U. S. PHARMACOPEIA

NATIONAL FORMULARY

SUPPLEMENT

8

PAGES 4125–4481
OFFICIAL
MAY 15, 1998

71 new monographs

New general tests chapter—<823> Radiopharmaceuticals for Positron Emission Tomography—Compounding

Water for Injection and Purified Water—Requirements for Total Organic Carbon <643> and Water Conductivity <645>

New general information chapter—<1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments

Title changes to become official May 15, 1998 (and others on November 15, 1998) for several injectable dosage forms

Revisions of <11> USP Reference Standards—Up-to-date cumulative list and label text

IMPORTANT!
Save Supplement 1 and all succeeding Supplements

USP 23–NF 18

USP 23 *Supplement 8* NF 18

The United States Pharmacopeia
TWENTY-THIRD REVISION

SINCE 1820

The National Formulary
EIGHTEENTH EDITION

By authority of the United States Pharmacopeial Convention, Inc.
Prepared by the Committee of Revision and published by the Board of Trustees

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Official May 15, 1998, except where otherwise noted. **Released March 15, 1998.**

Notice

This *Supplement* comprises revisions and new text pertaining to both *USP 23* and *NF 18*, and entries are listed in general in the order in which they occur in the respective compendia. IMPORTANT—Save the *First Supplement* and all succeeding *Supplements*. Changes and additions listed in the *Eighth Supplement* are effective from May 15, 1998, except where otherwise noted.

Supplement	*IRA**	*Release Date*	*Official Date*	*Entirely Superseded by*
1st		Nov. 1, 1994	Jan. 1, 1995	—
	1st, *PF* 20(6)	Dec. 10, 1994	Jan. 1, 1995	2S
	2nd, *PF* 21(1)	Jan. 10, 1995	Feb. 1, 1995	2S
	3rd, *PF* 21(2)	Mar. 10, 1995	Apr. 1, 1995	3S
2nd		Mar. 15, 1995	May 15, 1995	—
	4th, *PF* 21(3)	May 10, 1995	June 1, 1995	3S
	5th, *PF* 21(4)	July 10, 1995	Aug. 1, 1995	3S
	6th, *PF* 21(5)	Sept. 10, 1995	Oct. 1, 1995	4S
3rd		Sept. 15, 1995	Nov. 15, 1995	—
	7th, *PF* 21(6)	Nov. 10, 1995	Dec. 1, 1995	4S
	8th, *PF* 22(1)	Jan. 10, 1996	Feb. 1, 1996	4S
	9th, *PF* 22(2)	Mar. 10, 1996	Apr. 1, 1996	5S
4th		Mar. 15, 1996	May 15, 1996	—
	10th, *PF* 22(3)	May 10, 1996	June 1, 1996	5S
	11th, *PF* 22(3)	Apr. 22, 1996	May 15, 1996	5S
	12th, *PF* 22(4)	July 10, 1996	Aug. 1, 1996	5S
	13th, *PF* 22(5)	Sept. 10, 1996	Oct. 1, 1996	6S
5th		Sept. 15, 1996	Nov. 15, 1996	—
	14th, *PF* 22(6)	Nov. 10, 1996	Dec. 1, 1996	6S
	15th, *PF* 23(1)	Jan. 10, 1997	Feb. 1, 1997	6S
	16th, *PF* 23(2)	Mar. 10, 1997	Apr. 1, 1997	7S
6th		Mar. 15, 1997	May 15, 1997	—
	17th, *PF* 23(3)	May 10, 1997	June 1, 1997	7S
	18th, *PF* 23(4)	July 10, 1997	Aug. 1, 1997	7S
	19th, *PF* 23(5)	Sept. 10, 1997	Oct. 1, 1997	8S
7th		Sept. 15, 1997	Nov. 15, 1997	—
	20th, *PF* 23(6)	Nov. 10, 1997	Dec. 1, 1997	8S
	21st, *PF* 24(1)	Jan. 10, 1998	Feb. 1, 1998	8S
8th		Mar. 15, 1998	May 15, 1998	—

* Interim Revision Announcements (IRAs) are published as needed in *Pharmacopeial Forum* and are incorporated into the next succeeding *Supplement*. This column shows the Vol. and No. of the issue of *PF* in which each IRA appeared.

All inquiries and comments regarding *USP 23* text and *NF 18* text should be addressed to the Division of Standards Development, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852.

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Admissions

New Monographs Appearing in This Supplement

USP 23

Acyclovir Ointment
Alfentanil Hydrochloride
Alfentanil Injection
Aminophylline Delayed-release Tablets
Bacitracin for Injection
Bisacodyl Rectal Suspension
Bisacodyl Delayed-release Tablets
Calcium Acetate Tablets
Cefamandole Nafate
Cefmenoxime Hydrochloride
Cefonicid Sodium
Cefonicid for Injection
Cefoperazone Injection
Cefoperazone for Injection
Cefotaxime for Injection
Cefotiam Hydrochloride
Ceftizoxime Injection
Ceftizoxime for Injection
Ceftriaxone Injection
Ceftriaxone for Injection
Cefuroxime Injection
Cefuroxime for Injection
Cephalothin Injection
Cephalothin for Injection
Cephapirin Sodium
Cephapirin for Injection
Clarithromycin for Oral Suspension
Cyclosporine Injection
Dimethyl Sulfoxide Gel
Dimethyl Sulfoxide Topical Solution
Doxycycline for Injection
Enalapril Maleate and Hydrochlorothiazide Tablets
Eucalyptol
Guaifenesin for Injection
Indium In 111 Satumomab Pendetide Injection
Isradipine
Lactase
Menthol Lozenges
Methenamine Mandelate Delayed-release Tablets
Mitoxantrone Injection
Moricizine Hydrochloride
Moricizine Hydrochloride Tablets
Naftifine Hydrochloride
Naftifine Hydrochloride Cream
Naftifine Hydrochloride Gel
Neomycin for Injection
Poloxalene
Polymyxin B for Injection
Potassium Iodide Delayed-release Tablets
Quazepam
Quazepam Tablets
Sargramostim
Sargramostim for Injection
Sulfamethoxazole and Trimethoprim Injection
Sulfaquinoxaline Oral Solution
Sulfasalazine Delayed-release Tablets
Trenbolone Acetate
Trifluridine
Tylosin
Tylosin Granulated
Vidarabine
Zidovudine
Zidovudine Capsules
Zidovudine Injection
Zidovudine Oral Solution

NF 18

Garlic
Powdered Garlic
Methacrylic Acid Copolymer Dispersion
Valerian
Powdered Valerian

Changes in Official Titles Appearing in This Supplement

The following title changes are official May 15, 1998:

USP 23 New Title	USP 23 Former Title
Cefmenoxime Hydrochloride	Sterile Cefmenoxime Hydrochloride
Cefonicid Sodium	Sterile Cefonicid Sodium
Cefonicid for Injection	Sterile Cefonicid Sodium
Cefoperazone Sodium	Sterile Cefoperazone Sodium
Cefoperazone Injection	Cefoperazone Sodium Injection
Cefoperazone for Injection	Sterile Cefoperazone Sodium
Cefotaxime Sodium	Sterile Cefotaxime Sodium
Cefotaxime Injection	Cefotaxime Sodium Injection
Cefotaxime for Injection	Sterile Cefotaxime Sodium
Cefotiam Hydrochloride	Sterile Cefotiam Hydrochloride
Cefotiam for Injection	Sterile Cefotiam Hydrochloride
Ceftizoxime Sodium	Sterile Ceftizoxime Sodium
Ceftizoxime Injection	Ceftizoxime Sodium Injection
Ceftizoxime for Injection	Sterile Ceftizoxime Sodium
Ceftriaxone Sodium	Sterile Ceftriaxone Sodium
Ceftriaxone Injection	Ceftriaxone Sodium Injection
Ceftriaxone for Injection	Sterile Ceftriaxone Sodium
Cefuroxime Sodium	Sterile Cefuroxime Sodium
Cefuroxime Injection	Cefuroxime Sodium Injection
Cefuroxime for Injection	Sterile Cefuroxime Sodium
Cephalothin Sodium	Sterile Cephalothin Sodium
Cephalothin Injection	Cephalothin Sodium Injection
Caphalothin for Injection	Cephalothin Sodium for Injection
Cephapirin Sodium	Sterile Cephapirin Sodium
Cephapirin for Injection	Sterile Cephapirin Sodium
Cephradine	Sterile Cephradine
Cephradine for Injection	Sterile Cephradine
Spectinomycin Hydrochloride	Sterile Spectinomycin Hydrochloride

