarly apply 40 µL of a Standard solution in ether containing 10 µg of *p*-chloroacetanilide per mL, and allow the spots to dry. Develop the chromatogram, in an unsaturated chamber, with a solvent system consisting of solvent hexane and acetone (75:25), until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots in the chromatogram by examination under short-wavelength ultraviolet light: any spot obtained from the solution under test, at an R_f value corresponding to the main spot from the Standard solution, is not greater in size or intensity than the main spot obtained from the Standard solution, corresponding to not more than 0.001% of *p*-chloroacetanilide.

Assay—Dissolve about 120 mg of Acetaminophen, accurately weighed, in 10 mL of methanol in a 500-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Concomitantly determine the absorbances of this solution and of a Standard solution of USP Acetaminophen RS, in the same medium, at a concentration of about 12 µg per mL in 1-cm cells, at the wavelength of maximum absorbance at about 244 nm, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg, of $C_8H_9NO_2$ in the Acetaminophen taken by the formula $10C(A_U/A_S)$, in which C is the concentration, in µg per mL, of USP Acetaminophen RS in the Standard solution, and A_U and A_S are the absorbances of the solution of Acetaminophen and the Standard solution, respectively.

Acetaminophen Capsules

» Acetaminophen Capsules contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_9NO_2$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Acetaminophen Reference Standard*—Dry over silica gel for 18 hours before using.

Identification—

A: The ultraviolet absorption spectrum of the solution of the Capsules prepared for the measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Acetaminophen RS, concomitantly measured.

B: Triturate an amount of the contents of the Capsules, equivalent to about 1 g of acetaminophen, with 30 mL of warm alcohol, cool, and filter. To 3 mL of the filtrate add 10 mL of water and 1 drop of ferric chloride TS, and mix: a violet-blue color is produced.

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_8H_9NO_2$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 249 nm of filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Acetaminophen RS in the same medium.

Tolerances—Not less than 75% (Q) of the labeled amount of $C_8H_9NO_2$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Standard preparation and *Chromatographic column*—Prepare as directed in the *Assay* under *Acetaminophen Elixir*.

Assay preparation—Weigh the contents of not fewer than 20 Acetaminophen Capsules. Mix the contents, and transfer an accurately weighed portion of the powder, equivalent to about 250 mg of acetaminophen, to a 250-mL volumetric flask, add 2 mL of 1 *N* sodium hydroxide, dilute with water to volume, mix, and filter, discarding the first 20 mL of the filtrate. Proceed as directed for *Assay preparation* in the *Assay* under *Acetaminophen Elixir*, beginning with "Transfer 2.0 mL of this solution to a 100-mL beaker."

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Acetaminophen Elixir*. Calculate the quantity, in mg, of $C_8H_9NO_2$ in the portion of Capsules taken by the formula $31.25C(A_U/A_S)$, in which C is the concentration, in µg per mL, of USP Acetaminophen RS in the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Acetaminophen Capsules, Chlorzoxazone and—*see* Chlorzoxazone and Acetaminophen Capsules

Acetaminophen Elixir

» Acetaminophen Elixir contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_9NO_2$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Acetaminophen Reference Standard*—Dry over silica gel for 18 hours before using.

Identification—The ultraviolet absorption spectrum of a portion of the *Assay preparation* employed for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Acetaminophen RS, concomitantly measured.

pH ⟨791⟩: between 3.8 and 6.1.

Alcohol content, *Method II* ⟨611⟩: between 6.5% and 10.5% of C_2H_5OH, determined by the gas-liquid chromatographic procedure, acetone being used as the internal standard.

Assay—

Standard preparation—Transfer about 80 mg of USP Acetaminophen RS, accurately weighed, to a 100-mL volumetric flask, add methanol to volume, and mix. Transfer 10.0 mL of this solution to a second 100-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 10.0 mL of the resulting solution to a 100-mL volumetric flask, add 1 mL of 0.1 *N* hydrochloric acid, then add methanol to volume, and mix.

Chromatographic column—Pack a pledget of fine glass wool in the base of a chromatographic tube (25-mm × 250-mm tube to which is fused a 5-cm length of 7-mm tubing) with the aid of a tamping rod about 45 cm in length and having a disk with a diameter about 1 mm less than that of the tube. To 2 g of purified siliceous earth in a 100-mL beaker add 2.0 mL of a solution containing 1.0 g of sodium bicarbonate and 4.5 g of sodium carbonate in each 100 mL, and mix until a fluffy mixture is obtained. Transfer the mixture to the chromatographic tube, and tamp gently to compress the material to a uniform mass.

Assay preparation—Transfer an accurately measured volume of Acetaminophen Elixir, equivalent to about 250 mg of acetaminophen, to a 250-mL volumetric flask, add 2 mL of 1 *N* sodium hydroxide, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a 100-mL beaker, add 1 drop of hydrochloric acid, swirl to mix, then add 3.0 g of purified siliceous earth. Mix, and transfer to the chromatographic column. Scrub the beaker with 1 g of purified siliceous earth mixed with 2 drops of water, transfer the washings to the column, and tamp gently. Place a pledget of fine glass wool on top of the column. Wash the column with 100 mL of water-saturated chloroform, and discard the eluate. Elute the acetaminophen with 150 mL of water-saturated ether, collecting the eluate in a 400-mL beaker. Evaporate the ether on a steam bath with the aid of a current of air just to dryness. [NOTE—Avoid prolonged drying, to prevent loss of acetaminophen.] Without delay, dissolve the residue in a solvent mixture consisting of 1 mL of dilute hydrochloric acid (1 in 100) per 100 mL of methanol, and transfer to a 50-mL volumetric flask. Rinse the beaker with the

solvent mixture, adding the rinsings to the flask, dilute with the solvent mixture to volume, and mix. Transfer 10.0 mL of this solution to a second 50-mL volumetric flask, dilute with the solvent mixture to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 1-cm cells at the wavelength of maximum absorbance at about 249 nm, with a suitable spectrophotometer, using a solvent mixture consisting of 1 mL of 0.1 *N* hydrochloric acid per 100 mL of methanol as the blank. Calculate the quantity, in mg, of $C_8H_9NO_2$ in each mL of the Elixir taken by the formula $31.25(C/V)(A_U/A_S)$, in which C is the concentration, in µg per mL, of USP Acetaminophen RS in the *Standard preparation*, V is the volume, in mL, of Elixir taken, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Acetaminophen for Effervescent Oral Solution

» Acetaminophen for Effervescent Oral Solution contains, in each 100 g, not less than 5.63 g and not more than 6.88 g of $C_9H_8NO_2$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Acetaminophen Reference Standard*—Dry over silica gel for 18 hours before using.

Identification—

A: A 10-g portion dissolves, with effervescence, in 200 mL of water.

B: The ultraviolet absorption spectrum of the solution prepared for the measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Acetaminophen RS, concomitantly measured.

Assay—Dissolve about 10 g of Acetaminophen for Effervescent Oral Solution, accurately weighed, in about 200 mL of 0.1 *N* hydrochloric acid in a 500-mL volumetric flask, using gentle heat if necessary, until effervescence subsides, then dilute with 0.1 *N* hydrochloric acid to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with 0.1 *N* hydrochloric acid to volume, and mix. Transfer 10.0 mL of the resulting solution to a 100-mL volumetric flask, dilute with 0.1 *N* hydrochloric acid to volume, and mix. Concomitantly determine the absorbances of this solution and of a Standard solution of USP Acetaminophen RS, in the same medium, at a concentration of about 12 µg per mL in 1-cm cells, at the wavelength of maximum absorbance at about 243 nm, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg, of $C_9H_8NO_2$ in the portion of Acetaminophen for Effervescent Oral Solution taken by the formula $50C(A_U/A_S)$, in which C is the concentration, in µg per mL, of USP Acetaminophen RS in the Standard solution, and A_U and A_S are the absorbances of the solution of Acetaminophen for Effervescent Oral Solution and the Standard solution, respectively.

Acetaminophen Oral Suspension

» Acetaminophen Oral Suspension is a suspension of Acetaminophen in a suitable aqueous vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_8H_9NO_2$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Acetaminophen Reference Standard*—Dry over silica gel for 18 hours before using.

Identification—Transfer a volume of Oral Suspension, equivalent to about 240 mg of acetaminophen, to a separator, add 50 mL of ethyl acetate, and shake well. Filter the ethyl acetate extract through a funnel containing glass wool and about 10 g of anhydrous sodium sulfate. Collect the filtrate in a beaker, and evaporate on a steam bath to dryness. Dry the residue in vacuum over silica gel: the crystals so obtained respond to *Identification test A* under *Acetaminophen*.

pH ⟨791⟩: between 5.4 and 6.9.

Assay—

Standard preparation—Dissolve an accurately weighed quantity of USP Acetaminophen RS in water, and dilute quantitatively and stepwise, if necessary, with water to obtain a solution having a known concentration of about 100 µg per mL.

