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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

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 exceptions to the *General Notices* are made, 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-third Revision. This title may be abbreviated to *United States Pharmacopeia*, Twenty-third Revision, or to *USP 23*. The *United States Pharmacopeia*, Twenty-third 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 23* 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 means 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 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 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, or a pharmaceutic ingredient (see also *NF 18*) 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*, 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.

Nutritional Supplements—The designation of an official preparation containing recognized nutrients as "USP" or the use of the designation "USP" in conjunction with the title of such nutritional supplement preparation may be made only if the article contains two or more of the recognized nutrients and the preparation meets the applicable requirements contained in the individual Class Monograph and General Chapters. 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 it is of USP quality or recognized by USP. If a preparation does not comply with applicable requirements but contains nutrients that are recognized in the USP, the article may not designate the individual nutrients 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 1991 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 ap-

pear 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⟩).

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
EPA	U.S. Environmental Protection Agency
FCC	Food Chemicals Codex
FDA	U.S. Food and Drug Administration
HIMA	Health Industry Manufacturers Association
ISO	International Standards Organization
IUPAC	International Union of Pure and Applied Chemistry
NBS	National Bureau of Standards
NIST	National Institute of Standards and Technology (formerly NBS)
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, 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. 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 acceptable 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.

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 an observed or calculated result is to be rounded off to the number of places that is in agreement with the limit expression by the following pro-

cedure. [NOTE—Limits, which are fixed numbers, are not rounded off.]

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 ≤3 ppm	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., ⟨601⟩ *Aerosols*). General chapters that include general *requirements* for tests and assays are numbered from ⟨1⟩ to ⟨999⟩, chapters that are *informational* are numbered from ⟨1000⟩ to ⟨1999⟩, and chapters pertaining to *nutritional supplements* are numbered above ⟨2000⟩.

The use of the general chapter numbers is encouraged for the identification 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 Committee of Revision. 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 and for Nutritional Supplements.

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

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

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 proposed and new United States Adopted Names (USAN) and International Nonproprietary Names (INN).

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.

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

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."

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 antibiotics (see *Antibiotics—Microbial Assays* ⟨81⟩), USP Units are defined by the corresponding USP Reference Standards in terms of the units of activity established by the FDA. Each unit is established through the corresponding antibiotic master standard, which in many instances is the basis also for the definition of the WHO International Unit. For most antibiotics, however, biological units of potency are not necessary, and their activity is expressed in metric units (micrograms or milligrams) in terms of the chemically defined substances described in the individual monographs.

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

INGREDIENTS AND PROCESSES

Official preparations are prepared from ingredients that meet the requirements of the compendial monographs for those individual ingredients for which monographs are provided (see also *NF 18*).

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 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.

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 federal 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 to provide 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 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 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 (a) they do not interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards, and (b) that such additional ingredients are listed separately on the label from those ingredients recognized in the definition of the USP article.

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.

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 manufacturing practice or good pharmaceutical practice, 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.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. 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 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* 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 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 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 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 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 less 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. 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 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 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 3 drops, of the solution shall be added, unless otherwise directed.

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

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 0.50 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°. 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 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.

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 assure 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 (see *Test and Assays* under *General Notices*).

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. The compendial procedures demonstrate compliance of the attributes of an article with compendial standards for a specimen (of one or more dosage units) that is subjected to analysis. 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.

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	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.

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 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 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-resistant packaging and labeling requirements of the FDA 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 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 a light-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 re-closure. 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 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 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 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, when stability data indicate that storage at a lower or a higher temperature produces 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.

Freezer—A place in which the temperature is maintained thermostatically between −20° and −10° (−4° and 14°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° and 59°F). An article for which storage in a *cool place* is directed may, alternatively, be stored in a *refrigerator*, unless otherwise specified by the individual monograph.

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° and 30° (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. 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 *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩.)

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

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 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.

Storage under Nonspecific Conditions—For articles, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution 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.

Amount of Ingredient per Dosage Unit—The strength of a drug product is expressed on the con-

tainer 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. 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. 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-milliliter 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*.

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 one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

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 Pharmacopeial preparations 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 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 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—The label of an official drug product or nutritional supplement 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," "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.

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 article. 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 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.

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

* 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 due to 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).

The International System of Units (SI) is also used in all radiopharmaceutical monographs. The symbols commonly employed are as follows.

Bq = becquerel	GBq = gigabecquerel
kBq = kilobecquerel	Gy = gray
MBq = megabecquerel	mGy = milligray

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.

