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NF 26

THE NATIONAL FORMULARY

Volume 1

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Official from May 1, 2008

The designation on the cover of this publication, "USP NF 2008," is for ease of identification only. The publication contains two separate compendia: *The United States Pharmacopeia*, Thirty-First Revision, and *The National Formulary*, Twenty-Sixth Edition.

THE UNITED STATES PHARMACOPEIAL CONVENTION
12601 Twinbrook Parkway, Rockville, MD 20852

SIX-MONTH IMPLEMENTATION GUIDELINE

The *United States Pharmacopeia–National Formulary* and its *Supplements* become official **six months** after being released to the public. The *USP–NF*, which is released on November 1 of each year, becomes official on May 1 of the following year.

This change was adopted to give users more time to bring their methods and procedures into compliance with new and revised *USP–NF* requirements.

The table below describes the new official dates. The 2007 *USP30–NF25*, and the *Supplements* and *Interim Revision Announcements (IRAs)* to that edition, will be official until May 1, 2008, at which time the *USP31–NF26* becomes official.

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	Nov. 1, 2007	May 1, 2008	May 1, 2009 (except as superceded by 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	Feb. 1, 2008	Aug. 1, 2008	May 1, 2009 (except as superceded by 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	June 1, 2008	Dec. 1, 2008	May 1, 2009 (except as superceded by 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	Nov. 1, 2008	May 1, 2009	May 1, 2010 (except as superceded by 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

IRAs will continue to become official on the first day of the second month of the *Pharmacopeial Forum (PF)* issue in which they are published as final. For instance, *IRAs* published as final in the May–June *PF* (issue 3) will become official on June 1. This table gives the details of the *IRAs* that will apply to *USP30–NF25* and *USP31–NF26*.

<i>IRA</i> *	Release Date	Official Date	Revises
Jan. 1, 2008 <i>IRA</i> , <i>PF</i> 34(1)	Jan. 1, 2008	Feb. 1, 2008	<i>USP30–NF25</i> and its <i>Supplements</i>
Mar. 1, 2008 <i>IRA</i> , <i>PF</i> 34(2)	Mar. 1, 2008	April 1, 2008	<i>USP30–NF25</i> and its <i>Supplements</i>
May 1, 2008 <i>IRA</i> , <i>PF</i> 34(3)	May 1, 2008	June 1, 2008	<i>USP31–NF26</i>
July 1, 2008 <i>IRA</i> , <i>PF</i> 34(4)	July 1, 2008	Aug. 1, 2008	<i>USP31–NF26</i> and <i>First Supplement</i>
Sept. 1, 2008 <i>IRA</i> , <i>PF</i> 34(5)	Sept. 1, 2008	Oct. 1, 2008	<i>USP31–NF26</i> and <i>First Supplement</i>
Nov. 1, 2008 <i>IRA</i> , <i>PF</i> 34(6)	Nov. 1, 2008	Dec. 1, 2008	<i>USP31–NF26</i> and its <i>Supplements</i>
Jan. 1, 2009 <i>IRA</i> , <i>PF</i> 35(1)	Jan. 1, 2009	Feb. 1, 2009	<i>USP31–NF26</i> and its <i>Supplements</i>
Mar. 1, 2009 <i>IRA</i> , <i>PF</i> 35(2)	Mar. 1, 2009	April 1, 2009	<i>USP31–NF26</i> and its <i>Supplements</i>

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

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

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

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

NOTICE AND WARNING

Concerning U.S. Patent or Trademark Rights

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

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Mission and Preface

USP 31–NF 26

This section provides background information on the United States Pharmacopeial Convention (USP), as well as general information about the 31st revision of the *United States Pharmacopeia* (USP 31) and the 26th edition of the *National Formulary* (NF 26). Additional official information about the specific uses of these texts is provided in the *General Notices and Requirements* (page 1).

MISSION STATEMENT

USP–NF is published in continuing pursuit of the mission of USP: *The United States Pharmacopeia promotes the public health and benefits practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other health care technologies, and related practices used to maintain and improve health and promote optimal health care delivery.*

Working with many constituencies and stakeholders around the world, USP's compendial activities support the availability of safe, effective, good-quality pharmaceutical care for all.

HISTORY

On January 1, 1820, 11 physicians met in the Senate Chamber of the U.S. Capitol building to establish a pharmacopeia for the United States. These practitioners sought to create a compendium of the best therapeutic products, give them useful names, and provide recipes for their preparation. Nearly a year later, on December 15, 1820, the first edition of *The Pharmacopoeia of the United States* was published. The preface to the 1820 edition read, *It is the object of a Pharmacopoeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries.* This mission continues today within USP.

Over time, the nature of the *United States Pharmacopeia* (USP) changed from being a compendium of recipes to a compendium of drug product standards. Its publishing schedule also changed. From 1820 to 1942, the USP was published at 10-year intervals; from 1942 to 2000, at 5-year intervals; and beginning in 2002, annually.

In 1888, the American Pharmaceutical Association published the first national formulary under the title *The National Formulary of Unofficial Preparations* (NF). Both the USP and the NF were recognized in the Federal Food and Drugs Act of 1906 and again in the Federal Food, Drug, and Cosmetic Act of 1938. In 1975, USP acquired the *National Formulary* (NF) and began publishing both compendia in a single volume, titled USP–NF.

Today, USP continues to develop USP–NF through the work of the Council of Experts into compendia that provide standards for articles based on advances in analytical and metrological science. As these and allied sciences evolve, so do USP and NF.

USP 31–NF 26

USP 31–NF 26 text is official May 1, 2008, unless otherwise noted. USP–NF contains official substance and preparation (product) monographs. The terms *official substance* and *official preparation* are defined in the *General Notices* of this *Pharmacopeia*. USP 31–NF 26 contains science-based standards for drugs, biologics,

dietary supplements, and excipients used in dosage forms and products. With few exceptions, all articles for which monographs are provided in USP 31–NF 26 are legally marketed in the United States or are contained in legally marketed articles.

A USP–NF monograph for an official substance or preparation includes the article's definition; packaging, storage, and other requirements; and a specification. The specification consists of a series of universal (description, identification, impurities, assay) and specific tests, one or more analytical procedures for each test, and acceptance criteria. Ingredients are defined as either drug substances or excipients. An excipient is any component, other than the active substance(s), intentionally added to the formulation of a dosage form. Excipients are not necessarily inert. Drug substances and excipients may be synthetic, semi-synthetic, drawn from nature (natural source), or manufactured using recombinant technology. Larger molecules and mixtures requiring a potency test are usually referred to as biologicals or biotechnological articles.

USP 31–NF 26 contains approximately 4,240 monographs and more than 220 *General Tests and Assays* (General Chapters numbered 1,000 and below) and *General Information Chapters* (numbered above 1,000). General Chapters provide frequently cited procedures, sometimes with acceptance criteria, in order to compile into one location repetitive information that appears in many monographs. New and revised monographs and *General Chapters* and obsolete matter deleted from this edition are indicated on page xxvii in the *Admissions* section.

Organization of USP 31–NF 26—USP 31–NF 26 is printed as a three-volume set, due to the increase in content. Volume 1 includes Front Matter (Mission and Preface, People, Members, Governance websites, Admissions/Annotations, and Commentary). It also includes USP *General Notices*, General Chapters, Dietary Supplement Chapters, Reagents, Reference Tables, Dietary Supplement Monographs, NF General Notices, Excipients, and NF Monographs. Volume 2 includes USP monographs A–L, and Volume 3 includes USP monographs M–Z. Volumes 2 and 3 also include the *USP General Notices* and the Guide to General Chapters, and all three volumes include the full index. Monographs for drug substances and preparations—with the exception of dietary supplements—appear in the first section of USP. Monographs for dietary supplements appear in a separate section of USP. General Chapters specific to dietary supplements are included in numerical order with the rest of the General Chapters in USP. Excipient monographs usually are presented in NF but also may appear in USP with suitable cross-referencing when they are also drug substances. A tabulation of excipients by functional category appears on page 1057.