The following title changes are official May 15, 1999:

USP 23 New Title	USP 23 Former Title
Bisacodyl Delayed-release Tablets	Bisacodyl Tablets
Cyclosporine Injection	Cyclosporine Concentrate for Injection
Mitoxantrone Injection	Mitoxantrone for Injection Concentrate
Sulfamethoxazole and Trimethoprim Injection	Sulfamethoxazole and Trimethoprim for Injection Concentrate
Vidarabine	Sterile Vidarabine

The following title changes are official January 1, 2000:

USP 23 New Title	USP 23 Former Title
Bacitracin	Sterile Bacitracin
Bacitracin for Injection	Sterile Bacitracin
Bacitracin Zinc	Sterile Bacitracin Zinc
Cefamandole Nafate	Sterile Cefamandole Nafate
Cefamandole Nafate for Injection	Sterile Cefamandole Nafate
Chlortetracycline Hydrochloride	Sterile Chlortetracycline Hydrochloride
Cloxacillin Benzathine	Sterile Cloxacillin Benzathine
Cloxacillin Sodium	Sterile Cloxacillin Sodium
Doxycycline Hyclate	Sterile Doxycycline Hyclate
Doxycycline for Injection	Doxycycline Hyclate for Injection
Neomycin Sulfate	Sterile Neomycin Sulfate
Neomycin for Injection	Sterile Neomycin Sulfate
Polymyxin B Sulfate	Sterile Polymyxin B Sulfate
Polymyxin B For Injection	Sterile Polymyxin B Sulfate

ANNOTATED LIST

General Notices, Monographs, General Chapters, Reagents, and Tables Affected by Changes Appearing in This Supplement

Page citations refer to the pages of this Supplement. Note—The absence of a parenthetic term after the section heading denotes a change in the text, as distinguished from a newly added or deleted section.

General Notices and Requirements

Monographs (USP 23)

General Chapters

General Tests and Assays

General Requirements for Tests and Assays

Apparatus for Tests and Assays

Microbiological Tests

Biological Tests and Assays

Chemical Tests and Assays

IDENTIFICATION TESTS

LIMIT TESTS

OTHER TESTS AND ASSAYS

Physical Tests and Determinations

General Information

Reagents, Indicators, and Solutions

Reference Tables

NF General Notices and Requirements

Monographs (NF 18)

EIGHTH SUPPLEMENT

to *USP 23* and to *NF 18*

IMPORTANT—Save this *Supplement.* All of the *Supplements* are needed to keep the compendia up to date. The *index* to each *Supplement* will be cumulative to facilitate reference to all changes in and additions to the main volume of *USP 23–NF 18.*

Introduction

Changes and additions listed herein constitute revisions to *USP 23* and to *NF 18* effective May 15, 1998, except where otherwise noted.

This combined *USP* and *NF Supplement* is arranged in the order in which the items appear in the *USP 23–NF 18* main volume.

The last numbered page of the main volume of *USP 23–NF 18* is 2391. The *First Supplement* commences with page 2393, and pages thereafter will be numbered consecutively throughout all succeeding *Supplements* (see the tabulated pagination in the introduction to the index in this *Supplement*).

See the index to this *Supplement* first: each entry will show a page reference to the main volume only where the portion of text is revised herein, and it is necessary then to consult both the main volume and this *Supplement* in order to find the complete, up-to-date text.

As is stated above, the *Supplements* will not be cumulative, except that the individual revisions in a given monograph, chapter, or other section of text will be cumulated in the latest *Supplement* in which that portion of text is revised. Thus, it will be necessary to consult only the index to the latest *Supplement* and the main volume in order to find the complete, up-to-date text on any given item of the compendia.

The format and general editorial style employed in the *Supplement* serve not only for printing convenience but also for accommodation to computer storage and retrieval processes.

Explanation of Symbols—

Superscript symbol denotes the start of a change; *subscript* symbol with numeral denotes the end of a change.

Where the superscript and subscript symbols appear together with no intervening text, it means simply that a word or words have been deleted.

The number following a subscript symbol also denotes the official date of the change; thus, the numeral "1" refers to the *First Supplement* and by inference denotes the official date January 1, 1995.

USP 23–NF 18 Revision Document			
Supplement	*Interim Revision Announcement*	*Official Date*	*Symbols*
1		Jan. 1, 1995	■ and ■$_1$
	1	Jan. 1, 1995	• and •$_1$
	2	Feb. 1, 1995	• and •$_2$
	3	Apr. 1, 1995	• and •$_3$
2		May 15, 1995	■ and ■$_2$
	4	June 1, 1995	• and •$_4$
	5	Aug. 1, 1995	• and •$_5$
	6	Oct. 1, 1995	• and •$_6$
3		Nov. 15, 1995	■ and ■$_3$
	7	Dec. 1, 1995	• and •$_7$
	8	Feb. 1, 1996	• and •$_8$
	9	Apr. 1, 1996	• and •$_9$
4		May 15, 1996	■ and ■$_4$
	10	June 1, 1996	• and •$_{10}$
	11	May 15, 1996	• and •$_{11}$
	12	Aug. 1, 1996	• and •$_{12}$
	13	Oct. 1, 1996	• and •$_{13}$
5		Nov. 15, 1996	■ and ■$_5$
	14	Dec. 1, 1996	• and •$_{14}$
	15	Feb. 1, 1997	• and •$_{15}$
	16	Apr. 1, 1997	• and •$_{16}$
6		May 15, 1997	■ and ■$_6$
	17	June 1, 1997	• and •$_{17}$
	18	Aug. 1, 1997	• and •$_{18}$
	19	Oct. 1, 1997	• and •$_{19}$
7		Nov. 15, 1997	■ and ■$_7$
	20	Dec. 1, 1997	• and •$_{20}$
	21	Feb. 1, 1998	• and •$_{21}$
8		May 15, 1998	■ and ■$_8$

Interim Revision Announcements—Interim Revision Announcements are published as needed in *Pharmacopeial Forum* and are incorporated into the next

USP 23 and *NF 18* are published by the U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Pkwy., Rockville, MD 20852. All correspondence and suggestions for revisions with respect to either *USP* or *NF* should be addressed to Division of Standards Development USP-NF, 12601 Twinbrook Pkwy., Rockville, MD 20852.

succeeding *Supplement*. (*PF* offprints of Interim Revision Announcements also are made available separately.)

Official Title Changes—NOTE—In all instances where "*Monograph title change* (*see Note in Introduction*)" is specified, it is to be understood that the official title given after that specification is to be substituted for the former title in the appropriate places throughout the monograph concerned.

In succeeding *Supplements*, further revisions of the monograph concerned will be shown under the new, currently official title in its respective alphabetic position.

Official Title Changes for Injectable Dosage Forms—Title changes are being implemented, on deferred schedules, by supplemental revisions of applicable standards for Pharmacopeial articles that have been characterized by title as "Sterile" but for which there is nothing in the names that relates to injection as the intended route of administration of the drugs. These revisions necessarily are postponed to ensure that ample time is provided for labeling changes and for interested parties to become familiar with the new terminology and related requirements. Accordingly, the date on which deferred nomenclature-related revisions are to become effective is designated by prominent notations stating that the official date usually is to be eighteen months later than the official date of the supplement.

If the title change is the only revision of a Sterile [DRUG] monograph:

- The current title is followed by reference to new monographs for the drug substance and dosage form that are to become effective on the designated future date.
- The latter monographs are shown in their entirety where necessary to unambiguously represent the complete standards as of the deferred effective date. The symbols ■and■n appear at the beginning and end of the monographs.

If the title change is the only revision of a Sterile [DRUG] Suspension or Sterile [DRUG] for Suspension monograph:

- The current title is followed by the new title that is to become official on the designated future date.
- The symbols ■and■n appear at the beginning and end of the new title.

Any monograph revisions separately identified with ■and■n symbols that are not directly related to title and nomenclature changes and that are not accompanied by notations of deferred implementation become effective on the official date of the nth Supplement.

New USP Reference Standards—The following USP Reference Standards, which were indicated on page 3839 of the *Seventh Supplement* to *USP 23* and to *NF 18* as being not yet available, have since become available. Thus, the official date of each *USP 23* or *NF 18* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Bismuth Subsalicylate RS (March 1, 1998)
USP 8-Bromotheophylline RS (January 1, 1998)
USP Fluoxetine Hydrochloride RS (March 1, 1998)
USP Fluoxetine Related Compound A RS (March 1, 1998)
USP Iopamidol Related Compound B RS (January 1, 1998)
USP Mechlorethamine Hydrochloride RS (March 1, 1998)
USP Oxytocin RS (December 1, 1997)
USP Perflubron RS (December 1, 1997)

The official dates of any *USP 23* or *NF 18* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

As each of these Reference Standards becomes available, notice to that effect will be given in an Interim Revision Announcement in *Pharmacopeial Forum* and cumulated in the following *Supplement*.

USP Alfentanil Hydrochloride RS
USP Alteplase RS
USP Amdinocillin RS
USP Amitraz RS
USP Anti-thrombin III RS
USP Arsanilic Acid RS
USP Positive Bioreaction RS
USP Cefixime RS
USP Cefmenoxime Hydrochloride RS
USP Cefotiam Hydrochloride RS
USP Cefpiramide RS
USP Ceftriaxone Sodium RS
USP Cephapirin Benzathine RS
USP Chlorophyllin Copper Complex Sodium RS
USP Cinoxate RS
USP Clavam-2-carboxylate Potassium RS
USP Clobetasol Propionate RS
USP Decoquinate RS
USP Desflurane RS
USP Desflurane Related Compound A RS
USP Dextran Vo Marker RS
USP Dichloralphenazone RS
USP Diethylstilbestrol Diphosphate RS
USP Ethchlorvynol RS
USP Ethopabate RS
USP Ethopabate Related Compound A RS
USP Factor X_a RS
USP Flecainide Related Compound A RS
USP Fluoxetine Related Compound B RS
USP Gadopentate Monomeglumine RS
USP Powdered Ginger RS
USP Hexylresorcinol RS
USP Ioversol RS
USP Ioversol Related Compound A RS
USP Ioversol Related Compound B RS
USP Ioxaglic Acid RS
USP Isometheptene Mucate RS
USP Lactase RS
USP Levmetamfetamine RS
USP Mandelic Acid RS
USP Menotropins RS
USP Methyldopa-glucose Reaction Product RS
USP Monensin Sodium RS
USP Naftifine Hydrochloride RS
USP Narasin RS
USP Pheniramine Maleate RS
USP Phenylpropanolamine Bitartrate RS
USP Poloxalene RS
USP Proinsulin (Beef) RS
USP Proinsulin (Pork) RS
USP Pyrethrum Extract RS
USP Quazepam RS
USP Quazepam Related Compound A RS

USP Sargramostim RS
USP Sulfaquinoxaline RS
USP Sulfaquinoxaline Related Compound A RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Thiostrepton RS
USP Tilmicosin RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Tylosin RS
USP Valerenic Acid RS
USP Powdered Valerian RS
USP Vasopressin RS
USP Zalcitabine RS
USP Zalcitabine Related Compound A RS

Product Contact Areas—Areas and surfaces in a controlled environment that are in direct contact with either products, containers, or closures and the microbiological status of which can result in potential microbial contamination of the product/container/closure system. Once identified, these areas should be tested more frequently than non–product-contact areas or surfaces.

Risk Assessment Analysis—Analysis of the identification of contamination potentials in controlled environments that establish priorities in terms of severity and frequency and that will develop methods and procedures that will eliminate, reduce, minimize, or mitigate their potential for microbial contamination of the product/container/closure system.

Sampling Plan—A documented plan that describes the procedures and methods for sampling a controlled environment; identifies the sampling sites, the sampling frequency, and number of samples; and describes the method of analysis and how to interpret the results.

Sampling Sites—Documented geographical location, within a controlled environment, where sampling for microbiological evaluation is taken. In general, sampling sites are selected because of their potential for product/container/closure contacts.

Standard Operating Procedures—Written procedures describing operations, testing, sampling, interpretation of results, and corrective actions that relate to the operations that are taking place in a controlled environment and auxiliary environments. Deviations from standard operating procedures should be noted and approved by responsible managers.

Sterile Field—In aseptic processing or in other controlled environments, it is the space at the level of or above open product containers, closures, or product itself, where the potential for microbial contamination is highest.

Sterility—Within the strictest definition of sterility, an article is deemed sterile when there is complete absence of viable microorganisms. Absolute sterility cannot be practically demonstrated without testing every article in a batch. Sterility is defined in probabilistic terms, where the likelihood of a contaminated article is acceptably remote.

Swabs—Devices provided that are used to sample irregular as well as regular surfaces for determination of microbial status. The swab, generally composed of a stick with an absorbent extremity, is moistened before sampling and used to sample a specified unit area of a surface. The swab is then rinsed in sterile saline or other suitable menstruum and the contents plated on nutrient agar plates to obtain an estimate of the viable microbial load on that surface.

Trend Analysis—Data from a routine microbial environmental monitoring program that can be related to time, shift, facility, etc. This information is periodically evaluated to establish the status or pattern of that program to ascertain whether it is under adequate control. A trend analysis is used to facilitate decision-making for requalification of a controlled environment or for maintenance and sanitization schedules.■8

⟨1151⟩ PHARMACEUTICAL DOSAGE FORMS

Change to read:

STABILITY

The term "stability," with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit, and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply throughout the shelf life of the product.

The stability parameters of a drug dosage form can be influenced by environmental conditions of storage (temperature, light, air, and humidity), as well as the package components. Pharmacopeial articles should include required storage conditions on their labeling. These are the conditions under which the expiration date shall apply. The storage requirements specified in the labeling for the article must be observed throughout the distribution of the article (i.e., beyond the time it leaves the manufacturer up to and including its handling by the dispenser or seller of the article to the consumer). Although labeling for the consumer should indicate proper storage conditions, it is recognized that control beyond the dispenser or seller is difficult.

•■Beyond-use dating information must be provided by the manufacturer in the labeling of all solid oral Pharmacopeial dosage forms intended for dispensing on prescription, unless the dosage form is packaged by the manufacturer in a container that is labeled for dispensing directly to the patient. To meet this requirement, there must be a recommendation for an appropriate dispensing container (e.g., "tight," "well-closed," "light-resistant") and, for unit-dose packaging, a recommendation for the appropriate class of package (see Class A, B, C, or D under *Results* in *Containers—Permeation* ⟨671⟩) and the length of time that is appropriate for a beyond-use date in that type of container or package. Such a beyond-use date may be based on an "open dish" study in which the dosage forms are found to remain stable (i.e., conform to all monograph requirements for the declared beyond-use time period). The open dish study is a study in which the dosage forms are exposed to 60% relative humidity at 25° for •$30_{•20}$ days without any container protection: three samples of 30-unit doses from one lot are analyzed at 0 •and $30_{•20}$ days. The dosage forms may be protected from light during the study. Beyond-use dating information supported by such "open dish" studies need only indicate that, other than regarding the need for light resistance, any appropriate dispensing container may be used for repackaging the dosage form. Alternatively, studies conducted in containers that are one class below (i.e., more permeable to water vapor) the class being recommended for repackaging the dosage form may be substituted for "open dish" studies. For example, a study conducted in Class C unit-dose containers that demonstrates stability will support a recommendation for use of a Class B, or better, package. Beyond-use dating information may be obtained by any other type of stability study including, but not limited to, accelerated stability studies. Exempt from these requirements are drugs dispensed in a container to be used within a day and drugs in container-closure systems that are known to be equivalent in protection to the marketed container system.■7 •21

•(Postponed until November 15, 1998)•21

Stability Protocols—Stability of manufactured dosage forms must be demonstrated by the manufacturer by the use of methods adequate for the purpose. Monograph assays may be used for stability testing if they are stability-indicating (i.e., if they accurately differentiate between the intact drug molecules and their degradation products). Stability considerations should include not only the specific compendial requirements, but also changes in physical appearance of the product that would warn users that the product's continued integrity is questionable.

Stability studies on active substances and packaged dosage forms are conducted by means of "real-time," long-term tests at specific temperatures and relative humidities representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned. Labeling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air, and light on its stability. Label temperature storage warnings will reflect both the results of the real-time storage tests and also allow for expected seasonal excursions of temperature.

Controlled room temperature (see the *Storage Temperature* section under *General Notices and Requirements—Preservation, Packaging, Storage, and Labeling*) delineates the allowable tolerance in storage circumstances at any location in the chain of distribution (e.g., pharmacies, hospitals, and warehouses). This terminology also allows patients or consumers to be counseled as to appropriate storage for the product. Products may be labeled either to store at "Controlled room temperature" or to store at temperatures "up to 25°" where labeling is supported by long-term stability studies at the designated storage condition of 25°. *Controlled room temperature* limits the permissible excursions to those consistent with the maintenance of a mean kinetic temperature calculated to be not more than 25°. See *Mean Kinetic Temperature*. The common international guideline for long-term stability studies specifies 25 ± 2° at 60 ± 5% relative humidity. Accelerated studies are specified at 40 ± 2° and at 75 ± 5% relative humidity. Accelerated studies

Change to read:

Table 1. International Climatic Zones.

Climatic Zone	Calculated Data °C*	°C MKT**	% ■RH■6	mbar***	Derived Data °C	% ■RH■6	mbar
I. *Temperate* United Kingdom Northern Europe Canada Russia	20.0	20.0	42	9.9	21	45	11.2
II *Mediterranean, Subtropical* United States Japan Southern Europe (Portugal-Greece)	21.6	22.0	52	13.5	25	60	19.0
III. *Hot, Dry* Iran Iraq Sudan	26.4	27.9	35	11.9	30	35	15.0
IV. *Hot, Humid* Brazil Ghana Indonesia Nicaragua Philippines	26.7	27.4	76	26.6	30	70	30.0

* Data recorded as <19° calculated as 19°.
** Calculated mean kinetic temperature.
***Partial pressure of water vapor.

also allow the interpretation of data and information on short-term spikes in storage conditions in addition to the excursions allowed for by controlled room temperature.

The term "room temperature" is used in different ways in different countries, and it is usually preferable for product labeling for products to be shipped outside the continental U.S. to refer to a maximum storage temperature or temperature range in degrees Celsius.

Mean Kinetic Temperature—Mean kinetic temperature is defined as a single calculated temperature at which the degradation of an article would be equivalent to the actual degradation that would result from temperature fluctuations during the storage period. It is not a simple arithmetic mean. The mean kinetic temperature is calculated from average storage temperatures recorded over a one-year period, with a minimum of twelve equally spaced average storage temperature observations being recorded. Average temperature may be determined using automated recording devices or as the arithmetic mean of the highest and lowest temperatures attained during the observation period as measured on a high-low thermometer. The mean kinetic temperature is calculated by the following equation (derived from the Arrhenius equation):

$$T_k = \frac{\Delta H / R}{-ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)},$$

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144kJ·mole^{-1} (unless more accurate information is available from experimental studies); R is the universal gas constant, 8.3144×10^{-3} kJ· mole^{-1}· degree^{-1}; T_1 is the average storage temperature during the first time period (e.g., month); T_2 is the average storage temperature during the second time period; T_n is the average storage temperature during the nth time period, n being the total number of average storage temperatures recorded (minimum of twelve) during the observation period; and all temperatures (T) being absolute temperatures in degrees Kelvin (°K).

Climatic Zones—For convenience in planning for packaging and storage, and for stability studies, international practice identifies four climatic zones, which are described in Table 1. The United States, Europe, and Japan are characterized by zones I and II. The values in Table 1 are based on observed temperatures and relative humidities, both outside and in rooms, from which mean kinetic temperatures and average humidity values are calculated.[1] Derived values are based on inspection of data from individual cities and on allowances for a margin of safety in assignment of these specified conditions.

A discussion of aspects of drug product stability that are of primary concern to the pharmacist in the dispensing of medications may be found under *Stability Considerations in Dispensing Practice* ⟨1191⟩.

Inasmuch as this chapter is for purposes of general information only, no statement herein is intended to modify or supplant any of the specific requirements pertinent to pharmaceutical preparations, which are given elsewhere in this Pharmacopeia.

Change to read:

AEROSOLS

Pharmaceutical aerosols are products that are packaged under pressure and contain therapeutically active ingredients that are released upon activation of an appropriate valve system. They are intended for topical application to the skin as well as local application into the nose (nasal aerosols), mouth (lingual aerosols), or lungs (inhalation aerosols).

The term "aerosol" refers to the fine mist of spray that results from most pressurized systems. However, the term has been broadly misapplied to all self-contained pressurized products, some of which deliver foams or semisolid fluids. In the case of *Inhalation Aerosols*, the particle size of the delivered medication must be carefully controlled and the average size of the particles should be under 10 μm. These products are also known as metered-dose inhalers (MDIs). ■■6 Other aerosol sprays may contain particles up to several hundred micrometers in diameter.

The basic components of an aerosol system are the container, the propellant, the concentrate containing the active ingredient(s), the

[1] The source of the data and information in Table 1 is the International Conference on Harmonization sponsored by the International Federation of Pharmaceutical Manufacturers Associations.

valve, and the actuator. The nature of these components determines such characteristics as particle size distribution, uniformity of valve delivery for metered valves, delivery rate, wetness and temperature of the spray, foam density, or fluid viscosity.

Types of Aerosols

Aerosols consist of two-phase (gas and liquid) or three-phase (gas, liquid, and solid or liquid) systems. The two-phase aerosol consists of a solution of active ingredients in liquefied propellant and the vaporized propellant. The solvent is composed of the propellant or a mixture of the propellant and co-solvents such as alcohol, propylene glycol, and polyethylene glycols, which are often used to enhance the solubility of the active ingredients.

Three-phase systems consist of a suspension or emulsion of the active ingredient(s) in addition to the vaporized propellants. A suspension consists of the active ingredient(s) that may be dispersed in the propellant system with the aid of suitable excipients such as wetting agents and / or solid carriers such as talc or colloidal silicas.

A foam aerosol is an emulsion containing one or more active ingredients, surfactants, aqueous or nonaqueous liquids, and the propellants. If the propellant is in the internal (discontinuous) phase (i.e., of the oil-in-water type), a stable foam is discharged; and if the propellant is in the external (continuous) phase (i.e., of the water-in-oil type), a spray or a quick-breaking foam is discharged.

Propellants

The propellant supplies the necessary pressure within an aerosol system to expel material from the container and, in combination with other components, to convert the material into the desired physical form. Propellants may be broadly classified as liquefied or compressed gases having vapor pressures generally exceeding atmospheric pressure. Propellants within this definition include various hydrocarbons, especially ■halogenated■ derivatives of methane, ■■ ethane, ■and propane,■ low molecular weight hydrocarbons such as the butanes and pentanes, and compressed gases such as carbon dioxide, nitrogen, and nitrous oxide. Mixtures of propellants are frequently used to obtain desirable pressure, delivery, and spray characteristics. A good propellant system should have the proper vapor pressure characteristics consistent with the other aerosol components.

Valves

The primary function of the valve is to regulate the flow of the therapeutic agent and propellant from the container. The spray characteristics of the aerosol are influenced by orifice dimension, number, and location. Most aerosol valves provide for continuous spray operation and are used on most topical products. However, pharmaceutical products for oral or nasal inhalation often utilize metered-dose valves that must deliver a uniform quantity of spray upon each valve activation. The accuracy and reproducibility of the doses delivered from metering valves are generally good, comparing favorably to the uniformity of solid dosage forms such as tablets and capsules. However, when aerosol packages are stored improperly, or when they have not been used for long periods of time, valves must be primed before use. Materials used for the manufacture of valves should be inert to the formulations used. Plastic, rubber, aluminum, and stainless steel valve components are commonly used. Metered-dose valves must deliver an accurate dose within specified tolerances.

Actuators

An actuator is the fitting attached to an aerosol valve stem, which when depressed or moved, opens the valve, and directs the spray containing the drug preparation to the desired area. The actuator usually indicates the direction in which the preparation is dispensed and protects the hand or finger from the refrigerant effects of the propellant. Actuators incorporate an orifice which may vary widely in size and shape. The size of this orifice, the expansion chamber design, and the nature of the propellant and formulation influence the physical characteristics of the spray, foam, or stream of solid particles dispensed. For inhalation ■■ aerosols, an actuator capable of delivering the medication in the proper particle size range is utilized.

Containers

Aerosol containers usually are made of glass, plastic, or metal, or a combination of these materials. Glass containers must be precisely engineered to provide the maximum in pressure safety and impact resistance. Plastics may be employed to coat glass containers for improved safety characteristics, or to coat metal containers to improve corrosion resistance and enhance stability of the formulation. Suitable metals include stainless steel, aluminum, and tin-plated steel.

Manufacture

Aerosols are usually prepared by one of two general processes. In the "cold-fill" process, the concentrate (generally cooled to a temperature below 0°) and the refrigerated propellant are measured into open containers (usually chilled). The valve-actuator assembly is then crimped onto the container to form a pressure-tight seal. During the interval between propellant addition and crimping, sufficient volatilization of propellant occurs to displace air from the container. In the "pressure-fill" method, the concentrate is placed in the container, and either the propellant is forced under pressure through the valve orifice after the valve is sealed, or the propellant is allowed to flow under the valve cap and then the valve assembly is sealed ("under-the-cap" filling). In both cases of the "pressure-fill" method, provision must be made for evacuation of air by means of vacuum or displacement with a small amount of propellant ■vapor.■ Manufacturing process controls usually include monitoring of proper formulation and propellant fill weight, and pressure testing and leak testing of the finished aerosol.

■Extractable Substances

Since pressurized inhalers and aerosols are normally formulated with organic solvents as the propellant or the vehicle, leaching of extractables from the elastomeric and plastic components into the formulation is a potentially serious problem. Thus, the composition and the quality of materials used in the manufacture of the valve components (e.g., stem, gaskets, housing, etc.) must be carefully selected. Their compatibility with formulation components should be well established so as to prevent distortion of the valve components and to minimize changes in the medication delivery, leak rate, and impurity profile of the drug product over time. The extractable profiles of a representative sample of each of the elastomeric and plastic components of the valve should be established under specified conditions to ensure reproducible quality and purity of the drug product. Extractables, which may include polynuclear aromatics, nitrosamines, vulcanization accelerators, antioxidants, plasticizers, monomers, etc., should be identified and minimized wherever possible.

Specifications and limits for individual and total extractables from different valve components may require the use of different analytical methods. In addition, the standard USP biological testing (see the general test chapters *Biological Reactivity Tests, In Vitro* ⟨87⟩ and *Biological Reactivity Tests, In Vivo* ⟨88⟩) as well as other safety data may be needed.■

Labeling

Medicinal aerosols should contain at least the following warning information on the label as in accordance with appropriate regulations.

Warning—Avoid inhaling. Keep away from eyes or other mucous membranes.

NOTE—The statement "Avoid inhaling" is not necessary for preparations specifically designed for use by inhalation. The phrase "or other mucous membranes" is not necessary for preparations specifically designed for use on mucous membranes.

Warning—Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120° F (49° C). Keep out of reach of children.

In addition to the aforementioned warnings, the label of a drug packaged in an aerosol container in which the propellant consists in whole or in part of a halocarbon or hydrocarbon shall, where required under regulations of the FDA, bear either of the following warnings:

Warning—Do not inhale directly; deliberate inhalation of contents can cause death.

Warning—Use only as directed; intentional misuse by deliberately concentrating and inhaling the contents can be harmful or fatal.

Add the following:

■BOLUSES

Boluses are large elongated tablets intended for administration to animals (see *Tablets*).■2

(Nomenclature related changes—to become official May 15, 1999)

CAPSULES

Capsules are solid dosage forms in which the drug is enclosed within either a hard or soft soluble container or "shell." The shells are usually formed from gelatin; however, they also may be made from starch or other suitable substances. Hard shell capsule sizes range from No. 5, the smallest, to No. 000, which is the largest, except for veterinary sizes. However, size No. 00 generally is the largest size acceptable to patients. Size 0 hard gelatin capsules having an elongated body (known as size OE) also are available, which provide greater fill capacity without an increase in diameter. Hard gelatin capsules consist of two, telescoping cap and body pieces. Generally, there are unique grooves or indentations molded into the cap and body portions to provide a positive closure when fully engaged, which helps prevent the accidental separation of the filled capsules during shipping and handling. Positive closure also may be affected by spot fusion ("welding") of the cap and body pieces together through direct thermal means or by application of ultrasonic energy. Factory-filled hard gelatin capsules may be completely sealed by banding, a process in which one or more layers of gelatin are applied over the seam of the cap and body, or by a liquid fusion process wherein the filled capsules are wetted with a hydroalcoholic solution that penetrates into the space where the cap overlaps the body, and then dried. Hard shell capsules made from starch consist of two, fitted, cap and body pieces. Since the two pieces do not telescope or interlock positively, they are sealed together at the time of filling to prevent their separation. Starch capsules are sealed by the application of a hydroalcoholic solution to the recessed section of the cap immediately prior to its being placed onto the body.

The banding of hard shell gelatin capsules or the liquid sealing of hard shell starch capsules enhances consumer safety by making the capsules difficult to open without causing visible, obvious damage, and may improve the stability of contents by limiting O_2 penetration. Industrially filled hard shell capsules also are often of distinctive color and shape or are otherwise marked to identify them with the manufacturer. Additionally, such capsules may be printed axially or radially with strengths, product codes, etc. Pharmaceutical grade printing inks are usually based on shellac and employ FDA-approved pigments and lake dyes.

In extemporaneous prescription practice, hard shell capsules may be hand-filled; this permits the prescriber a latitude of choice in selecting either a single drug or a combination of drugs at the exact dosage level considered best for the individual patient. This flexibility gives hard shell capsules an advantage over compressed tablets and soft shell capsules as a dosage form. Hard shell capsules are usually formed from gelatins having relatively high gel strength. Either type may be used, but blends of pork skin and bone gelatin are often used to optimize shell clarity and toughness. Hard shell capsules also may be formed from starch or other suitable substances. Hard shell capsules may also contain colorants, such as D&C and FD&C dyes or the various iron oxides, opaquing agents such as titanium dioxide, dispersing agents, hardening agents such as sucrose, and preservatives. They normally contain between 10% and 15% water.

Hard gelatin capsules are made by a process that involves dipping shaped pins into gelatin solutions, after which the gelatin films are dried, trimmed, and removed from the pins, and the body and cap pieces are joined. Starch capsules are made by injection molding a mixture of starch and water, after which the capsules are dried. A separate mold is used for caps and bodies, and the two parts are supplied separately. The empty capsules should be stored in tight containers until they are filled. Since gelatin is of animal origin and starch is of vegetable origin, capsules made with these materials should be protected from potential sources or microbial contamination.

Hard shell capsules typically are filled with powder, beads, or granules. Inert sugar beads (nonpareils) may be coated with active ingredients and coating compositions that provide extended-release profiles or enteric properties. Alternatively, larger dose active ingredients themselves may be suitably formed into pellets and then coated. Semisolids or liquids also may be filled into hard shell capsules; however, when the latter are encapsulated, one of the sealing techniques must be employed to prevent leakage.

In hard gelatin capsule filling operations, the body and cap of the shell are separated prior to dosing. In hard starch shell filling operations, the bodies and caps are supplied separately and are fed into separate hoppers of the filling machine. Machines employing various dosing principles may be employed to fill powders into hard shell capsules; however, most fully automatic machines form powder plugs by compression and eject them into empty capsule bodies. Accessories to these machines generally are available for the other types of fills. Powder formulations often require adding fillers, lubricants, and glidants to the active ingredients to facilitate encapsulation. The formulation, as well as the method of filling, particularly the degree of compaction, may influence the rate of drug release. The addition of wetting agents to the powder mass is common where the active ingredient is hydrophobic. Disintegrants also may be included in powder formulations to facilitate deaggregation and dispersal of capsule plugs in the gut. Powder formulations often may be produced by dry blending; however, bulky formulations may require densification by roll compaction or other suitable granulation techniques.

Powder mixtures that tend to liquefy may be dispensed in hard shell capsules if an absorbent such as magnesium carbonate, colloidal silicon dioxide, or other suitable substance is used. Potent drugs are often mixed with an inert diluent before being filled into capsules. Where two mutually incompatible drugs are prescribed together, it is sometimes possible to place one in a small capsule and then enclose it with the second drug in a larger capsule. Incompatible drugs also can be separated by placing coated pellets or tablets, or soft shell capsules of one drug into the capsule shell before adding the second drug.

Thixotropic semisolids may be formed by gelling liquid drugs or vehicles with colloidal silicas or powdered high molecular weight polyethylene glycols. Various waxy or fatty compounds may be used to prepare semisolid matrices by fusion.

Soft shell capsules made from gelatin (sometimes called softgels) or other suitable material require large-scale production methods. The soft gelatin shell is somewhat thicker than that of hard shell capsules and may be plasticized by the addition of a polyol such as sorbitol or glycerin. The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and may be varied to accommodate environmental conditions as well as the nature of the contents. Like hard shells, the shell composition may include approved dyes and pigments, opaquing agents such as titanium dioxide, and preservatives. Flavors may be added and up to 5% sucrose may be included for its sweetness and to produce a chewable shell. Soft gelatin shells normally contain 6% to 13% water. Soft shell capsules also may be printed with a product code, strength, etc. In most cases, soft shell capsules are filled with liquid contents. Typically, active ingredients are dissolved or suspended in a liquid vehicle. Classically, an oleaginous vehicle such as a vegetable oil was used; however, nonaqueous, water-miscible liquid vehicles such as the lower molecular weight polyethylene glycols are more common today due to fewer bioavailability problems.

Available in a wide variety of sizes and shapes, soft shell capsules are both formed, filled, and sealed in the same machine; typically, this is a rotary die process, although a plate process or reciprocating die process also may be employed. Soft shell capsules also may be manufactured in a bubble process that forms seamless spherical capsules. With suitable equipment, powders and other dry solids also may be filled into soft shell capsules.

Liquid-filled capsules of either type involve similar formulation technology and offer similar advantages and limitations. For instance, both may offer advantages over dry-filled capsules and tablets in content uniformity and drug dissolution. Greater homogeneity is possible in liquid systems, and liquids can be metered more

accurately. Drug dissolution may benefit because the drug may already be in solution or at least suspended in a hydrophilic vehicle. However, the contact between the hard or soft shell and its liquid content is more intimate than exists with dry-filled capsules, and this may enhance the chances for undesired interactions. The liquid nature of capsule contents presents different technological problems than dry-filled capsules in regard to disintegration and dissolution testing. From formulation, technological, and biopharmaceutical points of view, liquid-filled capsules of either type have more in common than liquid-filled and dry-filled capsules having the same shell composition. Thus, for compendial purposes, standards and methods should be established based on capsule contents rather than on whether the contents are filled into hard or soft shell capsules.

Change to read:

ENTERIC-COATED CAPSULES

Capsules may be coated, or, more commonly, encapsulated granules may be coated to resist releasing the drug in the gastric fluid of the stomach where a delay is important to alleviate potential problems of drug inactivation or gastric mucosal irritation. The term "delayed-release" is used for Pharmacopeial monographs on enteric-coated capsules that are intended to delay the release of medicament until the capsule has passed through the stomach, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* ⟨724⟩).

(The above *Enteric-coated Capsules* section is official until May 15, 1999)

■DELAYED-RELEASE■8 CAPSULES

Capsules may be coated, or, more commonly, encapsulated granules may be coated to resist releasing the drug in the gastric fluid of the stomach where a delay is important to alleviate potential "delayed-release" is used for Pharmacopeial monographs on enteric coated capsules that are intended to delay the release of medicament until the capsule has passed through the stomach, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* ⟨724⟩) ■or *Disintegration* (see *Disintegration* ⟨701⟩).■8

(The above *Delayed-release Capsules* section will become official May 15, 1999)

EXTENDED-RELEASE CAPSULES

Extended-release capsules are formulated in such manner as to make the contained medicament available over an extended period of time following ingestion. Expressions such as "prolonged-action," "repeat-action," and "sustained-release" have also been used to describe such dosage forms. However, the term "extended-release" is used for Pharmacopeial purposes and requirements for *Drug release* (see *Drug Release* ⟨724⟩) typically are specified in the individual monographs.

Add the following:

■CONCENTRATE FOR DIP

Concentrate for Dip is a preparation containing one or more active ingredients usually in the form of a paste or solution. It is used to prepare a diluted suspension, emulsion, or solution of the active ingredient(s) for the prevention and treatment of ectoparasitic infestations of animals. The diluted preparation (Dip) is applied by complete immersion of the animal or, where appropriate, by spraying. Concentrate for Dip may contain suitable antimicrobial preservatives.■2

Change to read:

INJECTIONS

■An Injection is a preparation intended for parenteral administration or for constituting or diluting a parenteral article prior to administration (see *Injections* ⟨1⟩).

Each container of an Injection is filled with a volume in slight excess of the labeled "size" or that volume that is to be withdrawn. The excess volumes recommended in the accompanying table are usually sufficient to permit withdrawal and administration of the labeled volumes.

Labeled Size	Recommended Excess Volume: For Mobile Liquids	Recommended Excess Volume: For Viscous Liquids
0.5 mL	0.10 mL	0.12 mL
1.0 mL	0.10 mL	0.15 mL
2.0 mL	0.15 mL	0.25 mL
5.0 mL	0.30 mL	0.50 mL
10.0 mL	0.50 mL	0.70 mL
20.0 mL	0.60 mL	0.90 mL
30.0 mL	0.80 mL	1.20 mL
50.0 mL or more	2%	3%

■6

Change to read:

PASTES

Pastes are semisolid dosage forms that contain one or more drug substances intended for topical application. One class is made from a single phase aqueous gel (e.g., *Carboxymethylcellulose Sodium Paste*). The other class, the fatty pastes (e.g., *Zinc Oxide Paste*), consists of thick, stiff ointments that do not ordinarily flow at body temperature, and therefore serve as protective coatings over the areas to which they are applied.

The fatty pastes appear less greasy and more absorptive than ointments by reason of a high proportion of drug substance(s) having an affinity for water. These pastes tend to absorb serous secretions, and are less penetrating and less macerating than ointments, so that they are preferred for acute lesions that have a tendency towards crusting, vesiculation, or oozing.

A dental paste is intended for adhesion to the mucous membrane for local effect (e.g., *Triamcinolone Acetonide Dental Paste*). ■Some paste preparations intended for administration to animals are applied orally. The paste is squeezed into the mouth of the animal, generally at the back of the tongue, or is spread inside the mouth.■2

Change to read:

POWDERS

Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal (Oral Powders) or external (Topical Powders) use. Because of their greater specific surface area, powders disperse and dissolve more readily than compacted dosage forms. Children and those adults who experience difficulty in swallowing tablets or capsules may find powders more acceptable. Drugs that are too bulky to be formed into tablets or capsules of convenient size may be administered as powders. Immediately prior to use, oral powders are mixed in a beverage or apple sauce.

Often, stability problems encountered in liquid dosage forms are avoided in powdered dosage forms. Drugs that are unstable in aqueous suspensions or solutions may be prepared in the form of granules or powders. These are intended to be constituted by the pharmacist by the addition of a specified quantity of water just prior to dispensing. Because these constituted products have limited stability, they are required to have a specified expiration date after constitution and may require storage in a refrigerator.

Oral powders may be dispensed in doses premeasured by the pharmacist, i.e., divided powders, or in bulk. Traditionally, divided powders have been wrapped in materials such as bond paper and parchment. However, the pharmacist may provide greater protection from the environment by sealing individual doses in small cellophane or polyethylene envelopes.

■Granules for veterinary use may be administered by sprinkling the dry powder on animal feed or by mixing it with animal food.■2

Bulk oral powders are limited to relatively nonpotent drugs such as laxatives, antacids, dietary supplements, and certain analgesics that the patient may safely measure by the teaspoonful or capful. Other bulky powders include douche powders, tooth powders, and

dusting powders. Bulk powders are best dispensed in tight, wide-mouth glass containers to afford maximum protection from the atmosphere and to prevent the loss of volatile constituents.

Dusting powders are impalpable powders intended for topical application. They may be dispensed in sifter-top containers to facilitate dusting onto the skin. In general, dusting powders should be passed through at least a 100-mesh sieve to assure freedom from grit that could irritate traumatized areas (see *Powder Fineness* ⟨811⟩).

Add the following:

■PREMIXES

Premixes are mixtures of one or more drug substances with suitable vehicles. Premixes are intended for admixture to animal feedstuffs before administration. They are used to facilitate dilution of the active drug components with animal feed. Premixes should be as homogeneous as possible. It is essential that materials of suitable fineness be used and that thorough mixing be achieved at all stages of premix preparation. Premixes may be prepared as powder, pellets, or in granulated form. The granulated form is free-flowing and free from aggregates.■2

Change to read:

SYSTEMS

In recent years, a number of dosage forms have been developed using modern technology that allows for the uniform release or targeting of drugs to the body. These products are commonly called delivery systems. The most widely used of these are Transdermal Systems.

Transdermal Systems

Transdermal drug delivery systems are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation. Systems typically comprise an outer covering (barrier), a drug reservoir, which may have a rate controlling membrane, a contact adhesive applied to some or all parts of the system and the system / skin interface, and a protective liner that is removed before applying the system. The activity of these systems is defined in terms of the release rate of the drug(s) from the system. The total duration of drug release from the system and the system surface area may also be stated.

Transdermal drug delivery systems work by diffusion: the drug diffuses from the drug reservoir, directly or through the rate controlling membrane and / or contact adhesive if present, and then through the skin into the general circulation. Typically, modified-release systems are designed to provide drug delivery at a constant rate, such that a true steady state blood concentration is achieved and maintained until the system is removed. At that time, blood concentration declines at a rate consistent with the pharmacokinetics of the drug.

Transdermal drug delivery systems are applied to body areas consistent with the labeling for the product(s). As long as drug concentration at the system / skin interface remains constant, the amount of drug in the dosage form does not influence plasma concentrations. The functional lifetime of the system is defined by the initial amount of drug in the reservoir and the release rate from the reservoir.

NOTE—Drugs for local rather than systemic effect are commonly applied to the skin embedded in glue on a cloth or plastic backing. These products are defined traditionally as plasters or tapes.

Ocular System

Another type of system is the ocular system, which is intended for placement in the lower conjunctival fornix from which the drug diffuses through a membrane at a constant rate ■ ■2 (e.g., *Pilocarpine Ocular System*).

Intrauterine System

An intrauterine system, based on a similar principle but intended for release of drug over a much longer period of time, i.e., one year, is also available (e.g., *Progesterone Intrauterine Contraceptive System*).

(Nomenclature related changes—to become official May 15, 1999)

Change to read:

TABLETS

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets.

The vast majority of all tablets manufactured are made by compression, and compressed tablets are the most widely used dosage form in this country. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Tablets can be produced in a wide variety of sizes, shapes, and surface markings, depending upon the design of the punches and dies. Capsule-shaped tablets are commonly referred to as caplets. Boluses are large tablets intended for veterinary use, usually for large animals.

Molded tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process, and not upon the compaction force.

Tablet triturates are small, usually cylindrical, molded or compressed tablets. Tablet triturates were traditionally used as dispensing tablets in order to provide a convenient, measured quantity of a potent drug for compounding purposes. Such tablets are rarely used today. Hypodermic tablets are molded tablets made from completely and readily water-soluble ingredients and formerly were intended for use in making preparations for hypodermic injection. They are employed orally, or where rapid drug availability is required such as in the case of *Nitroglycerin Tablets*, sublingually.

Buccal tablets are intended to be inserted in the buccal pouch, and sublingual tablets are intended to be inserted beneath the tongue, where the active ingredient is absorbed directly through the oral mucosa. Few drugs are readily absorbed in this way, but for those that are (such as nitroglycerin and certain steroid hormones), a number of advantages may result.

Soluble, effervescent tablets are prepared by compression and contain, in addition to active ingredients, mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water. They are intended to be dissolved or dispersed in water before administration. Effervescent tablets should be stored in tightly closed containers or moisture-proof packs and labeled to indicate that they are not to be swallowed directly.

Chewable Tablets

Chewable tablets are ■formulated and manufactured so that they may■7 be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant after-taste. These tablets have been used in tablet formulations for children, especially multivitamin formulations, and for the administration of antacids and selected antibiotics. Chewable tablets are prepared by compression, usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and containing colors and flavors to enhance their appearance and taste.