Apparatus

The apparatus[1] consists of a basket-rack assembly, a 1000-mL, ... form beaker for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device ... raising and lowering the basket in the immersion fluid at a ... frequency rate between 29 and 32 cycles per minute ... a distance of not less than 5.3 cm and not more than 5.7 ... The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least ... below the surface of the fluid and descends to not less ... 2.5 cm from the bottom of the vessel on the downward stroke. ... time required for the upward stroke is equal to the time ... for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of ... The basket-rack assembly moves vertically along its axis. ... is no appreciable horizontal motion or movement of the ... from the vertical.

Basket-rack Assembly—The basket-rack assembly consists of ... open-ended transparent tubes, each 7.75 ± 0.25 cm long and ... an inside diameter of approximately 21.5 mm and a wall ... approximately 2 mm thick; the tubes are held in a vertical position ... two plastic plates, each about 9 cm in diameter and 6 mm in ... thickness, with six holes, each about 24 mm in diameter, equidistant from the center of the plate and equally spaced from one ... another. Attached to the under surface of the lower plate is 10-mesh No. 23 (0.025-inch) W. and M. gauge woven stainless-steel wire cloth having a plain square weave. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks[2]—The use of disks is permitted only where specified in the monograph. If specified in the individual monograph, each tube is provided with a slotted and perforated cylindrical disk ... ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five 2-mm holes extend between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it equally spaced on a 6-mm radius from it. Equally spaced on the sides of the cylinder are four notches that form V-shaped planes that are perpendicular to the ends of the cylinder. The dimensions of each notch are such that the openings on the bottom of the cylinder are 1.60 mm square and those on the top are 9.5 mm wide ... 2.55 mm deep. All surfaces of the disk are smooth. If the use of disks is specified in the individual monograph, add a disk to each tube, and operate the apparatus as directed under *Procedure*.

Procedure

Uncoated Tablets—Place 1 tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at ... as the immersion fluid unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or ... tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Apply the test for *Uncoated Tablets*, operating the apparatus for the time specified in the individual monograph.

Enteric-coated Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, suspend the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*. Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable 10-mesh wire cloth,[3] as described under *Basket-rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.

[1] A suitable apparatus, meeting these specifications, is available from laboratory supply houses, from Van-Kel Industries, ... 36 Meridian Rd., Edison, NJ 08820, or from Hanson Research Corp., P. O. Box 35, Northridge, CA 91324.

[2] Disks meeting these specifications are obtainable from Van-Kel Industries, Inc.

[3] A suitable wire cloth cover is available as Van-Kel Industries Part TT-1030.

⟨711⟩ DISSOLUTION

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form, except where the label states that the tablets are to be chewed unless otherwise directed in the monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. Of the types of apparatus described herein, use the one specified in the individual monograph.

USP Reference Standards ⟨11⟩—*USP Prednisone Tablets RS* (*Dissolution Calibrator, Nondisintegrating*). *USP Salicylic Acid Tablets RS* (*Dissolution Calibrator, Nondisintegrating*).

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 to 175 mm high, its inside diameter is 98 to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

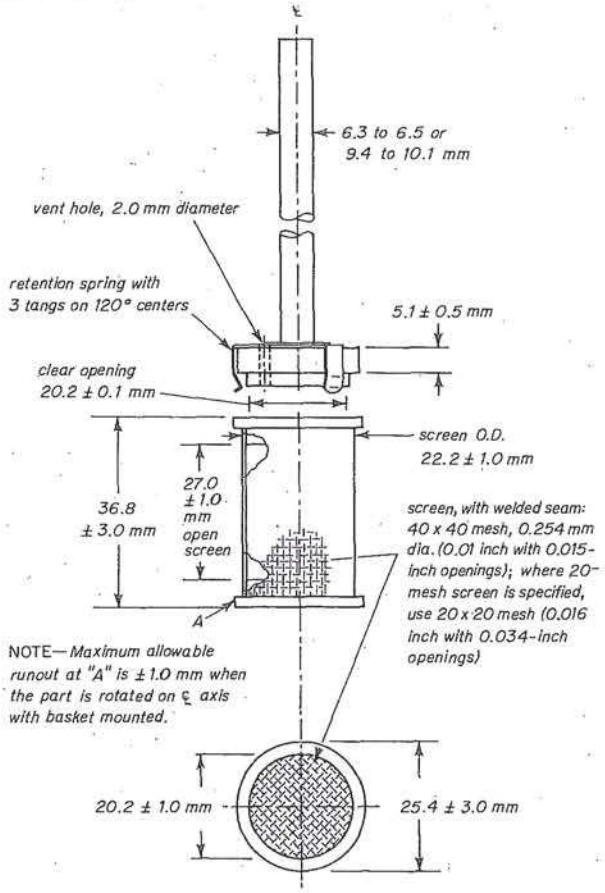

Fig. 1. Basket Stirring Element.