Revisions—USP–NF is continuously revised. Revisions are presented annually, in twice-yearly *Supplements*, in *Interim Revision Announcements* (IRAs), and in *Revision Bulletins* (on the USP website).

Supplements—The *First Supplement* to USP 31–NF 26 will be published in February 2008 and will become official in August 2008. The *Second Supplement* will be published in June 2008 and will become official in December 2008. Users of USP print products must retain *Supplements* and subscriptions to *Pharmacopeial Forum* (PF) in order to have up-to-date information. The USP–NF online version is updated with each *Supplement* or annual revision. Each time a new edition or *Supplement* is released during the subscription period, a new CD-ROM will be issued. The Index in each *Supplement* is cumulative and includes citations to the annual revision and, for the *Second Supplement*, citations to the *First Supplement*. The contents of the two *Supplements* are integrated into the annual edition of the following year, along with new, official revi-

sions that have been adopted since the *Second Supplement* to the previous compendia.

Interim Revision Announcements (IRAs)—IRAs contain revisions that become official in the interval between publication of the annual revision and *Supplements*, and thus provide an expedited mechanism for making revisions official. They appear in USP's bi-monthly journal, *Pharmacopeial Forum (PF)*, with the official date noted in the publication. They are subsequently incorporated into the next published *Supplement* or annual revision, although their official dates may precede the official date of that publication. One reprint of each IRA is available to USP-NF subscribers on request.

Pharmacopeial Forum (PF)—Each PF contains several sections. The *Policies and Announcements* section provides information about publication and comment deadlines, USP news, and summaries of issues discussed by the Council of Experts and its Expert Committees. Proposals for revision are presented either as *Pharmacopeial Previews* or *In-Process Revisions*. Previews focus on monographs and General Chapters at an early stage of consideration. They also present new monographs for controversial items needing a longer public comment period. Depending on public comment, a *Preview* proposal may or may not advance to the in-process revision stage. *In-Process Revisions* represent draft revisions that are expected to advance to official status pending final review and approval by the relevant Expert Committee.

PF also includes *Pending and Canceled Proposals* and a *Harmonization* section. The *Stimuli to the Revision Process* section presents reports or statements of authoritative bodies, scientific articles relevant to compendial issues, general commentaries by interested parties, and summaries of comments received in response to policy initiatives. PF concludes with sections containing *Nomenclature*, *Index*, and *Chromatographic Reagents* used in USP-NF and PF. Each issue of PF also provides a cumulative index for the given calendar year.

Symbols Indicating Change to Official Text—Symbols identify the beginning and end of each revision. For *Supplements*, a black square superscript marks the beginning of each revision, and a black square subscript marks the end. For the six possible yearly *Interim Revision Announcements* in PF, black circles are used. Next to the subscript is a number that links the official date of the revision with the corresponding *Supplement* or PF. For example, a black square subscript with the numeral 1 next to it indicates that the revision will become official via the *First Supplement*. [NOTE—When *Interim Revision Announcements* are incorporated into the next *Supplement* or annual edition, the black circles will be replaced with either the appropriate *Supplement* black square and number or annual edition triangle and number.]

The following table shows symbols and official dates for *Interim Revision Announcements* and *Supplements* to USP 31-NF 26:

USP 31-NF 26			
Revision Document			
Supplement	Interim Revision Announcement	Official Date	Symbols
1	34(1)	Feb. 1, 2008	and • ₁
	34(2)	Apr. 1, 2008	and • ₂
	34(3)	June 1, 2008	and • ₃
		Aug. 1, 2008	and ¹ 1S (USP31)
	34(4)	Aug. 1, 2008	and • ₄
2	34(5)	Oct. 1, 2008	and • ₅
		Dec. 1, 2008	and ² 2S (USP31)
	34(6)	Dec. 1, 2008	and • ₆

Chemical Names and CAS Registry Numbers—Chemical subtitles given in the monographs are index names used by the Chemical Abstracts Service (CAS) of the American Chemical Society. They are provided only in monographs in which the titles specify substances that are definable chemical entities. The first subtitle is the inverted form of the systematic chemical name developed by CAS. This is presented in accordance with the rules established over the years by the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry, and this form is employed in the current issues of *Chemical Ab-*

stracts (CA). The second subtitle, given in uninverted form, is of a systematic type formerly used in CA. It is identical with, or closely resembles, the chemical name sanctioned and employed by IUPAC and by the World Health Organization (WHO). IUPAC names make generous use of nonsystematic and semisystematic (often referred to as "trivial") names and qualifying terms, all of which impede electronic manipulation. In contrast, CAS names are fully systematic for most substances and are amenable to search and retrieval. The two subtitles referred to above are frequently identical, and a CAS synonym is occasionally supplied as a third subtitle. Monographs with chemical subtitles generally also carry CAS registry numbers. These italicized, bracketed numbers function independently of nomenclature as invariant numerical designators of unique, unambiguous chemical substances in the CAS registry and thus are convenient and widely used.

USP 31-NF 26 Spanish Edition—In 2006, USP began providing an official Spanish edition of USP-NF. Maintenance of this edition follows the same revision approaches as the English edition.

Print and Electronic Presentations—All USP-NF publications are available in print form. In addition, USP-NF and its two annual *Supplements* are available in compact disc (CD) and Internet versions. The CD version makes USP-NF accessible to users on their computer hard drives. The Internet format allows individual registered users to access the online format through the World Wide Web. Both electronic formats provide access to official USP-NF content, along with extensive search options. The electronic formats are cumulatively updated to integrate the content of *Supplements*. Searchable electronic versions of PF and of the *USP Dictionary* (see below) also are available.

OTHER USP-NF RELATED PUBLICATIONS

Chromatographic Reagents—This comprehensive reference provides detailed information needed to conduct chromatographic procedures found in USP-NF. *Chromatographic Reagents* lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic analytical procedures that have been published in PF since 1980. *Chromatographic Reagents* also helps to track which column reagents were used to validate analytical procedures that have become official. The branded column reagents list is updated bimonthly in PF.

USP Pharmacists' Pharmacopeia—USP-NF is directed primarily to pharmaceutical and dietary supplement manufacturers, although it contains many monographs and allied text useful for the compounding practitioners. To better accommodate the needs of these practitioners and more generally the needs of the pharmacy community, USP has made available the *USP Pharmacists' Pharmacopeia*. This text provides pharmacy-relevant abridged official text from the USP-NF as well as authorized information. The former refers to standards for official articles, while the latter is more general information designed to be useful to practitioners. Both types of text are developed under the Rules and Procedures of the Council of Experts. The *USP Pharmacists' Pharmacopeia* is available both in print and in a web-based version.

USP Dictionary—The *USP Dictionary of USAN and International Drug Names* provides in a single volume the most up-to-date United States Adopted Names of drugs; official USP-NF names; nonproprietary, brand, and chemical names; graphic formulas; molecular formulas and weights; CAS registry numbers and code designations; drug manufacturers; and pharmacologic and therapeutic categories. The *Dictionary* helps to ensure the accuracy of the following: product labeling; reports, articles, and correspondence; FDA regulatory filings; and pharmaceutical package inserts. It is published annually (latest edition April 2007) and is recognized by FDA as the official source for established drug names (See *Nomenclature* section below.)