Preparation of Molded Tablets

Molded tablets are prepared from mixtures of medicinal substances and a diluent usually consisting of lactose and powdered sucrose in varying proportions. The powders are dampened with solutions containing high percentages of alcohol. The concentration of alcohol depends upon the solubility of the active ingredients and fillers in the solvent system and the desired degree of hardness of the finished tablets. The dampened powders are pressed into molds, removed, and allowed to dry. Molded tablets are quite friable and care must be taken in packaging and dispensing.

Formulation of Compressed Tablets

Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be

present. Diluents are added where the quantity of active ingredient is small or difficult to compress. Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as a filler. Where the amount of active ingredient is small, the overall tableting properties are in large measure determined by the filler. Because of problems encountered with bioavailability of hydrophobic drugs of low water-solubility, water-soluble diluents are used as fillers for these tablets.

Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolyzed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression.

A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and cross-linked povidone, are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play a role in effectiveness.

Lubricants reduce friction during the compression and ejection cycle. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc are used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such tend to reduce the rates of tablet disintegration and dissolution. Consequently, excessive concentrations of lubricant should be avoided. Polyethylene glycols and some lauryl sulfate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required.

Glidants are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silicas.

Colorants are often added to tablet formulations for esthetic value or for product identification. Both D&C and FD&C dyes and lakes are used. Most dyes are photosensitive and they fade when exposed to light. The federal Food and Drug Administration regulates the colorants employed in drugs.

Manufacturing Methods

Tablets are prepared by three general methods: wet granulation, dry granulation (roll compaction or slugging), and direct compression. The purpose of both wet and dry granulation is to improve flow of the mixture and / or to enhance its compressibility.

Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of both heat and moisture in the processing. Dry granulations can be produced also by extruding powders between hydraulically operated rollers to produce thin cakes which are subsequently screened or milled to give the desired granule size.

Excipients are available that allow production of tablets at high speeds without prior granulation steps. These directly compressible excipients consist of special physical forms of substances such as lactose, sucrose, dextrose, or cellulose, which possess the desirable properties of fluidity and compressibility. The most widely used direct-compaction fillers are microcrystalline cellulose, anhydrous lactose, spray-dried lactose, compressible sucrose, and some forms of modified starches. Direct compression avoids many of the problems associated with wet and dry granulations. However, the inherent physical properties of the individual filler materials are highly critical, and minor variations can alter flow and compression characteristics so as to make them unsuitable for direct compression.

Physical evidence of poor tablet quality is discussed under *Stability Considerations in Dispensing Practice* ⟨1191⟩.

WEIGHT VARIATION AND CONTENT UNIFORMITY

Tablets are required to meet a weight variation test (see *Uniformity of Dosage Units* ⟨905⟩) where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. Weight variation is not an adequate indication of content uniformity where the drug substance comprises a relatively minor portion of the tablet, or where the tablet is sugar-coated. Thus, the Pharmacopeia generally requires that coated tablets and tablets containing 50 mg or less of active ingredient, comprising less than 50% by weight of the dosage-form unit, pass a content uniformity test (see *Uniformity of Dosage Units* ⟨905⟩), wherein individual tablets are assayed for actual drug content.

DISINTEGRATION AND DISSOLUTION

Disintegration is an essential attribute of tablets intended for administration by mouth, except those intended to be chewed before being swallowed and except some types of extended-release tablets. A disintegration test is provided (see *Disintegration* ⟨701⟩), and limits on the times in which disintegration is to take place, appropriate for the types of tablets concerned, are given in the individual monographs.

For drugs of limited water-solubility, dissolution may be a more meaningful quality attribute than disintegration. A dissolution test (see *Dissolution* ⟨711⟩) is required in a number of monographs on tablets. In many cases, it is possible to correlate dissolution rates with biological availability of the active ingredient. However, such tests are useful mainly as a means of screening preliminary formulations and as a routine quality-control procedure.

Coatings

Tablets may be coated for a variety of reasons, including protection of the ingredients from air, moisture, or light, masking of unpleasant tastes and odors, improvement of appearance, and control of the site of drug release in the gastrointestinal tract.

PLAIN COATED TABLETS

Classically, tablets have been coated with sugar applied from aqueous suspensions containing insoluble powders such as starch, calcium carbonate, talc, or titanium dioxide, suspended by means of acacia or gelatin. For purposes of identification and esthetic value, the outside coatings may be colored. The finished coated tablets are polished by application of dilute solutions of wax in solvents such as chloroform or powdered mix. Water-protective coatings consisting of substances such as shellac or cellulose acetate phthalate are often applied out of nonaqueous solvents prior to application of sugar coats. Excessive quantities should be avoided. Drawbacks of sugar coating include the lengthy time necessary for application, the need for waterproofing, which also adversely affects dissolution, and the increased bulk of the finished tablet. These factors have resulted in increased acceptance of film coatings. Film coatings consist of water-soluble or dispersible materials such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, and mixtures of cellulose acetate phthalate and polyethylene glycols applied out of nonaqueous or aqueous solvents. Evaporation of the solvents leaves a thin film that adheres directly to the tablet and allows it to retain the original shape, including grooves or identification codes.

Change to read:

ENTERIC-COATED TABLETS

Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. The term "delayed-release" is used for Pharmacopeial purposes, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* ⟨724⟩).

(The above *Enteric-coated Tablets* section is official May 15, 1999)

■DELAYED-RELEASE■8 TABLETS

Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of ''enteric'' coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. The term ''delayed-release'' is used for Pharamcopeial purposes, and the individual monographs include tests and specifications for *Drug release* (see *Drug Release* ⟨724⟩) ■or *Disintegration* (see *Disintegration* ⟨701⟩).■8

(The above *Delayed-release Tablets* section will become official May 15, 1999)

EXTENDED-RELEASE TABLETS

Extended-release tablets are formulated in such manner as to make the contained medicament available over an extended period of time following ingestion. Expressions such as ''prolonged-action,'' ''repeat-action,'' and ''sustained-release'' have also been used to describe such dosage forms. However, the term ''extended-release'' is used for Pharmacopeial purposes, and requirements for *Drug release* typically are specified in the individual monographs.

⟨1191⟩ STABILITY CONSIDERATIONS IN DISPENSING PRACTICE

Change to read:

Stability Studies in Manufacturing

The scope and design of a stability study vary according to the product and the manufacturer concerned. Ordinarily the formulator of a product first determines the effects of temperature, light, air, pH, moisture, and trace metals, and commonly used excipients or solvents on the active ingredient(s). From this information, one or more formulations of each dosage form are prepared, packaged in suitable containers, and stored under a variety of environmental conditions, both exaggerated and normal. See *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩. At appropriate time intervals, samples of the product are assayed for potency by use of a stability-indicating method, observed for physical changes, and, where applicable, tested for sterility and/or for resistance to microbial growth and for toxicity and bioavailability. Such a study, in combination with clinical and toxicological results, enables the manufacturer to select the optimum formulation and container and to assign recommended storage conditions and an expiration date for each dosage form in its package.

• ■For solid oral dosage forms, the manufacturer may conduct ''open dish'' studies to determine what will constitute appropriate labeling information for the pharmacist concerning dispensing container selection and to provide beyond-use date recommendations for the dosage forms. The open dish study is a study in which the dosage forms are exposed to 60% relative humidity at 25° for •30●20 days without any container protection: three samples of 30-unit doses from one lot are analyzed at 0 •and 30●20 days. Other approaches to obtain this information include, but are not limited to, accelerated stability studies and stability studies in containers that are one class below that being recommended for use in repackaging the dosage form.■7 ●21

•(Postponed until November 15, 1998)●21