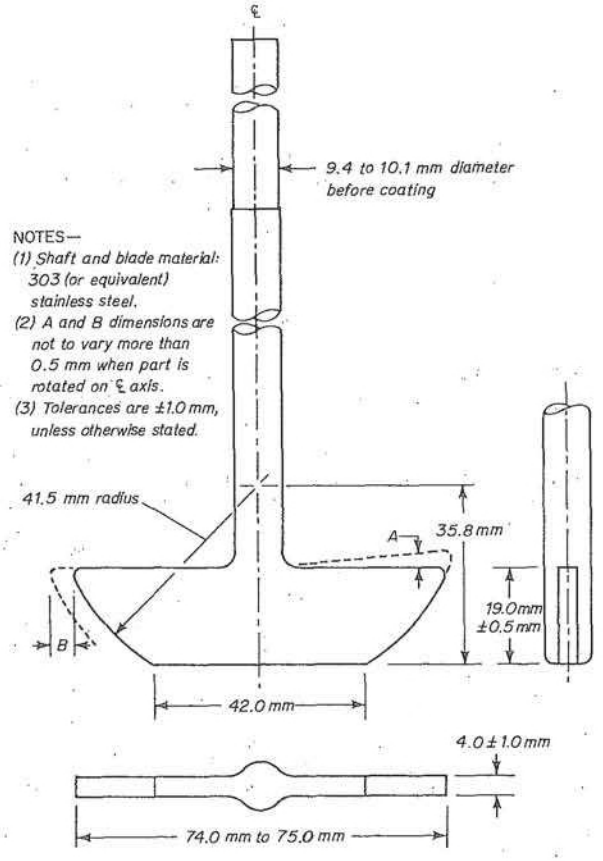

Fig. 2. Paddle Stirring Element.

positioned so that its axis is not more than 2 mm at any poir from the vertical axis of the vessel and rotates smoothly an without significant wobble. A speed-regulating device is use that allows the shaft rotation speed to be selected and maintaine at the rate specified in the individual monograph, within ±4%

Shaft and basket components of the stirring element are fal ricated of stainless steel, type 316 or equivalent, to the specif cations shown in Figure 1. Unless otherwise specified in the i dividual monograph, use 40-mesh cloth. A basket having a gol coating 0.0001 inch (2.5 μm) thick may be used. The dosag unit is placed in a dry basket at the beginning of each test. Th distance between the inside bottom of the vessel and the baske is maintained at 25 ± 2 mm during the test.

Apparatus 2—Use the assembly from *Apparatus 1*, except tha a paddle formed from a blade and a shaft is used as the stirrin element. The shaft is positioned so that its axis is not more tha 2 mm at any point from the vertical axis of the vessel, and rotate smoothly without significant wobble. The blade passes throug the diameter of the shaft so that the bottom of the blade is flus with the bottom of the shaft. The paddle conforms to the spec ifications shown in Figure 2. The distance of 25 ± 2 mm betwee the blade and the inside bottom of the vessel is maintained durin the test. The metallic blade and shaft comprise a single entit that may be coated with a suitable inert coating. The dosag unit is allowed to sink to the bottom of the vessel before rotatio of the blade is started. A small, loose piece of nonreactive ma terial such as not more than a few turns of wire helix may b attached to dosage units that would otherwise float.

Apparatus Suitability Test—Individually test 1 tablet of th *USP Dissolution Calibrator, Disintegrating Type* and 1 table of *USP Dissolution Calibrator, Nondisintegrating Type*, accord ing to the operating conditions specified. The apparatus is suit able if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Use the solvent specified in the individ ual monograph. If the *Dissolution Medium* is a buffered solution adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.[3]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of ±2%.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that re placement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the du ration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis as directed in the individual monograph.[4] Repeat the test with additional dosage form units.

[3] One method of deaeration is as follows: Heat the medium while stirring gently, to about 45°, immediately filter under vac uum using a filter having a porosity of 0.45 μm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

[4] If test specimens are filtered, use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

USP 23

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying acceptance table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; both the 5% and 15% values in the acceptance table are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

⟨721⟩ DISTILLING RANGE

To determine the range of temperatures within which an official liquid distils, or the percentage of the material that distils between two specified temperatures, use Method I or Method II as directed in the individual monograph. The *lower limit* of the range is the temperature indicated by the thermometer when the first drop of condensate leaves the tip of the condenser, and the *upper limit* is the Dry Point, i.e., the temperature at which the last drop of liquid evaporates from the lowest point in the distillation flask, without regard to any liquid remaining on the side of the flask, or the temperature observed when the proportion specified in the individual monograph has been collected.