Assay preparation—Transfer an accurately measured volume of Oral Suspension, previously well-shaken, equivalent to about 100 mg of acetaminophen, to a 100-mL volumetric flask, add 60 mL of water, insert the stopper, and shake by mechanical means for 30 minutes. Dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Transfer 10.0 mL each of the *Standard preparation*, the *Assay preparation*, and water to provide a blank, to separate 50-mL volumetric flasks, and treat each as follows: Add 2.0 mL of 6 *N* hydrochloric acid, and mix. Add 5.0 mL of sodium nitrite solution (1 in 10), mix, and allow to stand for 15 minutes. Add 5.0 mL of ammonium sulfamate solution (15 in 100), and swirl gently, allowing the solution to cool to room temperature. Add 15.0 mL of 2.5 *N* sodium hydroxide, allow to cool to room temperature, dilute with water to volume, and mix. Concomitantly determine the absorbances of the solutions obtained from the *Standard preparation* and the *Assay preparation* in 1-cm cells relative to the blank at the wavelength of maximum absorbance at about 430 nm, with a suitable spectrophotometer. Calculate the quantity, in mg, of $C_8H_9NO_2$ in each mL of the Oral Suspension taken by the formula $(C/V)(A_U/A_S)$, in which C is the concentration, in µg per mL, of USP Acetaminophen RS in the *Standard preparation*, V is the volume, in mL, of Oral Suspension taken, and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.

Acetaminophen Tablets

» Acetaminophen Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_8H_9NO_2$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Acetaminophen Reference Standard*—Dry over silica gel for 18 hours before using.

Identification—

A: The ultraviolet absorption spectrum of the solution of the Tablets prepared for measurement of absorbance in the *Assay* exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Acetaminophen RS, concomitantly measured.

B: Triturate an amount of powdered Tablets, equivalent to about 1 g of acetaminophen, with 30 mL of warm alcohol, cool, and filter. To 3 mL of the filtrate add 10 mL of water and 1 drop of ferric chloride TS, and mix: a violet-blue color is produced.

Dissolution ⟨711⟩—

Medium: pH 5.8 phosphate buffer (see *Buffer Solutions*, in the section, *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_8H_9NO_2$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 249 nm of filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Acetaminophen RS in the same medium.

Tolerances—Not less than 80% (Q) of the labeled amount of $C_8H_9NO_2$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Standard preparation and *Chromatographic column*—Prepare as directed in the *Assay* under *Acetaminophen Elixir*.

Assay preparation—Weigh and finely powder not less than 20 Acetaminophen Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mg of acetaminophen, to a 250-mL volumetric flask, add 2 mL of 1 *N* sodium hydroxide, dilute with water to volume, mix, and filter, discarding the first 20 mL of the filtrate. Proceed as directed for *Assay preparation* in the *Assay* under *Acetaminophen Elixir*, beginning with "Transfer 2.0 mL of this solution to a 100-mL beaker."

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Acetaminophen Elixir*. Calculate the quantity, in mg, of $C_8H_9NO_2$ in the portion of Tablets taken by the formula $31.25C(A_U/A_S)$, in which C is the concentration, in μg per mL, of USP Acetaminophen RS in the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Acetaminophen Tablets, Chlorzoxazone and—*see* Chlorzoxazone and Acetaminophen Tablets

Acetaminophen Tablets, Propoxyphene Hydrochloride and—*see* Propoxyphene Hydrochloride and Acetaminophen Tablets

Acetaminophen Tablets, Propoxyphene Napsylate and—*see* Propoxyphene Napsylate and Acetaminophen Tablets

Acetaminophen and Aspirin Tablets

» Acetaminophen and Aspirin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of acetaminophen ($C_8H_9NO_2$) and aspirin ($C_9H_8O_4$).

Packaging and storage—Preserve in tight containers.

Reference standards—*USP Acetaminophen Reference Standard*—Dry over silica gel for 18 hours before using. *USP Aspirin Reference Standard*—Dry over silica gel for 5 hours before using. *USP Salicylic Acid Reference Standard*—Dry over silica gel for 3 hours before using.

Identification—The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those of the *Standard preparation*, relative to the internal standard, as obtained in the *Assay*.

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Mobile phase—Prepare as directed under *Assay*.

Solvent mixture—Prepare as directed under *Assay*.

Internal standard solution—Prepare a solution of benzoic acid in methanol having a concentration of about 1 mg per mL.

Standard preparation I—Dissolve an accurately weighed quantity of USP Salicylic Acid RS in the *Solvent mixture* to obtain a solution having a known concentration of about 70 μg per mL. Combine 4.0 mL of this solution and 1.0 mL of the *Internal standard solution*, and mix.

Standard preparation II—Dissolve accurately weighed quantities of USP Acetaminophen RS and USP Aspirin RS in the *Solvent mixture* to obtain a solution having known concentrations of about 360 μg of acetaminophen and about 360 μg of aspirin per mL. Combine 4.0 mL of this solution and 1.0 mL of the *Internal standard solution*, and mix.

Test preparation—Combine 4.0 mL of a filtered portion of the solution under test and 1.0 mL of the *Internal standard solution*, and mix.

Chromatographic system—Proceed as directed under *Assay*.

Procedure—Separately inject equal volumes (about 20 μL) of the two *Standard preparations* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.3 for acetaminophen, 0.4 for salicylic acid, 0.6 for aspirin, and 1.0 for benzoic acid. Determine the amount of acetaminophen ($C_8H_9NO_2$) dissolved by the formula $90(C/W)(R_U/R_S)$, in which C is the concentration, in μg per mL, of USP Acetaminophen RS in *Standard preparation II*, R_U and R_S are the relative peak response ratios obtained from the *Test preparation* and *Standard preparation II*, respectively, and W is the labeled amount, in mg, of acetaminophen. Determine the amount of aspirin dissolved by the formula $[[90C_1(R_{U_1}/R_S)] + [90C_2(R_{U_2}/R_{S_2})(1.3044)]]/W$, in which C_1 and C_2 are the concentrations, in μg per mL, of USP Aspirin RS in *Standard preparation II* and USP Salicylic Acid RS in *Standard preparation I*, respectively, R_{U_1} and R_{S_1} are the relative peak response ratios for the aspirin peak and the internal standard peak obtained with the *Test preparation* and *Standard preparation II*, respectively, R_{U_2} and R_{S_2} are the relative peak response ratios for the salicylic acid peak and the internal standard peak obtained from the *Test preparation* and *Standard preparation I*, respectively, and W is the labeled amount, in mg, of aspirin.

Tolerances—Not less than 75% (Q) of the labeled amount of $C_8H_9NO_2$ and not less than 75% (Q) of the labeled amount of $C_9H_8O_4$ are dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements for *Content Uniformity* with respect to acetaminophen and to aspirin.

Salicylic acid—

Solvent mixture, *Mobile phase*, *Internal standard solution*, and *Chromatographic system*—Prepare as directed in the *Assay*.

Procedure—Dissolve a suitable quantity of USP Salicylic Acid RS, accurately weighed, in *Solvent mixture* to obtain a solution having a known concentration of about 1.0 mg per mL. Transfer 1.0-mL, 5.0-mL, and 10.0-mL portions, respectively, of this solution to separate 100-mL volumetric flasks, add 10.0 mL of *Internal standard solution* to each flask, dilute with *Solvent mixture* to volume, and mix. Chromatograph these three Standard solutions as directed in the *Assay*. Plot the ratios of the peak responses for salicylic acid and benzoic acid for each of the Standard solutions versus concentrations, in mg per mL, of salicylic acid, and draw the straight line best fitting the three plotted points. From the graph so obtained, and from the ratio of the peak responses for salicylic acid and benzoic acid in the chromatogram of the *Assay preparation* as obtained in the *Assay*, determine the concentration, in mg per mL, of salicylic acid ($C_7H_6O_3$) in the *Assay preparation*, and calculate the percentage of salicylic acid in relation to the concentration of aspirin in the *Assay preparation*, as determined in the *Assay*. Not more than 3.0% is found.

Assay—[NOTE—Use clean, dry glassware. Inject the *Standard preparation* and the *Assay preparation* promptly after preparation.]

Solvent mixture—Prepare a mixture of chloroform, methanol, and glacial acetic acid (78:20:2).

Mobile phase—Transfer 225 mg of tetramethylammonium hydroxide pentahydrate to a 1000-mL flask, and add 750 mL of water, 125 mL of methanol, 125 mL of acetonitrile, and 1.0 mL of glacial acetic acid. Stir for 3 minutes, filter through a membrane filter (0.5-μm or finer porosity), and degas.

Internal standard solution—Dissolve benzoic acid in *Solvent mixture* to obtain a solution having a concentration of about 20 mg per mL.

Standard preparation—Transfer about 325 mg of USP Acetaminophen RS and about 325 mg of USP Aspirin RS, each accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of *Internal standard solution*, dilute with *Solvent mixture* to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Acetaminophen and Aspirin Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 325 mg of acetaminophen, to a 100-mL volumetric flask, add 10.0 mL of *Internal standard solution* and about 50 mL of *Solvent mixture*, and sonicate for about 3 minutes. Dilute with *Solvent mixture* to volume, and mix. Filter a portion of this solution through a 2.5-μm or finer porosity filter, and use the filtrate as the *Assay preparation*.

Chromatographic system—The liquid chromatograph is equipped with a 280-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph four replicate injections of the *Standard preparation*, and record the peak responses as directed under *Procedure*: the relative standard deviation for either analyte is not more than 3.0%.

Procedure—Separately inject equal volumes (about 5 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The retention times are about 2, 3, 5, and 8 minutes for acetaminophen, salicylic acid (if present), aspirin, and benzoic acid, respectively. Calculate the quantity, in mg, of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets taken by the formula $100C(R_U/R_S)$, in which C is the concentration, in mg per mL, of USP Acetaminophen RS in the *Standard preparation*, and R_U and R_S are the ratios of the peak responses of acetaminophen and