Reference Standards Catalog—Use of official USP-NF Reference Standards promotes uniform quality of drugs and supports first-, second-, and third-party testing of all manufactured and compounded articles. The publication listing the collection of official

2005-2010 Council of Experts

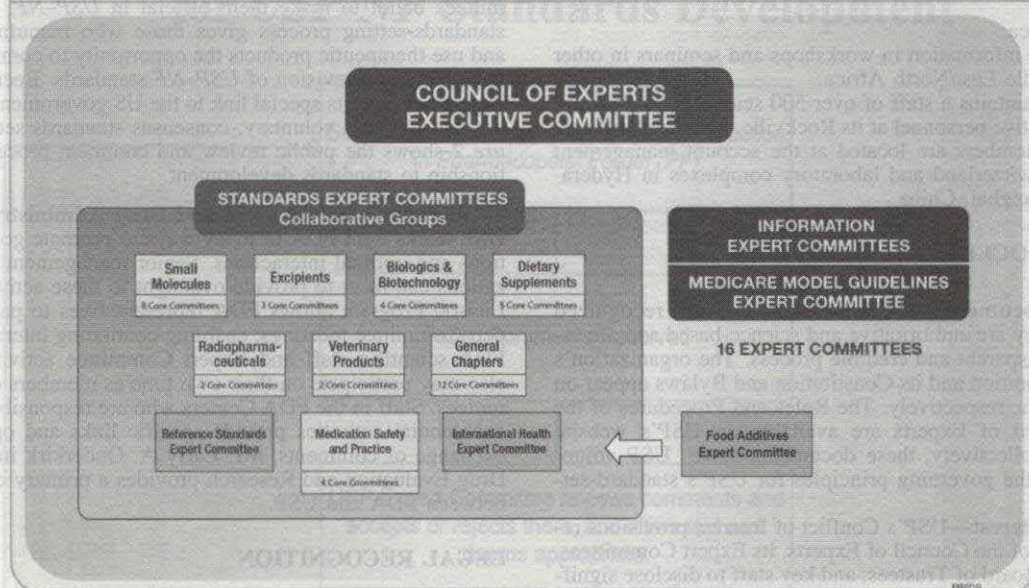


Figure 1. Organization of the 2005–2010 USP Council of Experts

USP–NF Reference Standards can be accessed on the USP website at www.usp.org and is available in print form by contacting USP Sales and Marketing staff at 301-816-8237. The listing identifies new items, replacement lots, lots of a single item that are simultaneously official, lots deleted from official status, and a preview of items eventually to be adopted. Purchase order information is included, and the names of distributors who can facilitate international availability of these items are suggested. This program benefits from the widespread voluntary contribution of suitable materials and test data from pharmaceutical manufacturers. USP advances this unofficial material to official status via careful characterization studies and collaborative testing, followed by review and, if appropriate, approval by the Reference Standards Committee of the Council of Experts.

USP GOVERNANCE, STANDARDS-SETTING, AND ADVISORY BODIES

USP's governing, standards-setting, and advisory bodies include the USP Convention, the Board of Trustees, the Council of Experts and its Expert Committees, Advisory Panels, and staff. Additional volunteer bodies include Stakeholder Forums, Project Teams, and Advisory Groups, which act in an advisory capacity to provide input to USP's governing, standards-setting, and management bodies.

USP Convention—USP's direction and priorities are determined by more than 400 Convention members divided into nine categories (page xviii). Eligible organizations within each membership category are invited to appoint a representative. Convention composition is determined so as to ensure suitable representation of those sections of the health care system that are influenced by, and in turn influence, USP's activities. Convention members elect USP's President, Treasurer, and other members of the Board of Trustees as well as the Council of Experts. They also vote on resolutions to guide USP's scientific policy and public health initiatives and update, as needed, USP's Constitution and By-Laws. The next meeting of the USP Convention is tentatively scheduled for spring 2010 in Washington, DC.

Board of Trustees—USP's Board of Trustees is entrusted with management of the business affairs, finances, and property of USP. During its five-year term, the Board defines USP's strategic direction through its key policy and operational decisions. A listing of

the members of the 2005–2010 Board of Trustees appears on page xi.

Council of Experts—The Council of Experts is the standards-setting body of USP. It is composed of 57 Expert Committee chairs elected to five-year terms by USP's Convention members. A Nominating Committee, consisting of the Chair of the Council of Experts, the Convention President, and the Vice Chair of the Nominating Committee for the Council of Experts, nominates individuals who are subsequently elected by the members of the Council of Experts to serve as Expert Committee members. Collectively, the Expert Committee chairs and members comprise more than 500 volunteers drawn from 50 countries. The 41 Standards Expert Committees are responsible for the content of USP–NF and associated publications (see Figure 1) and organized in Collaborative Groups for topics of common interest. The Information Expert Committees focus on development of Model Guidelines for the Medicare Modernization Act and other information activities. The Council of Experts' Executive Committee (see page xii) provides overall direction, is an appeals body, and performs other functions that support the Council's operations.

Advisory Panels to the Council of Experts—The Chair of the Council of Experts may appoint Advisory Panels to assist the Council of Experts in reaching scientific decisions and implementing new USP directives relating to USP–NF. A listing of Advisory Panels is provided in the People Section (page xv). This list changes frequently as advisory panels concluded, and new ones start their deliberations. There are more than 250 Advisory Panel members who contribute to the standards-setting activities of the Council of Experts.

Stakeholder Forums and Project Teams—USP has formed several domestic and international Stakeholder Forums and Project Teams in the 2005–2010 cycle to exchange information and receive comment on USP's standards-setting activities. Depending on the topic, a stakeholder forum may form project teams to work on selected topics. USP has also formed country- and regional Stakeholder Forums. The following are lists of Stakeholder Forums for the 2005–2010 cycle.

Domestic Stakeholder Forums (US and Canada)

- Prescription/Nonprescription
- Compounding
- Dietary Supplements
- Food Additives

- Patient Safety
- International Stakeholder Forums**
- Europe
- India
- Latin America

USP also provides information in workshops and seminars in other regions, e.g., Middle East/North Africa.

Staff—USP maintains a staff of over 500 scientists, professionals, and administrative personnel at its Rockville, Maryland, offices. Additional staff members are located at the account management office in Basel, Switzerland and laboratory complexes in Hyderabad, India and Shanghai, China.

RULES AND PROCEDURES

Governing Documents—*USP-NF* standards are recognized widely because they are authoritative and science-based and are established by a transparent and credible process. The organization's Articles of Incorporation and its Constitution and Bylaws appear on pages *xxiii* and *xxiv*, respectively. The Rules and Procedures of the 2005–2010 Council of Experts are available on USP's website (www.usp.org). Collectively, these documents serve USP volunteers and staff as the governing principles for USP's standard-setting activities.

Conflicts of Interest—USP's Conflict of Interest provisions require all members of the Council of Experts, its Expert Committees, Advisory Panels, Board of Trustees, and key staff to disclose significant financial interests in companies or other entities that are subject to *USP-NF* standards or that may be affected by *USP-NF* information. Members of the Board of Trustees, Council of Experts, and related bodies are not allowed to vote on any matter in which they have a conflict of interest or the appearance of a conflict of interest.

Confidentiality and Document Disclosure—Members of the Council of Experts, Expert Committees, and Advisory Panels sign confidentiality agreements, in keeping with the confidentiality provisions of the Rules and Procedures of the Council of Experts. The USP Document Disclosure Policy, available on USP's website, contributes to the transparency of the standards-setting process by making information available to the public, yet provides protection to manufacturers and others who submit confidential information to USP.

Authority for Publication—*USP-NF* is published in accordance with Chapter VI, Section 8, of the USP Bylaws, which states, "The Board of Trustees shall authorize the revision and release of text to the *United States Pharmacopeia* and the *National Formulary*. Upon approval of the content by the Council of Experts, in accordance with the rules and procedures adopted under Section 9, the Board of Trustees shall then act upon releasing the text and upon designating the date when it is to become official, said date to be reasonably distant from the date of its release. The Executive Vice President—CEO shall, annually or more frequently, upon specific request of the Board of Trustees, certify that the information contained in the *United States Pharmacopeia*, *National Formulary*, or other authorized publications have been prepared in accordance with the rules and procedures under Section 9."

USP-NF REVISION PROCESS

Public Participation—Although USP's Council of Experts is the ultimate decision-making body for *USP-NF* standards, these standards are developed by an exceptional process of public involvement and substantial interaction between USP and its stakeholders, both domestically and internationally. Participation in the revision process results from the support of many individuals and groups and also from scientific, technical, and trade organizations.

Requests for revision for monographs, either new monographs or those needing updating, contain information submitted voluntarily by manufacturers and other interested parties. At times USP staff may develop information to support a monograph *Request for Revision*. USP has prepared a document titled *Guideline for Submitting Requests for Revision to USP-NF* (available at www.usp.org, click on *USP-NF*). Via *PF*, USP solicits and encourages public comment on these monographs, General Chapters, and other draft

documents. USP scientific liaisons to Expert Committees review these responses and create draft proposals that are provided to the Council of Experts. These drafts become official when Expert Committees ballot to make them official in *USP-NF*. Thus, the USP standards-setting process gives those who manufacture, regulate, and use therapeutic products the opportunity to comment on the development and revision of *USP-NF* standards. Because of the voting process and its special link to the US government in law, USP is not considered a voluntary, consensus standards setting body. *Figure 2* shows the public review and comment process and its relationship to standards development.

Working with the Food and Drug Administration (FDA)—USP works with FDA in many ways to promote good communications and optimal interactions. Senior management of both organizations can meet to provide oversight to these activities. The FDA Liaison Program allows FDA representatives to participate in Expert Committee meetings, enabling continuing interactions between FDA scientific staff and Expert Committee activities. FDA staff also may participate on their own time as members of Expert Committees. Staff in the FDA Centers who are responsible for review of compendial activities provide specific links and opportunities for exchange of comments. Mr. Larry A. Ouderkirk in the Center for Drug Evaluation and Research provides a primary compendial link between FDA and USP.

LEGAL RECOGNITION

Recognition of *USP-NF*—*USP-NF* is recognized by law and custom in many countries throughout the world. In the United States, the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines the term "official compendium" as the official *USP*, the official *NF*, the official *Homeopathic Pharmacopeia of the United States*, or any supplement to them. FDA may enforce compliance with official standards in *USP-NF* under the adulteration and misbranding provisions of the FD&C Act. These provisions extend broad authority to FDA to prevent entry to or remove designated products from the United States market based on standards in the *USP-NF*.

The identity of an official article, as expressed by its name, is established if it conforms in all respects to the requirements of its monograph and other relevant portions of the compendia. The FD&C Act stipulates that an article may differ in strength, quality, or purity if the difference is stated on the article's label. Official preparations (a drug product, a dietary supplement including nutritional supplements, or a finished device) may contain additional suitable ingredients. (See *General Notices*.)

Drugs—USP's goal is to have substance and preparation (product) monographs in *USP-NF* for all FDA-approved drugs. USP also develops monographs for therapeutic products not approved by FDA, e.g., pre-1938 drugs, dietary supplements, and compounded preparations. Although submission of information needed to develop a monograph by the Council of Experts is voluntary, compliance with a *USP-NF* monograph, if available, is mandatory.

Biologics—In the United States, although some biologics are regulated under the provisions of the Public Health Service Act (PHSA), provisions of the FD&C Act also apply to these products. For this reason, products approved under the PHSA should comply with the adulteration and misbranding provisions of the FD&C Act at Section 501(b) and 502(g) and, thus, should conform to applicable official monographs in *USP-NF*.

Medical Devices—Section 201(h) of the FD&C Act defines a device as an instrument, apparatus, similar article, or component thereof recognized in *USP-NF*. Section 502(e) of the FD&C Act defines the established name of a device in the absence of an FDA designation of the official name as the official title in an official compendium. Despite these statutory provisions, there is no comparable recognition of USP's standards-setting authority and ability to define a medical device as exists for other FDA-regulated therapeutic products. Under authority granted by the Food and Drug Administration Modernization Act of 1997, the Center for Devices and Radiological Health recognizes national and international standards, including some *USP* tests and assays for medical devices.

Dietary Supplements—The Dietary Supplement Health and Education Act of 1994 amendments to the FD&C Act name *USP*

Public Review and Comment Process for USP-NF Standards Development

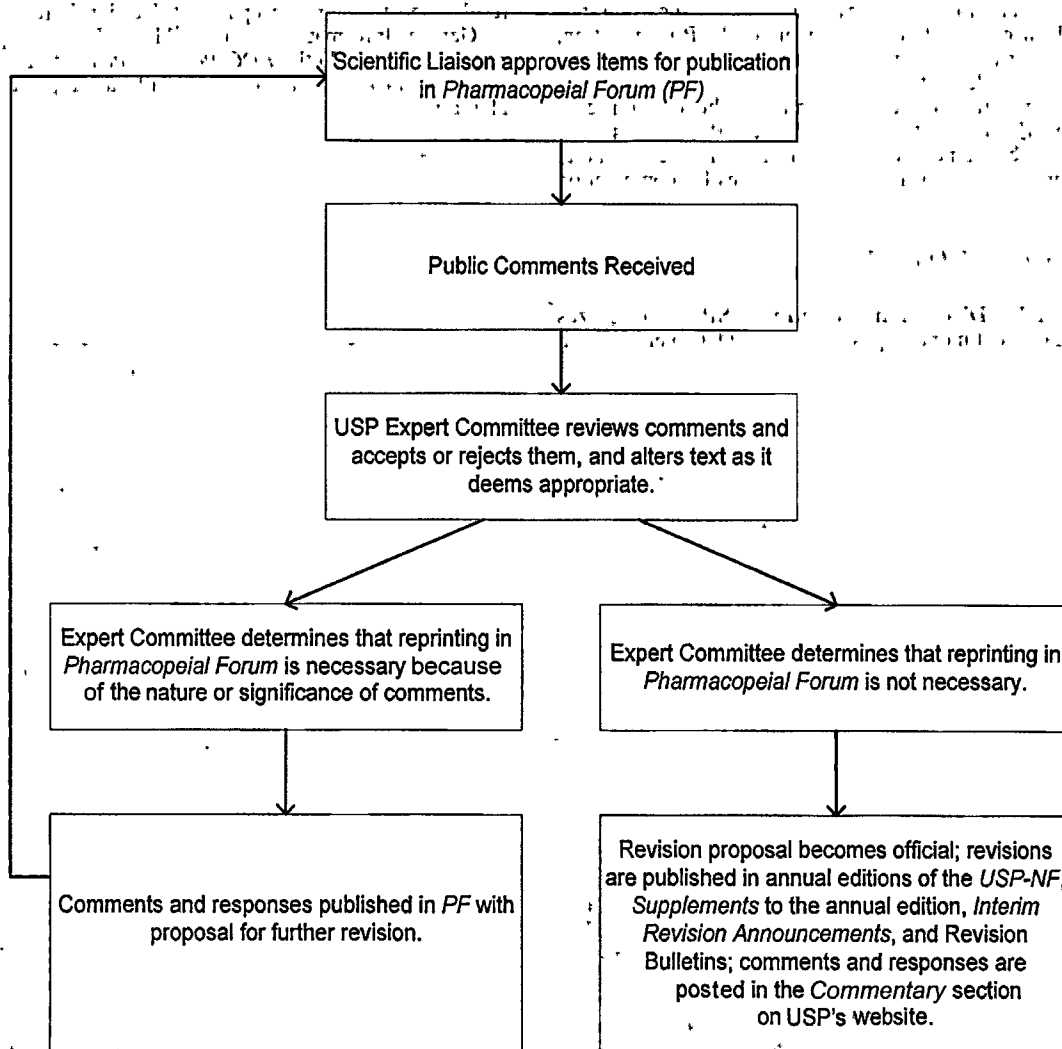


Figure 2. Public Review Process

and *NF* as the official compendia for dietary supplements. The amendments also provide that a dietary supplement may be deemed misbranded if it is covered by a monograph in an official compendium, is represented as conforming to this monograph, but fails to conform. The dietary supplement must be represented as conforming to a *USP-NF* dietary supplement monograph in order for the compendial standards to apply. This contrasts with pharmaceutical products, wherein conformance to the monograph is mandatory whether or not the product claims to conform.

Compounded Preparations—Preparation monographs provide information or standards applicable in compounding. Compounding means the preparation, mixing, assembling, packaging, or labeling of a drug or device or other article, as the result of a practitioner's order or in anticipation of such an order based on routine, regularly observed prescribing patterns. Standards in *USP-NF* for compounded preparations may be enforced at both the State and Federal levels, e.g., if a practitioner writes a prescription for a compounded preparation that is named in a *USP-NF* monograph, the prepara-

tion, when tested, must conform to the stipulations of the monograph so named.

Nomenclature—In the United States, FDA has authority to establish names for drug products and ingredients and to determine proper names for biologics. In most cases, however, FDA works with the United States Adopted Names (USAN) Council to determine names for drug and biological substances and with USP to determine drug product names. Oversight of proprietary names and proper names is the responsibility of FDA, working with applicants.

The USAN Council's program began in 1961 by providing ingredient names for drugs prior to their marketing. USP participates in this activity, together with the American Medical Association, the American Pharmacists Association, and FDA. The Council's output is incorporated, along with other names for drugs (including generic, proprietary, and chemical names and code designations), in the *USP Dictionary of USAN and International Drug Names*. Since 1988 this publication has been recognized by Federal regulation as the source of established names for drug substances in the United States.

Drug product names can be established by FDA, but more often are developed cooperatively by FDA and the USP Council of Ex-

perts' Nomenclature Expert Committee. The names developed by this Committee are used as the titles of the relevant monographs, and as such are recognized as the "established names" for drug products under section 502(e)(3) of the FD&C Act. The USP Drug Nomenclature Committee was formed in 1986 to supplement the Executive Committees of the Drug Standards Division and the Information Division and to prevent any inconsistency regarding nomenclature. Following the 2000 meeting of the USP Convention, the responsibility for devising and, when necessary, revising labeling requirements was delegated to this Committee, which is now named the Nomenclature Expert Committee. The Committee's work does not overlap that of the USAN Council. Rather, it is complementary and is concerned with standardization of compendial names, particularly dosage form names, and names for combination drug products.

HARMONIZATION ACTIVITIES

Pharmacopeial Discussion Group—USP harmonizes pharmacopeial excipient monographs and General Chapters through

the Pharmacopeial Discussion Group (PDG), which includes representatives from the European, Japanese, and United States pharmacopeias, and WHO (as an observer). According to the PDG definition, "a pharmacopeial general chapter or other pharmacopeial document is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results, and the same accept/reject decision is reached."

General Information Chapter (1196), *Pharmacopeial Harmonization*, provides (1) the *PDG Policy Statement*, (2) the *PDG Working Procedures*, (3) a discussion, (4) a status report, and (5) a glossary.

of powder recommended in the operating manual for the pycnometer. Seal the test cell in the pycnometer, and purge the pycnometer system with the test gas according to the procedure given in the manufacturer's operating instructions. If the sample must be degassed under vacuum, follow the recommendations in the individual monographs and the instructions in the operating manual for the pycnometer.

The measurement sequence above describes the procedure for the gas pycnometer shown in Figure 1. If the pycnometer differs in operation or in construction from the one shown in Figure 1, follow the operating procedure given in the manual for the pycnometer.

Repeat the measurement sequence for the same powder sample until consecutive measurements of the sample volume, V_s , agree to within 0.2%. Unload the test cell and measure the final powder weight, w . Calculate the pycnometric density, ρ , of the sample according to Equation 2.

(701) DISINTEGRATION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia*. The texts of these pharmacopoeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present general chapter. These pharmacopoeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national USP text, and therefore not part of the harmonized text, are marked with symbols (*) to specify this fact.

This test is provided to determine whether tablets or capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions presented below. Compliance with the limits on Disintegration stated in the individual monographs is required except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as extended-release dosage forms or, delayed-release dosage forms. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.

APPARATUS

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 160 mm in height and having an inside diameter of 97 to 115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm. 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 15 mm below the surface of the fluid and descends to not less than 25 mm from the bottom of the vessel on the downward stroke. At no time should the top of the basket-rack assembly become submerged. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly.—The basket-rack assembly consists of six open-ended transparent tubes, each 77.5 ± 2.5 mm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plates, each 88 to 92 mm in diameter and 5 to 8.5 mm in thickness, with six holes, each 22 to 26 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 a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm apertures and with a wire diameter of 0.57 to 0.66 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two 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. The basket-rack assembly conforms to the dimensions found in Figure 1.

Disks.—The use of disks is permitted only where specified or allowed in the monograph. If specified in the individual monograph, each tube is provided with a cylindrical disk 9.5 ± 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 parallel 2 ± 0.1 -mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 ± 0.2 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 ± 0.1 mm, and its bottom edges lie at a depth of 1.6 ± 0.1 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.4 ± 0.2 mm, and its center lies at a depth of 2.6 ± 0.1 mm from the cylinder's circumference. 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. The disks conform to dimensions found in Figure 1.

PROCEDURE

Uncoated Tablets.—Place 1 dosage unit in each of the six tubes of the basket and, if prescribed, add a disk. Operate the apparatus, using water or the specified medium as the immersion fluid, maintained at $37 \pm 2^\circ$. 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 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested are disintegrated.

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

Delayed-Release (Enteric-Coated) Tablets.—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at $37 \pm 2^\circ$ 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 $37 \pm 2^\circ$ 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

The use of automatic detection employing modified disks is permitted where the use of disks is specified or allowed. Such disks must comply with the requirements for density and dimension given in this chapter.

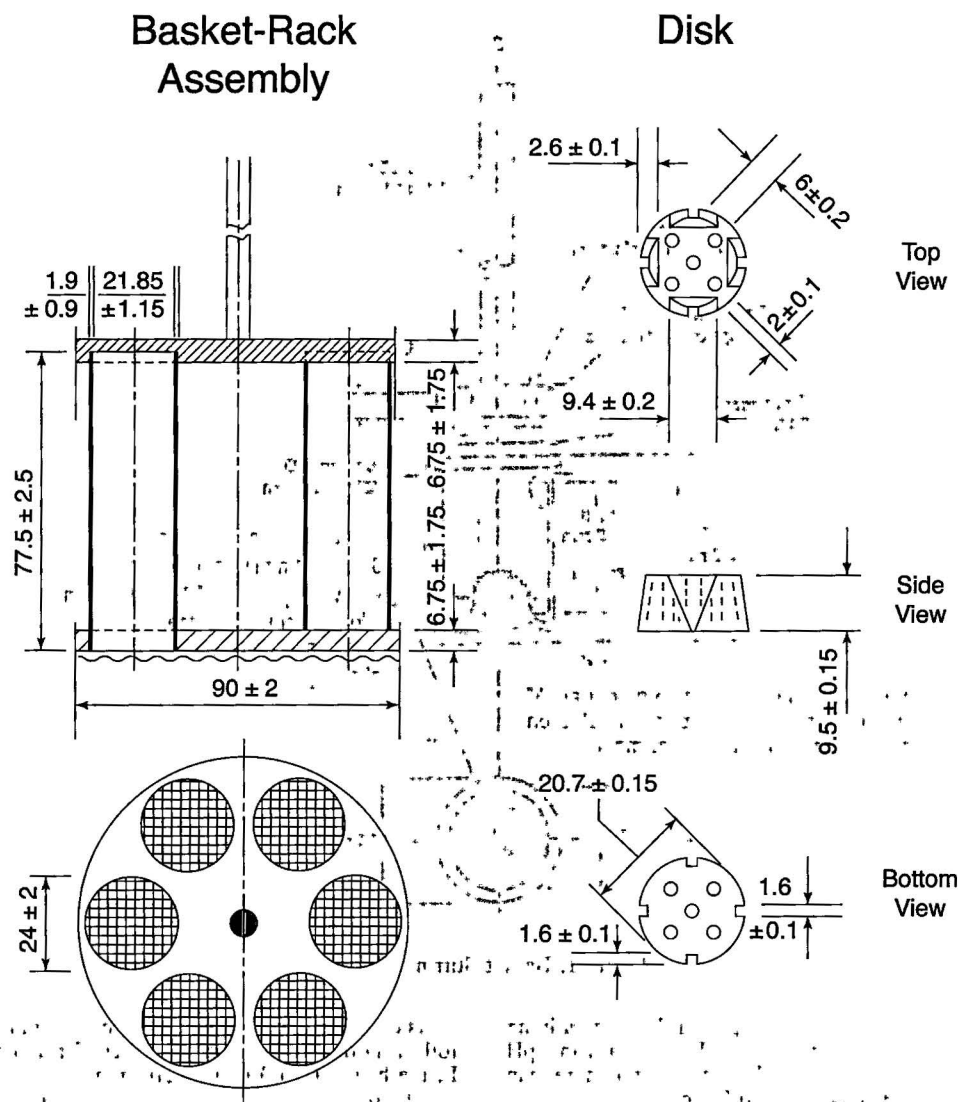


Fig. 1. Disintegration apparatus. (All dimensions are expressed in mm.)

disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer 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 fewer than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*. At the end of 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 fewer than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, 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 fewer than 16 of the total of 18 capsules tested disintegrate completely.

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

<711> DISSOLUTION

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia*. These pharmacopoeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national USP text, and therefore not part of the harmonized text, are marked with symbols (*) to specify this fact.

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph, for dosage forms administered orally. In this general chapter, a dosage unit is defined as 1 tablet or 1 capsule or the amount specified. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and where a dissolution or disintegration test that does not specifically state that it is to be applied to delayed-release articles is included in the individual monograph, the procedure and interpretation given for *Delayed-Release Dosage Forms* is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the *Dissolution* specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual monograph, the same *Medium* specified

should be tested for each filling machine, but the total number generally need not exceed 100 containers.

For small lots, in the case of either aseptic filling or terminal sterilization, if the number of final containers in the lot is between 20 and 200, about 10% of the containers should usually be tested. If the number of final containers in the lot is 20 or less, not fewer than 2 final containers should be tested.

PERFORMANCE, OBSERVATION, AND INTERPRETATION

The facility for sterility testing should be such as to offer no greater a microbial challenge to the articles being tested than that of an aseptic processing production facility. The sterility testing procedure should be performed by individuals having a high level of aseptic technique proficiency. The test performance records of these individuals should be documented.

The extensive aseptic manipulations required to perform sterility testing may result in a probability of non-product-related contamination of the order of 10^{-3} , a level similar to the overall efficiency of an aseptic operation and comparable to the microbial survivor probability of aseptically processed articles. This level of probability is significantly greater than that usually attributed to a terminal sterilization process, namely, 1 in 1 million or 10^{-6} microbial survivor probability. Appropriate, known-to-be-sterile finished articles should be employed periodically as negative controls as a check on the reliability of the test procedure. Preferably, the technicians performing the test should be unaware that they are testing negative controls. Of these tests, a false-positive frequency not exceeding 2% is desirable.

For aseptically processed articles, these facts support the routine use of the test set forth under *Sterility Tests* (71) or a more elaborate one. The production and validation documentation should be acceptable and complete. For effectively terminally sterilized products, however, the lower microbial survivor probability may direct the use of a less extensive test than the compendial procedure specified under *Sterility Tests* (71), or even preclude altogether the necessity for performing one. This added reliability of sterility assurance of terminal sterilization depends upon a properly validated and documented sterilization process. Sterility testing alone is no substitute.

Interpretation of Quality Control Tests—The overall responsibility for the operation of the test unit and the interpretation of test results in relation to acceptance or rejection of a lot should be in the hands of those who have appropriate formal training in microbiology and have knowledge of industrial sterilization, aseptic processing, and the statistical concepts involved in sampling. These individuals should be knowledgeable also concerning the environmental control program in the test facility to ensure that the microbiological quality of the air and critical work surfaces are consistently acceptable.

Quality control sterility tests (either according to the official reference test or modified tests) may be carried out in two separate stages in order to rule out false positive results. *First Stage*. Regardless of the sampling plan used, if no evidence of microbial growth is found, the results of the test may be taken as indicative of absence of intrinsic contamination of the lot.

If microbial growth is found, proceed to the *Second Stage* (unless the *First Stage* test can be invalidated). Evidence for invalidating a *First Stage* test in order to repeat it as a *First Stage* test may be obtained from a review of the testing environment and the relevant records thereto. Finding of microbial growth in negative controls need not be considered the sole grounds for invalidating a *First Stage* test. When proceeding to the *Second Stage*, particularly when depending on the results of the test for lot release, concurrently, initiate and document a complete review of all applicable production and control records. In this review, consideration should be paid to the following: (1) a check on monitoring records of the validated sterilization cycle applicable to the product, (2) sterility test-history relating to the particular product for both finished and in-process samples, as well as sterilization records of supporting equipment,

containers/closures, and sterile components, if any, and (3) environmental control data, including those obtained from media fills, exposure plates, filtering records, any sanitization records and microbial monitoring records of operators, gowns, gloves, and garbing practices.

Failing any lead from the above review, the current microbial profile of the product should be checked against the known historical profile for possible change. Records should be checked concomitantly for any changes in source of product components or in-processing procedures that might be contributory. Depending on the findings, and in extreme cases, consideration may have to be given to revalidation of the total manufacturing process. For the *Second Stage*, it is not possible to specify a particular number of specimens to be taken for testing. It is usual to select double the number specified for the *First Stage* under *Sterility Tests* (71), or other reasonable number. The minimum volumes tested from each specimen, the media, and the incubation periods are the same as those indicated for the *First Stage*.

If no microbial growth is found in the *Second Stage*, and the documented review of appropriate records and the indicated product investigation does not support the possibility of intrinsic contamination, the lot may meet the requirements of a test for sterility. If growth is found, the lot fails to meet the requirements of the test. As was indicated for the *First Stage* test, the *Second Stage* test may similarly be invalidated with appropriate evidence, and, if so done, repeated as a *Second Stage* test.

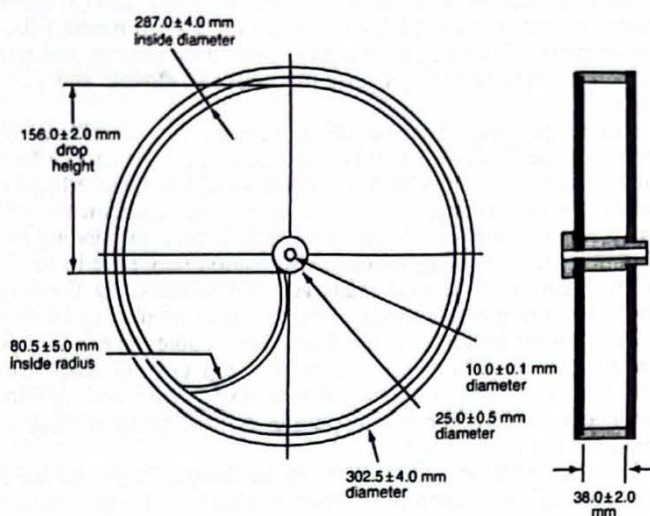
(1216) TABLET FRIABILITY

This general information chapter has been harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. The harmonized texts of these three pharmacopoeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present *United States Pharmacopoeia* general information chapter method. These pharmacopoeias have undertaken not to make any unilateral change to this harmonized chapter.

This chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure presented in this chapter is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet breaking force.

Use a drum, with an internal diameter between 283 and 291 mm and a depth between 36 and 40 mm, of transparent synthetic polymer with polished internal surfaces, and subject to minimum static build-up (see figure for a typical apparatus). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius between 75.5 and 85.5 mm that extends from the middle of the drum to the outer wall. The outer diameter of the central ring is between 24.5 and 25.5 mm. The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 rpm. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.

*The apparatus meeting these specifications is available from laboratory supply houses such as VanKel Technology Group, 13000 Weston Parkway, Cary, NC 27513, or from Erweka Instruments, Inc., 56 Quirk Road, Milford, CT 06460.



Tablet Friability Apparatus

For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablets corresponding as near as possible to 6.5 g. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

Generally, the test is run once. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are difficult to interpret or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. A maximum mean weight loss from the three samples of not more than 1.0% is considered acceptable for most products.

If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the horizontal and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned. In the case of hygroscopic tablets, an appropriate humidity-controlled environment is required for testing.

Drums with dual scooping projections, or an apparatus with more than one drum, for the running of multiple samples at one time, are also permitted.

(1217) TABLET BREAKING FORCE

INTRODUCTION

There are a variety of presentations for tablets as delivery systems for pharmaceutical agents, such as rapidly disintegrating, slowly disintegrating, eroding, chewable, and lozenge. Each of these presentations places a certain demand on the bonding, structure, and integrity of the compressed matrix. Tablets must be able to withstand the rigors of handling and transportation experienced in the manufacturing plant, in the drug distribution system, and in the

field at the hands of the end users (patients/consumers). Manufacturing processes such as coating, packaging, and printing can involve considerable stresses, which the tablets must be able to withstand. For these reasons, the mechanical strength of tablets is of considerable importance and is routinely measured. Tablet strength serves both as a criterion by which to guide product development and as a quality control specification.

One commonly employed test of the ability of tablets to withstand mechanical stresses determines their resistance to chipping and surface abrasion by tumbling them in a rotating cylinder. The percentage weight loss after tumbling is referred to as the *friability* of the tablets. Standardized methods and equipment for testing friability have been provided in general chapter *Tablet Friability* (1216).

Another measure of the mechanical integrity of tablets is their *breaking force*, which is the force required to cause them to fail (i.e., break) in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross-section) tablets, loading occurs across their diameter (sometimes referred to as diametral loading), and fracture occurs in that plane.

The breaking force of tablets is commonly called *hardness* in the pharmaceutical literature; however, the use of this term is misleading. In material science, the term *hardness* refers to the resistance of a surface to penetration or indentation by a small probe. The term *crushing strength* is also frequently used to describe the resistance of tablets to the application of a compressive load. Although this term describes the true nature of the test more accurately than does *hardness*, it implies that tablets are actually crushed during the test, which often is not the case. Moreover, the term *strength* in this application can be questioned, because in the physical sciences that term is often used to describe a stress (e.g., tensile strength). Thus, the term *breaking force* is preferred and will be used in the present discussion.

TABLET BREAKING FORCE DETERMINATIONS

Early measuring devices were typically hand operated. For example, the Monsanto (or Stokes) hardness tester was based on compressing tablets between two jaws via a spring gauge and screw. In the Pfizer hardness tester, the vertically mounted tablet was squeezed in a device that resembled a pair of pliers. In the Strong Cobb hardness tester, the breaking load was applied through the action of a small hydraulic pump that was first operated manually but was later motorized. Problems associated with these devices were related to operator variability in rates of loading and difficulties in proper setup and calibration. Modern testers employ mechanical drives, strain gauge-based load cells for force measurements, and electronic signal processing, and therefore are preferred. However, several important issues must be considered when using them for the analytical determination of breaking force; these are discussed below.

Platens

The platens should be parallel. Their faces should be polished smooth and precision-ground perpendicularly to the direction of movement. Perpendicularity must be preserved during platen movement, and the mechanism should be free of any bending or torsion displacements as the load is applied. The contact faces must be larger than the area of contact with the tablet.

Rate and Uniformity of Loading

Either the rate of platen movement or the rate at which the compressive force is applied (i.e., the loading rate) should be constant. Maintaining a constant loading rate avoids the rapid buildup of compressive loads, which may lead to uncontrolled crushing or shear failure and greater variability in the measured breaking force. However, constant loading rate measurements may be too slow for real time monitoring of tablet production.

The rate at which the compressive load is applied can significantly affect results, because time-dependent processes may be involved in tablet failure (1). How a tablet matrix responds to differences in the loading rate depends on the mechanism of failure. At low strain rates, some materials may fail in a ductile manner, but brittle failure is more likely at faster strain rates. The transition from ductile to brittle failure is accompanied by an increase in the breaking force. Devices that simply crush tablets may produce deceptively reproducible data because they lack sensitivity.

The test must be run consistently with equipment which has been routinely calibrated. Changing from testing units of different designs or from different manufacturers will require comparison of data to ensure that the two units are subjecting the dosage form to similar stress in a similar manner. Currently available equipment provides a constant loading rate of 20 newtons (N) or less per second or a constant platen movement of 3.5 mm or less per second. Controlled and consistent breaking is an important test procedure attribute. To ensure comparability of results, testing must occur under identical conditions of loading rate or platen movement rate. Since there are certain advantages to each system of load application, both are found in practice. Because the particular testing situation and the type of tablet matrix being evaluated will pose different constraints, there is also no basis to declare an absolute preference for one system over the other. This general chapter proposes consideration of both approaches.

The different methods may lead to numerically different results for a particular tablet sample, requiring that the rate of load application or displacement must be specified along with the determined breaking force.

Dependence of Breaking Force on Tablet Geometry and Mass

Measurements of breaking force do not take into account the dimensions or shape of the tablet. Thicker tablets of the same material compressed under conditions identical to those of thinner tablets, with the same tooling shape and to the same peak force, will require greater breaking forces. Tablet orientation and failure should occur in a manner consistent with those used during the development of the dosage form. For direct comparisons (i.e., without any normalizations of the data), breaking force measurements should be performed on tablets having the same dimensions, geometry, and consistent orientation in test equipment.

Tablet Orientation

Tablet orientation in diametral compression of round tablets without any scoring is unequivocal. That is, the tablet is placed between the platens so that compression occurs across a diameter. However, tablets with a unique or complex shape may have no obvious orientation for breaking force determination. Because the breaking force may depend on the tablet's orientation in the tester, to ensure comparability of results, it is best to settle on a standard orientation, preferably one that is most readily and easily reproduced by operators. In general, tablets are tested either across the diameter or parallel to the longest axis. Scored tablets have two orientation possibilities. When they are oriented with their scores perpendicular to the platen faces, the likelihood that tensile failure will occur along the scored line increases. This provides information about the strength of the matrix at the weakest point in the structure. When scored tablets are oriented with their scores parallel to the platen faces, more general information about the strength of the matrix is derived.

Capsule-shaped tablets or scored tablets may best be broken in a three-point flexure test (2). A fitting, which is either installed on the platens or substituted for the platens, supports the tablet at its ends and permits the breaking load to be applied to the opposite face at the unsupported midpoint of the tablet. The fittings are often available from the same source that supplies the hardness tester.

Units, Resolution, and Calibration

Modern breaking force testers are usually calibrated in kiloponds or newtons. The relationship between these units of force (3) is 1 kilopond (kp) = 1 kilogram-force (kgf) = 9.80 N. The test results should be expressed in standard units of force which facilitate communication. Some breaking force testers also will provide a scale in Strong Cobb units (SCU), a carryover from the days when Strong Cobb hardness testers were in common usage. The conversion between SCU and N or kp must be viewed with caution, because the SCU is derived from a hydraulic device and is a pressure.

Generally, contemporary breaking force testers use modern electronic designs with digital readouts. Some units also have an integral printer or may be interfaced with a printer. Breaking forces should be readable to within 1 N.

Breaking force testers should be calibrated periodically. The force sensor as well as the mechanics of the apparatus needs to be considered. For the force sensor, the complete measuring range (or, at a minimum, the range used for measuring the test sample) should be calibrated to a precision of 1 N, using either the static or dynamic method. Static calibration generally employs traceable counterweights; at least three different points are checked to assess linearity. Dynamic calibration makes use of a traceable reference-load cell that is compressed between the platens. The functional calibration of a breaking force test apparatus should also confirm that the velocity and the constancy of velocity for load application or displacement are within prescribed tolerances throughout the range of platen movement.

Sample Size

In order to achieve sufficient statistical precision for the determination of average breaking force, a minimum of 6 tablet samples should be tested. The average breaking force alone may be adequate to fulfill the purpose of process or product quality control. In cases where breaking force may be particularly critical, the average plus individual breaking force values should be accessible.

TENSILE STRENGTH

The measurement of tensile strengths provides a more fundamental measure of the mechanical strength of the compacted material and takes into account the geometry of the tablet. If tablets fail in tension, the breaking force can be used to calculate the tensile strength. Unfortunately, this is practical only for simple shapes. If flat-faced round tablets (right circular cylinders) fail in tension, as indicated by a clean split into halves under diametral compression, the breaking force may be used to compute the tensile strength from the following equation (4), which applies only to cylindrical tablets:

$$\sigma_x = \frac{2F}{\pi DH}$$

in which σ_x is the tensile strength, F is the breaking force, D is the tablet diameter, and H is the tablet thickness. Because only tablets that fail in tension are counted, the data are based on tablets that fail in a consistent way. Thus, reproducibility of data should be enhanced when compared to conventional breaking-strength testing. Moreover, the data will be normalized with respect to tablet dimensions, because both diameter and thickness are included in the equation. The derivation of this equation may be found in standard texts (5, 6); it is based on elastic theory and the following assumptions:

1. The tablet is an isotropic body
2. Hooke's law is obeyed
3. The modulus of elasticity in compression and in tension is the same
4. Ideal point loading occurs

The derivation has been extended to convex-faced tablets (7, 8):

$$\sigma_x = \frac{10F}{\pi D^2} \left[\frac{2.84H}{D} - \frac{0.126H}{W} + \frac{3.15W}{D} + 0.01 \right]^{-1}$$

where σ_x is the tensile strength, F is the breaking force, D is the tablet diameter, H is the tablet thickness, and W is the central cylinder thickness (tablet wall height).

The slow and constant loading rate of modern motorized break force testers encourages tensile failure. However, ideal point loading may not occur, because of crushing and the induction of shear failure at the interface with the surface of the platens. The addition of padding to the platens helps prevent shear at contact points and promotes true tensile failure. On that basis, padding is strongly recommended when highly precise measurements are needed. Padding should be relatively thin so that any deviation from the assumption of true point-source force application will not be large. The padding should also collapse very easily so that its deformation does not become part of the force measured by the test apparatus. In more routine settings involving measurements on a large number of samples, the addition of padding could contribute to inaccuracies in measurement as powder from previously tested samples becomes embedded in the collapsible matrix and thereby alters its properties. Unless provisions for frequent and routine replacement of the padding are made, it can be considered acceptable to ignore the use of padding material to maintain constancy of the test conditions.

Bending or flexure of tablets is another option for determining the tensile strength of tablets. Under ideal loading conditions, a breaking load applied to the unsupported midpoint of one face will result in the generation of pure tensile stress in the opposite face. If the tablets are right circular cylinders and are subjected to three-point flexure, the tensile strength may be estimated using the following equation (9):

$$\sigma_x = \frac{3FL}{2H^2D}$$

in which L is the distance between supports, and the other terms are as defined above. The assumptions are the same as those for calculating tensile strength from diametral compression. However, tensile strengths determined by flexure and diametral compression may not agree, because of likely nonideal loading and the induction of shear failure during testing.

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(1221) TEASPOON

For household purposes, an American Standard Teaspoon has been established by the American National Standards Institute² as containing 4.93 ± 0.24 mL. In view of the almost universal practice of employing teaspoons ordinarily available in the household for the administration of medicine, the teaspoon may be regarded as representing 5 mL. Preparations intended for administration by teaspoon should be formulated on the basis of dosage in 5-mL units. Any dropper, syringe, medicine cup, special spoon, or other device used to administer liquids should deliver 5 mL wherever a teaspoon calibration is indicated. Under ideal conditions of use, the volume error incurred in measuring liquids for individual dose administration by means of such calibrated devices should be not greater than 10% of the indicated amount.

Household units are used often to inform the patient of the size of the dose. Fifteen milliliters should be considered 1 standard table-spoonful; 10 mL, 2 standard teaspoonfuls; and 5 mL, 1 standard teaspoonful. Doses of less than 5 mL are frequently stated as fractions of a teaspoonful or in drops.

Because of the difficulties involved in measuring liquids under normal conditions of use, patients should be cautioned that household spoons are not appropriate for measuring medicines. They should be directed to use the standard measures in the cooking-and-baking measuring spoon sets or, preferably, oral dosing devices that may be provided by the practitioner. It must be kept in mind that the actual volume of a spoonful of any given liquid is related to the latter's viscosity and surface tension, among other influencing factors. These factors can also cause variability in the true volumes contained in or delivered by medicine cups. Where accurate dosage is required, a calibrated syringe or dropper should be used.

(1222) TERMINALLY STERILIZED PHARMACEUTICAL PRODUCTS—PARAMETRIC RELEASE

INTRODUCTION

Parametric release is defined as the release of terminally sterilized batches or lots of sterile products based upon compliance with the defined critical parameters of sterilization without having to perform the requirements under *Sterility Tests* (71). Parametric release is a possibility when the mode of sterilization is very well understood, the physical parameters of processing are well defined, predictable, and measurable, and the lethality of the cycle has been microbiologically validated through the use of appropriate biological indicators or, in the case of ionizing radiation, the appropriate microbiological and dosimetric tests. The use of parametric release for sterilization processes requires prior FDA approval. It should be expected that the regulatory agencies evaluating submissions including the use of parametric product release would insist upon a well supported scientific rationale for the sterilization process and well documented validation data. The agencies would need assurance that any marketed sample of product will be sterile and if tested after release would pass the requirements for sterility as found in the general chapter *Sterility Tests* (71).

It is important to consider the limitations of the *Sterility Tests* (71) in the evaluation of terminally sterilized products. The sterility

²American National Standards Institute, 1430 Broadway, New York, NY 10018.