[NOTE—Cool all liquids that distil below 80° to between 10° and 15° before measuring the sample to be distilled.]

METHOD I

Apparatus—Use apparatus similar to that specified for *Method II*, except that the distilling flask is of 50- to 60-mL capacity, and the neck of the flask is 10 to 12 cm long and 14 to 16 mm in internal diameter. The perforation in the upper asbestos board, if one is used, should be such that when the flask is set into it, the portion of the flask below the upper surface of the asbestos has a capacity of 3 to 4 mL.

Procedure—Proceed as directed for *Method II*, but place in the flask only 25 mL of the liquid to be tested.

METHOD II

Apparatus—Use an apparatus consisting of the following parts:

Distilling Flask—A round-bottom distilling flask, of heat-resistant glass, of 200-mL capacity, and having a total length of 17 to 19 cm and an inside neck diameter of 20 to 22 mm. Attached about midway on the neck, approximately 12 cm from the bottom of the flask, is a side-arm 10 to 12 cm long and 5 mm in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Condenser—A straight glass condenser 55 to 60 cm in length with a water jacket about 40 cm in length, or a condenser of other design having equivalent condensing capacity. The lower end of the condenser may be bent to provide a delivery tube, or it may be connected to a bent adapter that serves as a delivery tube.

Asbestos Boards—Two pieces of asbestos board, 5 to 7 mm thick and 14 to 16 cm square, suitable for confining the heat to the lower part of the flask. Each board has a hole in its center, and the two boards differ only with respect to the diameter of the hole, i.e., the diameters are 4 and 10 cm, respectively. In use, the boards are placed one upon the other, and resting on a tripod or other suitable support, with the board having the larger hole on top.

Receiver—A 100-mL cylinder graduated in 1-mL subdivisions.

Thermometer—In order to avoid the necessity for an emergent stem correction, an accurately standardized, partial-immersion thermometer having the smallest practical subdivisions (not greater than 0.2°) is recommended. Suitable thermometers are available as the ASTM E-1 series 37C through 41C, and 102C through 107C (see *Thermometers* ⟨21⟩). When placed in position, the stem is located in the center of the neck and the top of the contraction chamber (or bulb, if 37C or 38C is used) is level with the bottom of the outlet to the side-arm.

Heat Source—A small Bunsen burner or an electric heater or mantle capable of adjustment comparable to that possible with a Bunsen burner.

Procedure—Assemble the apparatus, and place in the flask 100 mL of the liquid to be tested, taking care not to allow any of the liquid to enter the side-arm. Insert the thermometer, shield the entire burner and flask assembly from external air currents, and apply heat, regulating it so that between 5 and 10 minutes elapse before the first drop of distillate falls from the condenser. Continue the distillation at a rate of 4 to 5 mL of distillate per minute, collecting the distillate in the receiver. Note the temperature when the first drop of distillate falls from the condenser, and again when the last drop of liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. Correct the observed temperature readings for any variation in the barometric pressure from the normal (760 mm), adding if the pressure is lower or subtracting if the pressure is higher than 760 mm, and apply the emergent stem correction where necessary. Unless otherwise specified in the individual monograph, allow 0.1° for each 2.7 mm (0.037° per mm) of variation.

⟨724⟩ DRUG RELEASE

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph.

Apparatus 1 and Apparatus 2—

APPARATUS 1 AND APPARATUS 2—Proceed as directed under *Dissolution* ⟨711⟩.

Apparatus Suitability Test, Dissolution Medium, and Procedure—Proceed as directed under *Dissolution* ⟨711⟩. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.]

Extended-release Articles—General Drug Release Standard

Apparatus 3—

APPARATUS—The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and polypropylene screens that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. An apparatus that permits observation of the specimens and reciprocating cylinders is

preferable. The components conform to the dimensions shown in Figure 1 unless otherwise specified in the individual monograph.

Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage-form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage-form unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder, moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the *Dissolution Medium* and the bottom of each vessel. Perform the analysis as directed in the individual monograph. If necessary, repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

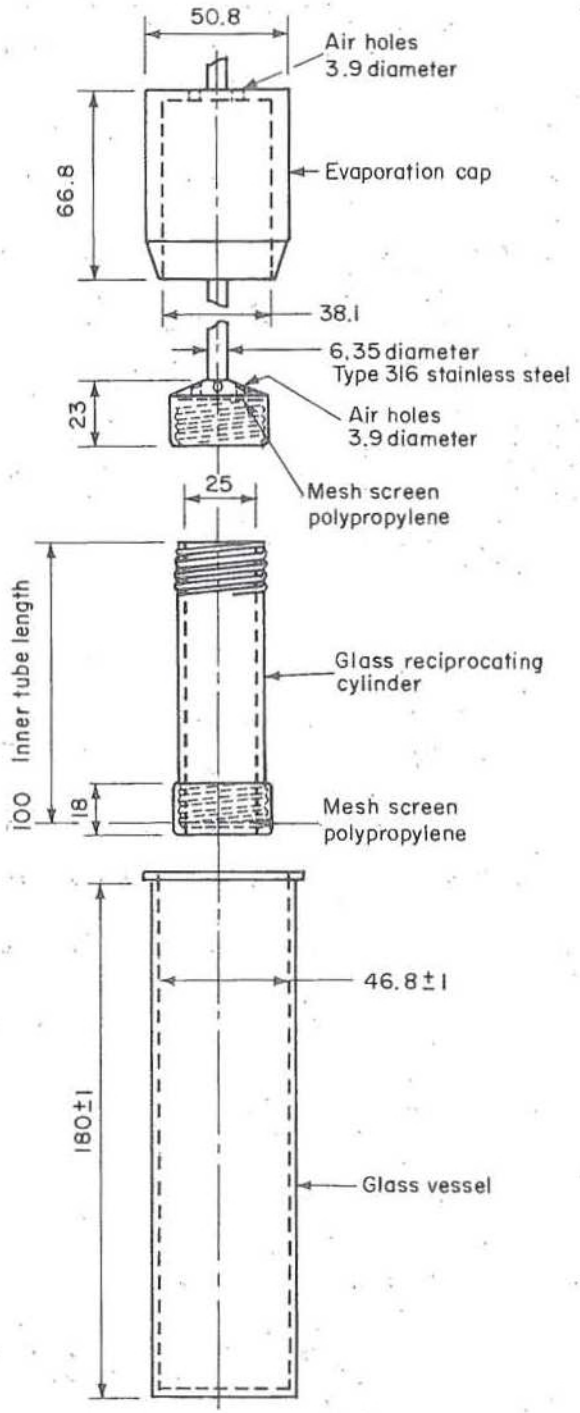

Fig. 1. Apparatus 3.
(All measurements are expressed in mm unless noted otherwise.)

Apparatus 4—

APPARATUS—The assembly consists of a reservoir and a pump for the *Dissolution Medium;* a flow-through cell; a water bath that maintains the *Dissolution Medium* at 37 ± 0.5° (see Figures 2 and 3). The cell size is specified in the individual monograph

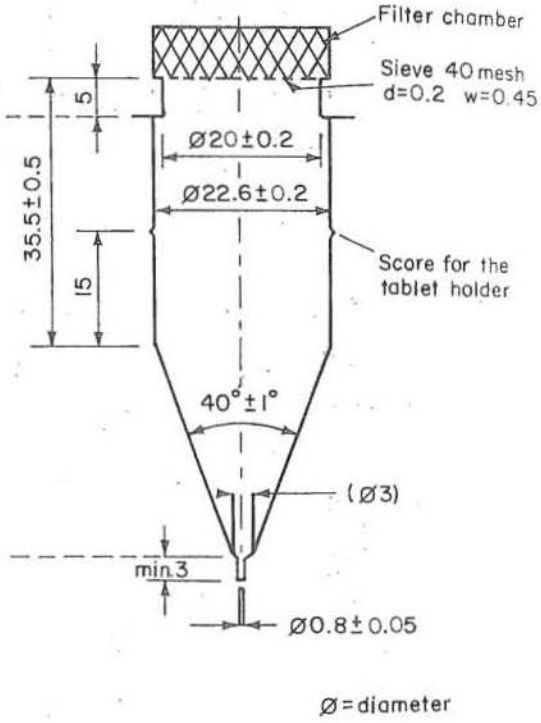

Fig. 2. Large cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

The pump forces the *Dissolution Medium* upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must be volumetric to deliver constant flow independent of flow resistance in the filter device; the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute.

The flow-through cell (see Figures 2 and 3), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; a tablet holder (see Figures 2a and 3a) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath and the temperature is maintained at 37 ± 0.5°.

The apparatus uses a clamp mechanism and two O-rings for the fixation of the cell assembly. The pump is separated from the dissolution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump