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PART III

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

DRUGS: GENERAL

Reorganization and Republication

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Recodification Docket No. 9]

SUBCHAPTER C—DRUGS: GENERAL

Reorganization and Republication

The Commissioner of Food and Drugs, for the purposes of establishing an orderly development of informative regulations for the Food and Drug Administration, furnishing ample room for expansion of such regulations in years ahead, and providing the public and affected industries with regulations that are easy to find, read, and understand, has initiated a recodification program for Chapter I of Title 21 of the Code of Federal Regulations.

This is the ninth document in a series of recodification documents that will eventually include all regulations administered by the Food and Drug Administration.

This recodification document represents a reorganization of material remaining in Subchapter C—Drugs that has general applicability, rather than strictly human or animal use. In addition certain related sections under Parts 1 and 3 have been redesignated as part of the revised Subchapter C—Drugs: General.

The following table shows the relationship of the CFR section numbers under the former Subchapters A and C to their redesignation reflected in the new Parts 200 through 299:

Old Section	*New Section*	*Old Section*	*New Section*
1.100	299.5	3.21	250.102
1.101	201.6	3.22	200.101
1.101a	201.60	3.27	250.203
1.102	201.50	3.28	200.50
1.102a	201.61	3.29	201.307
1.102b	201.1	3.30	201.308
1.102c	201.51	3.35	201.303
1.102d	201.62	3.36	250.103
1.103	201.15	3.37	201.309
1.104	201.10	3.40	250.201
1.105	202.1	3.43	201.310
1.106(a)	201.5	3.44	201.311
1.106(b)	201.100	3.45	200.30
1.106(c)	201.105	3.48	250.106
1.106(d)	201.109	3.50	250.104
1.106(f)	201.110	3.52	250.107
1.106(g)	201.115	3.53	250.10
1.106(h)	201.116	3.56	201.405
1.106(i)	201.117	3.61	200.18
1.106(j)	201.119	3.62	299.4
1.106(k)	201.120	3.63	250.11
1.106(l)	201.122	3.64	250.12
1.106(m)	201.125	3.67	201.305
1.106(n)	201.127	3.71	250.100
1.106(o)	201.128	3.74	201.56
1.107	201.150	3.76	200.10
1.108(a) & (b)	201.16	3.77	290.35
1.108(c)	290.6	3.81	201.200
1.109	290.5	3.84	201.410
1.110	290.10	3.90	250.300
1.115	200.15	3.91	250.250
3.3	201.300	3.94	250.109
3.4	201.302	3.95	250.110
3.7	250.108	3.501	200.5
3.8	250.101	3.502	201.19
3.11	201.301	3.503	201.312
3.12	201.304	3.505	201.313
3.15	201.306	3.506	200.11
3.16	200.100	3.507	201.17
3.508	201.18		
3.509	201.314	133.11	211.58
3.510	201.315	133.12	211.110
3.512	200.31	133.13	211.60
3.513	200.7	133.14	211.62
3.514	201.55	133.15	211.115
3.515	201.160	133.100	225.1
3.516	250.105	133.101	225.20
3.518	201.161	133.102	225.30
132.1	207.3	133.103	225.10
132.2	207.20	133.104	225.42
132.3	207.21	133.105	225.102
132.4	207.22	133.106	225.40
132.5	207.25	133.107	225.80
132.6	207.30	133.108	225.58
132.7	207.31	133.109	225.110
132.8	207.35	133.110	225.115
132.9	207.37	133.200	226.1
132.10	207.26	133.201	226.20
132.11	207.39	133.202	226.30
132.31	207.40	133.203	226.10
132.51	207.65	133.204	226.42
133.1	210.3	133.205	226.102
133.2	211.1	133.206	226.40
133.3	211.20	133.207	226.80
133.4	211.30	133.208	226.58
133.5	211.10	133.209	226.110
133.6	211.42	133.210	226.115
133.7	211.101	133.300	229.25
133.8	211.40	138.1	299.3
133.9	211.55	138.2	299.20
133.10	211.80		

The changes being made are nonsubstantive in nature and for this reason notice and public procedure are not prerequisites to this promulgation. For the convenience of the user, the entire text of Parts 200, 201, 202, 207, 210, 211, 225, 226, 229, 250, 290, and 299 of Subchapter C is set forth below.

Dated: March 21, 1975.

SAM D. FINE,
Associate Commissioner for Compliance.

Therefore, 21 CFR is amended by redesignating portions of Parts 1 and 3 of Subchapter A and Parts 132, 133, and 138 of Subchapter C as Parts 200, 201, 202, 207, 210, 211, 225, 226, 229, 250, 290, and 299 of Subchapter C—Drugs: General, and republished to read as follows:

SUBCHAPTER C—DRUGS: GENERAL

Part

200—General

201—Labeling

202—Prescription Drug Advertising

207—Registration of Producers of Drugs and Listing of Drugs in Commercial Distribution

210—Current Good Manufacturing Practices in Manufacturing, Processing, Packing, or Holding of Drugs: General

211—Current Good Manufacturing Practice for Finished Pharmaceuticals

225—Current Good Manufacturing Practice for Medicated Feeds

226—Current Good Manufacturing Practice for Medicated Premixes

229—Current Good Manufacturing Practice for Certain Other Drug Products

250—Special Requirements for Specific Human Drugs

290—Controlled Drugs

299—Drugs; Official Names and Established Names

PART 200—GENERAL

Subpart A—General Provisions

Sec.

Subpart B—Manufacturing Procedures Affecting New Drug Status

Subpart C—Requirements for Specific Classes of Drugs

Subpart D—Suitability of Specific Drug Components

AUTHORITY: Sec. 701, 52 Stat. 1055; 21 U.S.C. 371, unless otherwise noted.

Subpart A—General Provisions

§ 200.5 Mailing of important information about drugs.

Manufacturers and distributors of drugs and the Food and Drug Administration occasionally are required to mail important information about drugs to physicians and others responsible for patient care. In the public interest, such mail should be distinctive in appearance so that it will be promptly recognized and read. The Food and Drug Administration will make such mailings in accordance with the specifications set forth in this section. Manufacturers and distributors of drugs are asked to make such mailings as prescribed by this section and not to use the distinctive envelopes for ordinary mail.

(a) Use first class mail and No. 10 white envelopes.

(b) The name and address of the agency or the drug manufacturer or distributor is to appear in the upper left corner of the envelope.

(c) The following statements are to appear in the far left third of the envelope front, in the type and size indicated, centered in a rectangular space approximately 3 inches wide and 2¼ inches high with an approximately ⅜-inch-wide border in the color indicated:

(1) When the information concerns a significant hazard to health, the statement:

IMPORTANT
DRUG
WARNING

The statement shall be in three lines, all capitals, and centered. "Important" shall be in 36 point Gothic Bold type. "Drug" and "Warning" shall be in 36 point Gothic Condensed type. The rectangle's

border and the statement therein shall be red.

(2) When the information concerns important changes in drug package labeling, the statement:

IMPORTANT
PRESCRIBING
INFORMATION

The statement shall be in three lines, all capitals, and centered. "Important" shall be in 36 point Gothic Bold type. "Prescribing" and "Information" shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be blue.

(3) When the information concerns a correction of prescription drug advertising or labeling, the statement:

IMPORTANT
CORRECTION
OF DRUG
INFORMATION

The statement shall be in four lines, all capitals, and centered. "Important" shall be in 36 point Gothic Bold type. "Correction," "Of Drug," and "Information" shall be in 36 point Gothic Condensed type. The rectangle's border and the statement therein shall be brown.

(Sec. 705(b), 52 Stat. 1058; 21 U.S.C. 375(b))

§ 200.7 Supplying pharmacists with indications and dosage information.

There are presently no regulations under the Federal Food, Drug, and Cosmetic Act that prevent a manufacturer of prescription drugs from sending the pharmacist data he needs on indications and dosage in exercising his important professional function of checking against possible mistakes in a prescription. The Food and Drug Administration believes manufacturers should be encouraged to supply such printed matter to the pharmacist for his professional information. Obviously, such printed matter should not be displayed to prospective purchasers to promote over-the-counter sale of prescription drugs.

(Secs. 502(f)(1), 503(b)(1)(B), 52 Stat. 1051, 52 Stat. 1052, as amended 65 Stat. 648, 649; 21 U.S.C. 352(f)(1), 353(b)(1)(B))

§ 200.10 Contract facilities (including consulting laboratories) utilized as extramural facilities by pharmaceutical manufacturers.

(a) Section 704(a) of the Federal Food, Drug, and Cosmetic Act specifically authorizes inspection of consulting laboratories as well as any factory, warehouse, or establishment in which prescription drugs are manufactured, processed, packed, or held.

(b) The Food and Drug Administration is aware that many manufacturers of pharmaceutical products utilize extramural independent contract facilities, such as testing laboratories, contract packers or labelers, and custom grinders, and regards extramural facilities as an extension of the manufacturer's own facility.

(c) The Food and Drug Administration reserves the right to disclose to the pharmaceutical manufacturer, or to the applicant of a new drug application (NDA) or to the sponsor of a Notice of Claimed Exemption for Investigational New Drug (IND), any information obtained during the inspection of an extramural facility having a specific bearing on the compliance of the manufacturer's, applicant's, or sponsor's product with the Federal Food, Drug, and Cosmetic Act. The Food and Drug Administration's position is that by the acceptance of such contract work, the extramural facility authorizes such disclosures.

(d) The Food and Drug Administration does not consider results of validation studies of analytical and assay methods and control procedures to be trade secrets that may be withheld from the drug manufacturer by the contracted extramural facility.

(Secs. 501, 505, 704(a), 52 Stat. 1049–50, as amended, 1052–53, as amended, 67 Stat. 477, as amended, 76 Stat. 792; 21 U.S.C. 351, 355, 374(a))

§ 200.11 Use of octadecylamine in steam lines of drug establishments.

The Food and Drug Administration will not object to the use of octadecylamine in steam lines where the steam may be used for autoclaving surgical instruments and gauze if the octadecylamine in the steam is not more than 2.4 parts per million.

(Sec. 502, 52 Stat. 1051; 21 U.S.C. 352)

§ 200.15 Definition of term "insulin."

For the purposes of sections 502(k) and 506 of the act:

(a) The term "insulin" as used therein means the active principle of pancreas which affects the metabolism of carbohydrate in the animal body and which is of value in the treatment of diabetes mellitus.

(b) The following substances, when they are intended for use in the manufacture of insulin-containing drugs that will subsequently be submitted for certification, shall not be considered to be subject to certification as "drugs composed wholly or partly of insulin":

(1) Pancreas glands; and

(2) Materials prepared from pancreas glands, such as "salt cake" and "isoelectric precipitate," which materials must be subjected to further purification in order to meet the standards of purity established by Part 429 of this chapter.

(Sec. 506, 55 Stat. 851; 21 U.S.C. 356)

§ 200.18 Use of secondhand containers for the shipment or storage of food and animal feed.

(a) Investigations by the Food and Drug Administration, the National Communicable Disease Center of the U.S. Public Health Service, the Consumer and Marketing Service of the U.S. Department of Agriculture, and by various State public health agencies have revealed practices whereby food and animal feed stored or shipped in secondhand containers have been rendered dangerous to health. Such contamination has been the result of the original use of these containers for the storage and shipment of articles containing or bearing disease organisms or poisonous or deleterious substances.

(b) The Commissioner concludes that such dangerous or potentially dangerous practices include, but are not limited to, the following:

(1) Some vegetable growers and packers employ used poultry crates for shipment of fresh vegetables, including cabbage and celery. Salmonella organisms are commonly present on dressed poultry and in excreta and fluid exudates from dressed birds. Thus wooden crates in which dressed poultry has been iced and packed are potential sources of Salmonella or other enteropathogenic microorganisms that may contaminate fresh vegetables which are frequently consumed without heat treatment.

(2) Some potato growers and producers of animal feeds use secondhand bags for shipment of these articles. Such bags may have originally been used for shipping or storing pesticide-treated seed or other articles bearing or containing poisonous substances. Thus these secondhand bags are potential sources of contamination of the food or animal feed stored or shipped therein.

(c) In a policy statement issued April 11, 1968, the Food and Drug Administration declared adulterated within the meaning of section 402(a) of the Federal Food, Drug, and Cosmetic Act shipments of vegetables or other edible food in used crates or containers that may render the contents injurious to health. This policy statement is extended so that the Food and Drug Administration will regard as adulterated within the meaning of section 402(a) of the act shipments of vegetables, other edible food, or animal feed in used crates, bags, or other containers that may render the contents injurious to health.

(Secs. 402(a), 52 Stat. 1046, as amended; 21 U.S.C. 342(a))

Subpart B—Manufacturing Procedures Affecting New Drug Status

§ 200.30 Sterilization of drugs by irradiation.

There is a current interest in the utilization of newly developed sources of radiation for the sterilization of drugs. Prior to the marketing of a drug sterilized by such means, it is necessary in the interest of protecting the public health to establish by adequate investigations that the irradiation treatment does not cause the drug to become unsafe or otherwise unsuitable for use. Accordingly, all drug products, including injections, ophthalmic solutions, surgical sutures, and surgical dressings sterilized by means of irradiation are regarded as new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act. An effective new-drug application pursuant to section 505 of the act is therefore a prerequisite to interstate shipment of such articles, except as provided by section 505(i).

(Secs. 201, 505, 52 Stat. 1040, as amended, 1052, as amended; 21 U.S.C. 321, 355)

§ 200.31 Timed release dosage forms.

(a) Many drugs are now being offered in dosage forms that are designed to re-

lease the active ingredients over a prolonged period. There is a possibility of unsafe overdosage if such products are improperly made and the active ingredients are released at one time or over too short a time interval. Any such dosage form that contains per dosage unit (for example, capsule or tablet), a quantity of active drug ingredients which is not generally recognized as safe for administration as a single dose under the conditions suggested in its labeling, is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(b) The fact that the labeling of this type of drug may claim delayed or prolonged release of all or some of the active ingredients does not affect the new-drug status of such articles. A new-drug application is required in any such case to demonstrate that the drug is in fact safe because it is properly made and controlled to release the total dose at a safe rate. It should be noted particularly that such dosage forms are regarded as new drugs even when the total daily dosage recommended in the labeling is generally recognized as safe. For example, a capsule containing 50 milligrams of pyrilamine maleate and 15 milligrams of phenylephrine hydrochloride, offered for sale without prescription, is regarded as a new drug for which the distributor should have an effective new-drug application, even though the directions call for taking no more than two capsules daily. While the daily intake under such directions is within the range regarded as safe for use in self-medication, the single dose is too high for such use unless the release of the drug is sufficiently prolonged. It is obvious that, in filing a new-drug application for such an article, particular attention should be given to data which establish that the active ingredients are released over a period of time, as represented in the labeling.

(Sec. 201(p), 52 Stat. 1042; 21 U.S.C. 321(p))

Subpart C—Requirements for Special Classes of Drugs

§ 200.50 Ophthalmic preparations and dispensers.

(a) (1) Informed medical opinion is in agreement that all preparations offered or intended for ophthalmic use, including contact lens solutions and preparations for cleansing the eyes, should be sterile. It is further evident that such preparations purport to be of such purity and quality as to be suitable for safe use in the eye.

(2) The Food and Drug Administration concludes that all such preparations, if they are not sterile, fall below their professed standard of purity or quality and may be unsafe. In a statement of policy issued on September 1, 1964, the Food and Drug Administration ruled that liquid preparations offered or intended for ophthalmic use that are not sterile may be regarded as adulterated within the meaning of section 501(c) of the Federal Food, Drug, and Cosmetic Act, and, further, may be deemed misbranded within the meaning of section 502(j) of the act. This ruling is extended to affect all preparations for ophthalmic use.

(3) The containers of ophthalmic preparations shall be sterile at the time of filling and closing, and the container or individual carton shall be so sealed that the contents cannot be used without destroying the seal. To provide time for validation of sterility tests and changes to sterile production procedures, this ruling will be effective for nonantitbiotic ophthalmic ointment preparations recognized in the official compendia (U.S.P. and N.F.) on the dates specified in such official compendia. For all other ophthalmic ointments, this ruling will be effective 12 months after the date of publication in the FEDERAL REGISTER (10–28–72).

(b) Liquid ophthalmic preparations packed in multiple-dose containers should:

(1) Contain one or more suitable and harmless substances that will inhibit the growth of microorganisms; or

(2) Be so packaged as to volume and type of container and so labeled as to duration of use and with such necessary warnings as to afford adequate protection and minimize the hazard of injury resulting from contamination during use.

(c) Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. They should be so packaged as to maintain sterility until the package is opened and be so labeled, on or within the retail package, as to afford adequate directions and necessary warnings to minimize the hazard of injury resulting from contamination during use.

Subpart D—Suitability of Specific Drug Components

§ 200.100 Use of ox bile from condemned livers from slaughtered animals in the manufacture of drugs.

(a) Conferences have recently been held between members of the Department of Health, Education, and Welfare and representatives of the Agricultural Research Service, Department of Agriculture, concerning requests made to that agency for the release of ox bile from condemned livers of slaughtered animals for use in the manufacture of certain drugs.

(b) The Secretary of Health, Education, and Welfare has given careful consideration to this problem and has reached the conclusion that no hazard to public health will be involved in the release of such ox bile, after the addition to it of sufficient sodium hydroxide to give the mixture a sodium hydroxide content of not less than 5 percent, the mixture then being allowed to stand at least 24 hours. This Department will not regard as in violation of the provisions of the Federal Food, Drug, and Cosmetic Act such alkalized and aged ox bile, if labeled "Ox Bile and Sodium Hydroxide (or Ox Bile and Sodium Hydroxide Solution). Sodium hydroxide not less than 5 percent by weight. For manufacturing use only," together with a statement of the quantity of contents in the container (for example, "50 gallons") and the name and address of the manufacturer, packer, or shipper.

(c) Bile from the condemned livers of sheep and goats also may be released, under the same conditions as outlined in the preceding paragraph, except that the words "Sheep Bile" or "Goat Bile," as the case may be, shall be substituted for the words "Ox Bile" upon the label. In the case of mixtures of bile from any two or all three of the sources mentioned, the label shall indicate the sources of such bile.

§ 200.101 Suprarenal glands from hog carcasses prior to final inspection.

(a) The Agricultural Research Service of the U.S. Department of Agriculture has informed the Food and Drug Administration of the Department of Health, Education, and Welfare that, under appropriate conditions, it will permit the removal of suprarenal glands from hogs that have not been finally inspected by Federal Inspectors. The glands to be so obtained are intended for use in manufacturing extracts containing one or more of the therapeutically useful constituents of suparenal glands.

(b) Under the conditions specified in this section, the Secretary of Health, Education, and Welfare has determined that the public health will be adequately protected from any danger from the use of drugs, made in whole or in part from suprarenal glands of hogs that may be condemned by Federal inspectors of the Department of Agriculture after removal of such glands from the carcasses, arising from any abnormality of such carcasses if such glands are subjected to the following prescribed treatment, which will destroy or eliminate any microorganisms or toxins that might be present in the glands:

(c) The glands are subjected to quick freezing promptly upon removal from the carcasses and maintained in a frozen state until they are ground and immersed in 95 percent to 100 percent acetone. The ground tissues remain in the acetone for a period of not less than 6 days, the mixture is filtered, and the residue is burned.

PART 201—LABELING

Subpart A—General Labeling Provisions

Sec.

AUTHORITY: Sec. 701, 52 Stat. 1055–1056 as amended; 21 U.S.C. 371, unless otherwise noted.

Subpart A—General Labeling Provisions

§ 201.1 Drugs and devices; name and place of business of manufacturer, packer or distributor.

(a) The label of a drug or device in package form shall specify conspicuously the name and place of business of the manufacturer, packer, or distributor.

(b) The requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied, in the case of a corporation, only by the actual corporate name which may be preceded or followed by the name of the particular division of the corporation. Abbreviations for "Company," "Incorporated," etc., may be used and "The" may be omitted. In the case of an individual, partnership, or association, the name under which the business is conducted shall be used.

(c) Where a drug or device is not manufactured by the person whose name appears on the label, the name shall be qualified by a phrase that reveals the connection such person has with such drug or device; such as, "Manufactured for ------", "Distributed by ------", or any other wording that expresses the facts.

(d) The statement of the place of business shall include the street address, city, State, and ZIP Code; however, the street address may be omitted if it is shown in a current city directory or telephone directory. The requirement for inclusion of the ZIP Code shall apply only to consumer commodity labels developed or revised after the effective date of this section. In the case of nonconsumer packages, the ZIP Code shall appear either on the label or the labeling (including the invoice).

(e) If a person manufactures, packs, or distributes a drug or device at a place other than his principal place of business, the label may state the principal place of business in lieu of the actual place where such drug or device was manufactured or packed or is to be distributed, unless such statement would be misleading.

§ 201.5 Drugs and devices; adequate directions for use.

"Adequate directions for use" means directions under which the layman can use a drug or device safely and for the purposes for which it is intended (Section 201.128 defines "intended use.") Directions for use may be inadequate because (among other reasons) of omission, in whole or in part, or incorrect specification of:

(a) Statements of all conditions, purposes, or uses for which such drug or device is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the drug or device is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the drug or device can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.

(b) Quantity of dose (including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions).

(c) Frequency of administration or application.

(d) Duration of administration or application.

(e) Time of administration or application (in relation to time of meals, time of onset of symptoms, or other time factors).

(f) Route or method of administration or application.

(g) Preparation for use (shaking, dilution, adjustment of temperature, or other manipulation or process).

§ 201.6 Drugs and devices; misleading statements.

(a) Among representations in the labeling of a drug or device which render such drug or device misbranded is a false or misleading representation with respect to another drug or device or a food or cosmetic.

(b) The labeling of a drug which contains two or more ingredients may be misleading by reason (among other reasons) of the designation of such drug in such labeling by a name which includes or suggests the name of one or more but not all such ingredients, even though the names of all such ingredients are stated elsewhere in the labeling.

(Sec. 502, 52 Stat. 1050, as amended; 21 U.S.C. 352)

§ 201.10 Drugs; statement of ingredients.

(a) The ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter, except the proprietary names of ingredients, which may be included with the listing of established names, and such statements as "Warning—May be habit forming" that are specifically required for certain ingredients by the act or regulations in this chapter.

(b) The term "ingredient" applies to any substance in the drug, whether added to the formulation as a single substance or in admixture with other substances.

(c) The labeling of a drug may be misleading by reason (among other reasons) of:

(1) The order in which the names of the ingredients present in the drug appear in the labeling, or the relative prominence otherwise given such names.

(2) Failure to reveal the proportion of, or other fact with respect to, an ingredient present in such drug, when such proportion or other fact is material in the light of the representation that such ingredient is present in such drug.

(3) The employment of a fanciful proprietary name for a drug or ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.

(4) The featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.

(5) Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.

(d)(1) If the drug is in tablet or capsule form or other unit dosage form, any statement of the quantity of an ingredient contained therein shall express the quantity of such ingredient in each such unit. If the drug is not in unit dosage form, any statement of the quantity of an ingredient contained therein shall express the amount of such ingredient in a specified unit of weight or measure of the drug, or the percentage of such ingredient in such drug. Such statements shall be in terms that are informative to licensed practitioners, in the case of a prescription drug, and to the layman, in the case of a nonprescription drug.

(2) A statement of the percentage of an ingredient in a drug shall, if the term "percent" is used without qualification, mean percent weight-in-weight, if the ingredient and the drug are both solids, or if the ingredient is a liquid and the drug is a solid; percent weight in volume at 68° F. (20° C.), if the ingredient is a solid and the drug is a liquid; and percent volume in volume at 68° F. (20° C.), if both the ingredient and the drug are liquids, except that alcohol shall be stated in terms of percent volume of absolute alcohol at 60° F. (15.56° C.).

(e) A derivative or preparation of a substance named in section 502(e) of the act is an article derived or prepared from such substance by any method, including actual or theoretical chemical action

(f) If an ingredient is a derivative or preparation of a substance specifically named in section 502(e) of the act and the established name of such ingredient does not indicate that it is a derivative or preparation of the parent substance named in section 502(e) of the act, the labeling shall, in conjunction with the listing of the established name of such ingredient, declare that such article is a derivative or preparation of such parent substance.

(g) (1) If the label or labeling of a prescription drug bears a proprietary name or designation for the drug or any ingredient thereof, the established name, if such there be, corresponding to such proprietary name or designation shall accompany such proprietary name or designation each time it is featured on the label or in the labeling for the drug; but, except as provided in this subparagraph, the established name need not be used with the proprietary name or designation in the running text of the label or labeling. On any label or page of labeling in which the proprietary name or designation is not featured but is used in the running text, the established name shall be used at least once in the running text in association with such proprietary name or designation and in the same type size used in such running text: *Provided, however,* That if the proprietary name or designation is used in the running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such running text. If any labeling includes a column with running text containing detailed information as to composition, prescribing, side effects, or contraindications and the proprietary name or designation is used in such column but is not featured above or below the column, the established name shall be used at least once in such column of running text in association with such proprietary name or designation and in the same type size used in such column of running text: *Provided, however,* That if the proprietary name or designation is used in such column of running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such column of running text. Where the established name is required to accompany or to be used in association with the proprietary name or designation, the established name shall be placed in direct conjunction with the proprietary name or designation, and the relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as "brand of" preceding the established name, by brackets surrounding the established name, or by other suitable means.

(2) The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

(h)(1) In the case of a prescription drug containing two or more active ingredients, if the label bears a proprietary name or designation for such mixture and there is no established name corresponding to such proprietary name or designation, the quantitative ingredient information required on the label by section 502(e) of the act shall be placed in direct conjunction with the most prominent display of the proprietary name or designation. The prominence of the quantitative ingredient information shall bear a reasonable relationship to the prominence of the proprietary name.

(2) If the drug is packaged in a container too small to bear the quantitative ingredient information on the main display panel, the quantitative ingredient information required by section 502(e) of the act may appear elsewhere on the label, even though the proprietary name or designation appears on the main display panel of the label; but side- or back-panel placement shall in this case be so arranged and printed as to provide size and prominence of display reasonably related to the size and prominence of the front-panel display.

(i) A drug packaged in a container too small or otherwise unable to accommodate a label with sufficient space to bear the information required for compliance with section 502(e)(1)(A)(ii) and (B) of the act shall be exempt from compliance with those clauses: *Provided,* That:

(1) The label bears:

(i) The proprietary name of the drug;

(ii) The established name, if such there be, of the drug;

(iii) An identifying lot or control number; and

(iv) The name of the manufacturer, packer, or distributor of the drug; and

(2) All the information required to appear on the label by the act and the regulations in this chapter appears on the carton or other outer container or wrapper if such carton, outer container, or wrapper has sufficient space to bear such information, or such complete label information appears on a leaflet with the package.

§ 201.15 Drugs and devices; prominence of required label statements.

(a) A word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason (among other reasons) of:

(1) The failure of such word, statement, or information to appear on the part or panel of the label which is presented or displayed under customary conditions of purchase;

(2) The failure of such word, statement, or information to appear on two or more parts or panels of the label, each of which has sufficient space therefor, and each of which is so designed as to render it likely to be, under customary conditions of purchase, the part or panel displayed;

(3) The failure of the label to extend over the area of the container or package available for such extension, so as to provide sufficient label space for the prominent placing of such word, statement, or information;

(4) Insufficiency of label space (for the prominent placing of such word, statement, or information) resulting from the use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;

(5) Insufficiency of label space (for the prominent placing of such word, statement, or information) resulting from the use of label space to give materially greater conspicuousness to any other word, statement, or information, or to any design or device; or

(6) Smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.

(b) No exemption depending on insufficiency of label space, as prescribed in regulations promulgated under section 502 (b) or (e) of the act, shall apply if such insufficiency is caused by:

(1) The use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label;

(2) The use of label space to give greater conspicuousness to any word, statement, or other information than is required by section 502 (c) of the act; or

(3) The use of label space for any representation in a foreign language.

(c)(1) All words, statements, and other information required by or under authority of the act to appear on the label or labeling shall appear thereon in the English language: *Provided, however*, That in the case of articles distributed solely in the Commonwealth of Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English.

(2) If the label contains any representation in a foreign language, all words, statements, and other information required by or under authority of the act to appear on the label shall appear thereon in the foreign language.

(3) If the labeling contains any representation in a foreign language, all words, statements, and other information required by or under authority of the act to appear on the label or labeling shall appear on the labeling in the foreign language.

(Sec. 502, 52 Stat. 1050, as amended; 21 U.S.C. 352)

§ 201.16 Drugs and devices; Spanish-language version of certain required statements.

An increasing number of medications restricted to prescription use only are being labeled solely in Spanish for distribution in the Commonwealth of Puerto Rico where Spanish is the predominant language. Such labeling is authorized under § 201.15(c). Two required warnings, the wording of which is fixed by law in the English language, are presently being translated in various ways, from literal translation to loose interpretation. The statutory nature of these two statements requires that the translation must convey the meaning properly, in order to avoid confusion and dilution of the purposes of the warnings. The Commissioner of Food and Drugs hereby adopts the following Spanish-language versions as the accepted equivalents of the English wording of the following:

(a) Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act requires the statement: "Caution: Federal law prohibits dispensing without prescription." The Spanish version of this shall be: "Precaucion: La ley Federal prohibe su despacho sin prescripcion facultativa."

(b) Section 502(d) of the Federal Food, Drug, and Cosmetic Act requires the statement "Warning—May be habit forming" on habit-forming drugs. The Spanish version of this shall be: "Aviso—Puede formar habito o vicio."

§ 201.17 Drugs; location of expiration date.

Drugs which require an expiration date should show the expiration date on the immediate container. When the immediate container is packaged in an individual carton, the expiration date should also be placed on the carton. When single-dose containers are packed in individual cartons, the expiration date may properly appear on the carton only.

(Secs. 505, 506, 507, 52 Stat. 1052, as amended, 55 Stat. 851, 59 Stat. 463, 61 Stat. 12, 63 Stat. 409; 21 U.S.C. 355, 356, 357)

§ 201.18 Drugs; significance of control numbers.

The lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package. An incorrect lot number may be regarded as causing the article to be misbranded.

(Sec. 502, 52 Stat. 1050; 21 U.S.C. 352)

§ 201.19 Drugs; use of term "infant".

The regulations affecting special dietary foods (§ 125.1(d) of this chapter) define an infant as a child not more than 12 months old. Apart from this, the Food and Drug Administration has not established any definition of the term "infant." Some question has arisen whether, for the purposes of drug labeling, an infant means a child up to 1 year of age or a child up to 2 years of age. Until the term is more precisely defined by legislation or formal regulation, where the exact meaning of the term is significant, maufacturers should qualify any reference to "infant" to indicate whether it refers to a child who is not more than 1 year of age, or a child not more than 2 years of age.

(Sec. 502, 52 Stat. 1051; 21 U.S.C. 352)

Subpart B—Labeling Requirements for Prescription Drugs and/or Insulin

§ 201.50 Statement of identity.

(a) The label of prescription and insulin-containing drugs in package form shall bear as one of its principal features a statement of the identity of the drug.

(b) Such statement of identity shall be in terms of the established name of the drug. An insulin-containing drug shall be further identified by placement on the outside container or wrapper of the package, and on the label of the immediate container, of the distinguishing color(s) required by § 429.12 of this chapter. In the case of a prescription drug that is a mixture and that has no established name, the requirement for statement of identity shall be deemed to be satisfied by a listing of the quantitative ingredient information as prescribed by § 201.10.

(c) The statement of identity of a prescription drug shall also comply with the placement, size and prominence requirements of § 201.10.

§ 201.51 Declaration of net quantity of contents.

(a) The label of a prescription or insulin-containing drug in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination of numerical count and weight or measure. The statement of quantity of drugs in tablet, capsule, ampule, or other unit dosage form shall be expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semi-solid, or viscous, or in terms of fluid measure if the drug is liquid. When the drug quantity statement is in terms of the numerical count of the drug units, it shall be augmented to give the weight or measure of the drug units or the quantity of each active ingredient in each drug unit or, when quantity does not accurately reflect drug potency, a statement of the drug potency.

(b) Statements of weight of the contents shall in the case of prescription drugs be expressed in terms of avoirdupois pound, ounce, and grain or of kilogram, gram, and subdivisions thereof. A statement of liquid measure of the contents shall in the case of prescription drugs be expressed in terms of the U.S. gallon of 231 cubic inches and quart, pint, fluid-ounce, and fluid-dram subdivisions thereof, or of the liter and milliliter, or cubic centimeter, and shall express the volume at 68° F. (20° C.). A statement of the liquid measure of the contents in the case of insulin-containing drugs shall be expressed in terms of the liter and milliliter, or cubic centimeter, and shall express the volume at 68° F. (20° C.).

(c) The declaration shall contain only such fractions as are generally used in expressing the quantity of the drug. A common fraction shall be reduced to its lowest terms; a decimal fraction shall not be carried out to more than three places, except in the case of a statement of the quantity of an active ingredient in a unit of a drug.

(d) The declaration shall appear as a distinct item on the label and, in the case of large volume parenterals, may be embossed on the glass.

(e) The declaration shall accurately reveal the quantity of drug in the package exclusive of wrappers and other material packed therewith.

(f) A statement of the quantity of a prescription or insulin-containing drug in terms of weight or measure applicable to such drug, under the provisions of paragraph (a) of this section, shall express with prominence and conspicuousness the number of the largest whole unit, as specified in paragraph (b) of this section, that are contained in the package. Any remainder shall be expressed in terms of common or decimal fractions of such unit or in terms of the next smaller whole unit and common or decimal fractions thereof.

(g) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large. In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.

(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

§ 201.55 Statement of dosage.

Section 201.100(b)(2) requires that labels for prescription drugs bear a statement of the recommended or usual dosage. Since the dosage for some prescription drugs varies within extremely wide limits, depending upon the conditions being treated, it may not be possible in all cases to present an informative or useful statement of the recommended or usual dosage in the space available on the label or carton of the package. It is the view of the Food and Drug Administration that when such a situation prevails, compliance with this requirement would be met by a statement such as "See package insert for dosage information", where the detailed information is contained in such insert. However, if an informative, realistic, recommended or usual dosage can readily be set forth on the label, it should appear thereon.

§ 201.56 Content and format of labeling.

(a) To be most useful to practitioners, labeling information for prescription drugs should be orderly and uniform in the sequence and kinds of information presented. For this reason, the Food and Drug Administration recommends that prescription drug labeling purporting to furnish adequate information for the safe and effective use of a drug, as required under § 201.100, should ordinarily contain information in substantially the format and order and with the section headings as follows:

DESCRIPTION
ACTIONS
INDICATIONS
CONTRAINDICATIONS
WARNINGS
PRECAUTIONS
ADVERSE REACTIONS
DOSAGE AND ADMINISTRATION
OVERDOSAGE (WHERE APPLICABLE)
HOW SUPPLIED

(b) The following sections are optional. If used, they should be placed after the information described above.

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CLINICAL STUDIES
REFERENCES

(c) Although ordinarily prescription drug labeling should employ the format, order, and section headings described in paragraphs (a) and (b) of this section, in the case of some drugs special warnings may be required to appear conspicuously in the beginning of the labeling for special attention by physicians for the safety of patients. In the case of a drug for which there is no information applicable to a section heading described in paragraph (a) of this section, such heading and section may be omitted.

(Secs. 502, 503, 52 Stat. 1050–52, as amended; 21 U.S.C. 352, 353)

Subpart C—Labeling Requirements for Over-the-Counter Drugs and Devices

§ 201.60 Principal display panel.

The term "principal display panel," as it applies to over-the-counter drugs and devices in package form and as used in this part, means the part of a label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale. The principal display panel shall be large enough to accommodate all the mandatory label information required to be placed thereon by this part with clarity and conspicuousness and without obscuring designs, vignettes, or crowding. Where packages bear alternate principal display panels, information required to be placed on the principal display panel shall be duplicated on each principal display panel. For the purpose of obtaining uniform type size in declaring the quantity of contents for all packages of substantially the same size, the term "area of the principal display panel" means the area of the side or surface that bears the principal display panel, which area shall be:

(a) In the case of a rectangular package where one entire side properly can be considered to be the principal display panel side, the product of the height times the width of that side;

(b) In the case of a cylindrical or nearly cylindrical container, 40 percent of the product of the height of the container times the circumference; and

(c) In the case of any other shape of container, 40 percent of the total surface of the container: *Provided, however,* That where such container presents an obvious "principal display panel" such as the top of a triangular or circular package, the area shall consist of the entire top surface.

In determining the area of the principal display panel, exclude tops, bottoms, flanges at the tops and bottoms of cans, and shoulders and necks of bottles or jars. In the case of cylindrical or nearly cylindrical containers, information required by this part to appear on the principal display panel shall appear within that 40 percent of the circumference which is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.

§ 201.61 Statement of identity.

(a) The principal display panel of an over-the-counter drug or device in package form shall bear as one of its principal features a statement of the identity of the commodity.

(b) Such statement of identity shall be in terms of the established name of the drug, if any there be, or common name of the device followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug or device. In the case of an over-the-counter drug that is a mixture and that has no established name, this requirement shall be deemed to be satisfied by a prominent and conspicuous statement of the general pharmacological action(s) of the mixture or of its principal intended action(s) in terms that are meaningful to the layman. Such statements shall be placed in direct conjunction with the most prominent display of the proprietary name or designation and shall employ terms descriptive of general pharmacological category(ies) or principal intended action(s); for example, "antacid," "analgesic," "decongestant," "antihistaminic," etc. The indications for use shall be included in the directions for use of the drug, as required by section 502(f)(1) of the act and by the regulations in this part.

(c) The statement of identity shall be presented in bold face type on the principal display panel, shall be in a size reasonably related to the most prominent printed matter on such panel, and shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed.

§ 201.62 Declaration of net quantity of contents.

(a) The label of an over-the-counter drug or device in package form shall bear a declaration of the net quantity of contents. This shall be expressed in the terms of weight, measure, numerical count, or a combination or numerical count and weight, measure, or size. The statement of quantity of drugs in tablet, capsule, ampule, or other unit form and the quantity of devices shall be expressed in terms of numerical count; the statement of quantity for drugs in other dosage forms shall be in terms of weight if the drug is solid, semisolid, or viscous, or in terms of fluid measure if the drug

is liquid. The drug quantity statement shall be augmented when necessary to give accurate information as to the strength of such drug in the package; for example, to differentiate between several strengths of the same drug "100 tablets, 5 grains each" or "100 capsules, 125 milligrams each" or "100 capsules, 250 milligrams each": *Provided*, That:

(1) In the case of a firmly established, general consumer usage and trade custom of declaring the quantity of a drug or device in terms of linear measure or measure of area, such respective term may be used. Such term shall be augmented when necessary for accuracy of information by a statement of the weight, measure, or size of the individual units or of the entire drug or device; for example, the net quantity of adhesive tape in package form shall be expressed in terms of linear measure augmented by a statement of its width.

(2) If the declaration of contents for a device by numerical count does not give accurate information as to the quantity of the device in the package, it shall be augmented by such statement of weight, measure, or size of the individual units or of the total weight, measure, or size of the device as will give such information; for example, "100 tongue depressors, adult size," "1 rectal syringe, adult size," etc. Whenever the Commissioner determines for a specific packaged drug or device that an existing practice of declaring net quantity of contents by weight, measure, numerical count, or a combination of these does not facilitate value comparisons by consumers, he shall by regulation designate the appropriate term or terms to be used for such article.

(b) Statements of weight of the contents shall be expressed in terms of avoirdupois pound and ounce. A statement of liquid measure of the contents shall be expressed in terms of the U.S. gallon of 231 cubic inches and quart, pint, and fluid-ounce subdivisions thereof, and shall express the volume at 68° F. (20° C.) (see also paragraph (p) of this section).

(c) The declaration may contain common or decimal fractions. A common fraction shall be in terms of halves, quarters, eighths, sixteenths, or thirty-seconds; except that if there exists a firmly established, general consumer usage and trade custom of employing different common fractions in the net quantity declaration of a particular commodity, they may be employed. A common fraction shall be reduced to its lowest terms; a decimal fraction shall not be carried out to more than two places. A statement that includes small fractions of an ounce shall be deemed to permit smaller variations than one which does not include such fractions.

(d) The declaration shall be located on the principal display panel of the label, and with respect to packages bearing alternate principal panels it shall be duplicated on each principal display panel.

(e) The declaration shall appear as a distinct item on the principal display panel, shall be separated (by at least a space equal to the height of the lettering used in the declaration) from other printed label information appearing above or below the declaration and (by at least a space equal to twice the width of the letter "N" of the style of type used in the quantity of contents statement) from other printed label information appearing to the left or right of the declaration. It shall not include any term qualifying a unit of weight, measure, or count (such as "giant pint" and "full quart") that tends to exaggerate the amount of the drug in the container. It shall be placed on the principal display panel within the bottom 30 percent of the area of the label panel in lines generally parallel to the base on which the package rests as it is designed to be displayed: *Provided*, That:

(1) On packages having a principal display panel of 5 square inches or less the requirement for placement within the bottom 30 percent of the area of the label panel shall not apply when the declaration of net quantity of contents meets the other requirements of this part; and

(2) In the case of a drug that is marketed with both outer and inner retail containers bearing the mandatory label information required by this part and the inner container is not intended to be sold separately, the net quantity of contents placement requirement of this section applicable to such inner container is waived.

(3) The principal display panel of a drug marketed on a display card to which the immediate container is affixed may be considered to be the display panel of the card, and the type size of the net quantity of contents statement is governed by the dimensions of the display card.

(f) The declaration shall accurately reveal the quantity of drug or device in the package exclusive of wrappers and other material packed therewith: *Provided*, That in the case of drugs packed in containers designed to deliver the drug under pressure, the declaration shall state the net quantity of the contents that will be expelled when the instructions for use as shown on the container are followed. The propellant is included in the net quantity declaration.

(g) The declaration shall appear in conspicuous and easily legible boldface print or type in distinct contrast (by typography, layout, color, embossing, or molding) to other matter on the package; except that a declaration of net quantity blown, embossed, or molded on a glass or plastic surface is permissible when all label information is so formed on the surface. Requirements of conspicuousness and legibility shall include the specifications that:

(1) The ratio of height to width (of the letter) shall not exceed a differential of 3 units to 1 unit (no more than 3 times as high as it is wide)

(2) Letter heights pertain to upper case or capital letters. When upper and lower case or all lower case letters are used, it is the lower case letter "o" or its equivalent that shall meet the minimum standards.

(3) When fractions are used, each component numeral shall meet one-half the minimum height standards.

(h) The declaration shall be in letters and numerals in a type size established in relationship to the area of the principal display panel of the package and shall be uniform for all packages of substantially the same size by complying with the following type specifications:

(1) Not less than one-sixteenth inch in height on packages the principal display panel of which has an area of 5 square inches or less.

(2) Not less than one-eighth inch in height on packages the principal display panel of which has an area of more than five but not more than 25 square inches.

(3) Not less than three-sixteenths inch in height on packages the principal display panel of which has an area of more than 25 but not more than 100 square inches.

(4) Not less than one-fourth inch in height on packages the principal display 100 square inches, except not less than one-half inch in height if the area is more than 400 square inches.

Where the declaration is blown, embossed, or molded on a glass or plastic surface rather than by printing, typing, or coloring, the lettering sizes specified in paragraphs (h) (1) through (4) of this section shall be increased by one-sixteenth of an inch

(i) On packages containing less than 4 pounds or 1 gallon and labeled in terms of weight or fluid measure:

(1) The declaration shall be expressed both in ounces, with identification by weight or by liquid measure and, if applicable (1 pound or 1 pint or more) followed in parentheses by a declaration in pounds for weight units, with any remainder in terms of ounces or common or decimal fractions of the pound (see examples set forth in paragraph (k) (1) and (2) of this section), or in the case of liquid measure, in the largest whole units (quarts, quarts and pints, or pints, as appropriate) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart (see examples set forth in paragraph (k) (3) and (4) of this section). If the net weight of the package is less panel of which has an area of more than than 1 ounce avoirdupois or the net fluid measure is less than 1 fluid ounce, the declaration shall be in terms of common or decimal fractions of the respective ounce and not in terms of drams.

(2) The declaration may appear in more than one line. The term "net weight" shall be used when stating the net quantity of contents in terms of weight. Use of the terms "net" or "net contents" in terms of fluid measure or numerical count is optional. It is sufficient to distinguish avoirdupois ounce from fluid ounce through association of terms; for example, "Net wt. 6 oz." or "6 oz. net wt.," and "6 fl. oz." or "net contents 6 fl. oz."

(j) On packages containing 4 pounds or 1 gallon or more and labeled in terms of weight or fluid measure, the declaration shall be expressed in pounds for

weight units with any remainder in terms of ounces or common or decimal fractions of the pound; in the case of fluid measure, it shall be expressed in the largest whole unit (gallons, followed by common or decimal fractions of a gallon or by the next smaller whole unit or units (quarts or quarts and pints)) with any remainder in terms of fluid ounces or common or decimal fractions of the pint or quart (see paragraph (k) (5) of this section).

(k) Examples:

(1) A declaration of 1½ pounds weight shall be expressed as "Net wt. 24 oz. (1 lb. 8 oz.)," "Net wt. 24 oz. (1½ lb.)" or "Net wt. 24 oz. (1.5 lb.)."

(2) A declaration of three-fourths pound avoirdupois weight shall be expressed as "Net wt. 12 oz."

(3) A declaration of 1 quart liquid measure shall be expressed as "Net contents 32 fl. oz. (1 qt.)" or "32 fl. oz. (1 qt.)."

(4) A declaration of 1¾ quarts liquid measure shall be expressed as "Net contents 56 fl. oz. (1 qt. 1 pt. 8 oz.)" or "Net contents 56 fl. oz. (1 qt. 1.5 pt.)," but not in terms of quart and ounce such as "Net 56 fl. oz. (1 qt. 24 oz.)."

(5) A declaration of 2½ gallons liquid measure shall be expressed as "Net contents 2 gal. 2 qt.," "Net contents 2.5 gallons," or "Net contents 2½ gal." but not as "2 gal. 4 pt."

(l) For quantities, the following abbreviations and none other may be employed (periods and plural forms are optional):

gallon gal.	milliliter ml.
quart qt.	cubic centimeter cc.
pint pt.	yard yd.
ounce oz.	feet or foot ft.
pound lb.	inch in.
grain gr.	meter m.
kilogram kg.	centimeter cm.
gram g.	millimeter mm.
milligram mg.	fluid fl.
microgram mcg.	square sq.
liter l.	weight wt.

(m) On packages labeled in terms of linear measure, the declaration shall be expressed both in terms of inches and, if applicable (1 foot or more), the largest whole units (yards, yards and feet, feet). The declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of inches and any remainder shall be in terms of inches or common or decimal fractions of the foot or yard; if applicable (as in the case of adhesive tape), the initial declaration in linear inches shall be preceded by a statement of the width. Examples of linear measure are "86 inches (2 yd. 1 ft. 2 in.)," "90 inches (2½ yd.)," "30 inches (2.5 ft.)," "¾ inch by 36 in. (1 yd.)," etc.

(n) On packages labeled in terms of area measure, the declaration shall be expressed both in terms of square inches and, if applicable (1 square foot or more), the largest whole square unit (square yards, square yards and square feet, square feet). The declaration in terms of the largest whole units shall be in parentheses following the declaration in terms of square inches and any remainder shall be in terms of square inches or common or decimal fractions of the square foot or square yard; for example, "158 sq. inches (1 sq. ft. 14 sq. in.)."

(o) Nothing in this section shall prohibit supplemental statements at locations other than the principal display panel(s) describing in nondeceptive terms the net quantity of contents, provided that such supplemental statements of net quantity of contents shall not include any term qualifying a unit of weight, measure, or count that tends to exaggerate the amount of the drug or device contained in the package; for example, "giant pint" and "full quart." Dual or combination declarations of net quantity of contents as provided for in paragraphs (a) and (i) of this section are not regarded as supplemental net quantity statements and shall be located on the principal display panel.

(p) A separate statement of net quantity of contents in terms of the metric system of weight or measure is not regarded as a supplemental statement and an accurate statement of the net quantity of contents in terms of the metric system of weight or measure may also appear on the principal display panel or on other panels.

(q) The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large.

(r) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample," "physician's sample," or a substantially similar statement and the contents of the package do not exceed 8 grams.

Subpart D—Exemptions From Adequate Directions for Use

§ 201.100 Prescription drugs for human use.

A drug subject to the requirements of section 503 (b) (1) of the act shall be exempt from section 502 (f) (1) if all the following conditions are met:

(a) The drug is:

(1) (i) In the possession of a person (or his agents or employees) regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of prescription drugs; or

(ii) In the possession of a retail, hospital, or clinic pharmacy, or a public health agency, regularly and lawfully engaged in dispensing prescription drugs; or

(iii) In the possession of a practitioner licensed by law to administer or prescribe such drugs; and

(2) It is to be dispensed in accordance with section 503(b).

(b) The label of the drug bears:

(1) The statement "Caution: Federal law prohibits dispensing without prescription"; and

(2) The recommended or usual dosage, and

(3) The route of administration, if it is not for oral use; and

(4) The quantity or proportion of each active ingredient, as well as the information required by section 502 (d) and (e); and

(5) If it is for other than oral use, the names of all inactive ingredients, except that:

(i) Flavorings and perfumes may be designated as such without naming their components.

(ii) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in Part 8 of this chapter.

(iii) Trace amounts of harmless substances added solely for individual product identification need not be named. If it is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection it need not be named.

(6) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug;

Provided, however, That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraph (b) (2), (3) and (5) of this section may be contained in other labeling on or within the package from which it is to be dispensed, and the information referred to in paragraph (b) (1) of this section may be placed on such outer container only, and the information required by paragraph (b) (6) of this section may be on the crimp of the dispensing tube.

(c) (1) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and

(2) If the article is subject to section 505, 506, or 507 of the act, the labeling bearing such information is the labeling authorized by the approved new-drug application or required as a condition for the certification or the exemption from certification requirements applicable to preparations of insulin or antibiotic drugs: *Provided, however*, That the information required by paragraph (c) (1) of this section may be omitted from the dispensing package if, but only if, the article is a drug for which directions,

hazards, warnings, and use information are commonly known to practitioners licensed by law to administer the drug. Upon written request, stating reasonable grounds therefor, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and § 201.105(b)(2)) contains:

(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 505 or 507 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved or permitted under the provisions of section 505 or 507, respectively, and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling; and

(2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed: *Provided, however*, That the information required by paragraph (d)(1) and (2) of this section is not required on the so-called reminder-piece labeling which calls attention to the name of the drug but does not include indications or dosage recommendations for use of the drug: *And provided, however*, That reminder-piece labeling is not permitted for a drug for which an announcement has been published by the Food and Drug Administration pursuant to a review of the labeling claims for the drug by the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, and for which no claim has been evaluated as higher than "possibly effective." If the Commissioner finds the circumstances are such that reminder-piece labeling may be misleading to prescribers of drugs subject to NAS–NRC evaluation, such reminder labeling will not be allowed and the manufacturer, packer, or distributor will be notified either in the publication of the conclusions on the effectiveness of the drug or by letter.

(e) All labeling, except labels and cartons, bearing information for use of the drug also bears the date of the issuance or the date of the latest revision of such labeling.

§ 201.105 Veterinary drugs.

A drug intended for veterinary use which, because of toxicity or other potentiality for harmful effect, or the method of its use, is not safe for animal use except under the supervision of a licensed veterinarian, and hence for which "adequate directions for use" cannot be prepared, shall be exempt from section 502(f)(1) of the act if all the following conditions are met:

(a) The drug is:

(1) In the possession of a person (or his agents or employees) regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of veterinary drugs and is to be sold only to or on the prescription or other order of a licensed veterinarian for use in the course of his professional practice; or

(2) In the possession of a licensed veterinarian for use in the course of his professional practice.

(b) The label of the drug bears:

(1) The statement "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian"; and

(2) The recommended or usual dosage; and

(3) The route of administration, if it is not for oral use; and

(4) The quantity or proportion of each active ingredient as well as the information required by section 502(e) of the act; and

(5) If it is for other than oral use, the names of all inactive ingredients, except that:

(i) Flavorings and perfumes may be designated as such without naming their components.

(ii) Color additives may be designated as coloring without naming specific color components unless the naming of such components is required by a color additive regulation prescribed in Part 8 of this chapter.

(iii) Trace amounts of harmless substances added solely for individual product identification need not be named.

If it is intended for administration by parenteral injection, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust the pH or to make the drug isotonic may be declared by name and a statement of their effect; and if the vehicle is water for injection, it need not be named.

(6) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug;

Provided, however, That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, but which are packaged within an outer container from which they are removed for dispensing or use, the information required by paragraph (b)(2), (3), and (5) of this section may be contained in other labeling on or within the package from which it is to be so dispensed, and the information referred to in paragraph (b)(1) of this section may be placed on such outer container only, and the information required by paragraph (b)(6) of this section may be on the crimp of the dispensing tube.

(c)(1) Labeling on or within the package from which the drug is to be dispensed bears adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented; and

(2) If the article is subject to section 512 of the act, the labeling bearing such information is the labeling authorized by the approved new animal drug application or required as a condition for the certification or the exemption from certification requirements applicable to preparations of antibiotic drugs: *Provided, however*, That the information required by paragraph (c)(1) of this section may be omitted from the dispensing package if, but only if, the article is a drug for which directions, hazards, warnings, and use information are commonly known to veterinarians licensed by law to administer the drug. Upon written request, stating reasonable grounds therefor, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug (other than dose information required by paragraph (b)(2) of this section and § 201.100(b)(2)) contains:

(1) Adequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant warnings, hazards, contraindications, side effects, and precautions, and including information relevant to compliance with the new animal drug provisions of the act, under which veterinarians licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if the article is subject to section 512 of the act, the parts of the labeling providing such information are the same in language and emphasis as labeling approved or permitted under the provisions of section 512, and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling; and

(2) The same information concerning the ingredients of the drug as appears on the label and labeling on or within the package from which the drug is to be dispensed;

Provided, however, That the information required by paragraph (d)(1) and (2) of this section is not required on the so-called reminder-piece labeling which calls attention to the name of the drug but does not include indications or dosage recommendations for use of the drug.

(e) All labeling, except labels and cartons, bearing information for use of the drug also bears the date of the issuance or the date of the latest revision of such labeling.

(f) A prescription drug intended for both human and veterinary use shall comply with paragraphs (e) and (f) of this section and § 201.100.

§ 201.109 Prescription devices.

A device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use is not safe except under the supervision of a practitioner licensed by law to direct the use of such device, and hence for which "adequate directions for use" cannot be prepared, shall be exempt from section 502 (f)(1) of the act if all the following conditions are met:

(a) The device is:

(1)(i) In the possession of a person (or his agents or employees) regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of such device; or

(ii) In the possession of a practitioner, such as physicians, dentists, and veterinarians, licensed by law to use or order the use of such device; and

(2) Is to be sold only to or on the prescription or other order of such practitioner for use in the course of his professional practice.

(b) The label of the device (other than surgical instruments) bears:

(1) The statement "Caution: Federal law restricts this device to sale by or on the order of a _____", the blank to be filled with the word "physician", "dentist", "veterinarian", or with the descriptive designation of any other practitioner licensed by the law of the State in which he practices to use or order the use of the device; and

(2) The method of its application or use.

(c) Labeling on or within the package from which the device is to be dispensed bears information for use, including indications, effects, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the device can use the device safely and for the purpose for which it is intended, including all purposes for which it is advertised or represented: *Provided, however,* That such information may be omitted from the dispensing package if, but only if, the article is a device for which directions, hazards, warnings, and other information are commonly known to practitioners licensed by law to use the device. Upon written request, stating reasonable grounds therefor, the Commissioner will offer an opinion on a proposal to omit such information from the dispensing package under this proviso.

(d) Any labeling, as defined in section 201(m) of the act, whether or not it is on or within a package from which the device is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the device, that furnishes or purports to furnish information for use of the device contains adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented. This information will not be required on so-called reminder-piece labeling which calls attention to the name of the device but does not include indications or other use information.

(e) All labeling, except labels and cartons, bearing information for use of the device also bears the date of the issuance or the date of the latest revision of such labeling.

§ 201.110 Retail exemption for veterinary drugs and prescription devices.

A drug or device subject to §§ 201.105 or 201.109 shall be exempt at the time of delivery to the ultimate purchaser or user from section 502(f)(1) of the act if it is delivered by a licensed practitioner in the course of his professional practice or upon a prescription or other order lawfully issued in the course of his professional practice, with labeling bearing the name and address of such licensed practitioner and the directions for use and cautionary statements, if any, contained in such order.

§ 201.115 News drugs or new animal drugs.

A new drug shall be exempt from section 502(f)(1) of the act:

(a) To the extent to which such exemption is claimed in an approved application with respect to such drug under section 505 or 512 of the act; or

(b) If no application under section 505 of the act is approved with respect to such drug but it complies with section 505 (i) or 512 of the act and regulations thereunder.

No exemption shall apply to any other drug which would be a new drug if its labeling bore representations for its intended uses.

§ 201.116 Drugs and devices having commonly known directions.

A drug or device shall be exempt from section 502(f)(1) of the act insofar as adequate directions for common uses thereof are known to the ordinary individual.

§ 201.117 Inactive ingredients.

A harmless drug that is ordinarily used as an inactive ingredient, such as a coloring, emulsifier, excipient, flavoring, lubricant, preservative, or solvent, in the preparation of other drugs shall be exempt from section 502 (f) (1) of the act. This exemption shall not apply to any substance intended for a use which results in the preparation of a new drug, unless an approved new-drug application provides for such use.

§ 201.119 In vitro diagnostic products.

A product intended for use in the diagnosis of disease and which is an in vitro diagnostic product as defined in § 328.3(a) of this chapter shall be deemed to be in compliance with the requirements of this section and section 502(f)(1) of the act if it meets the requirements of Part 328 of this chapter.

§ 201.120 Prescription chemicals and other prescription components.

A drug prepared, packaged, and primarily sold as a prescription chemical or other component for use by registered pharmacists in compounding prescriptions or for dispensing in dosage unit form upon prescriptions shall be exempt from section 502(f)(1) of the act if all the following conditions are met:

(a) The drug is an official liquid acid or official liquid alkali, or is not a liquid solution, emulsion, suspension, tablet, capsule, or other dosage unit form; and

(b) The label of the drug bears:

(1) The statement "For prescription compounding"; and

(2) If in substantially all dosage forms in which it may be dispensed it is subject to section 503 (b) (1) of the act, the statement "Caution: Federal law prohibits dispensing without prescription"; or

(3) If it is not subject to section 503 (b) (1) of the act and is by custom among retail pharmacists sold in or from the interstate package for use by consumers, "adequate directions for use" in the conditions for which it is so sold.

Provided, however, That the information referred to in paragraph (b)(3) of this section may be contained in the labeling on or within the package from which it is to be dispensed.

(c) This exemption shall not apply to any substance intended for use in compounding which results in a new drug, unless an approved new-drug application covers such use of the drug in compounding prescriptions.

§ 201.122 Drugs and devices for processing, repacking, or manufacturing.

A drug in a bulk package (except tablets, capsules, or other dosage unit forms) or a device intended for processing, repacking, or use in the manufacture of another drug or device shall be exempt from section 502(f)(1) of the act if its label bears the statement "Caution: For manufacturing, processing, or repacking"; and, if in substantially all dosage forms in which it may be dispensed it is subject to section 503 (b) (1), the statement "Caution: Federal law prohibits dispensing without prescription". This exemption and the exemption under § 201.120 may be claimed for the same article. But the exemption shall not apply to a substance intended for a use in manufacture, processing, or repacking which causes

the finished article to be a new drug, unless:

(a) An approved new-drug application or new animal drug application held by the person preparing the dosage form or drug for dispensing covers the production and delivery to him of such substance; or

(b) If no application is approved with respect to such new drug or new animal drug, the label statement "Caution: For manufacturing, processing, or repacking" is immediately supplemented by the words "in the preparation of a new drug or new animal drug limited by Federal law to investigational use", and the delivery is made for use only in the manufacture of such new drug or new animal drug limited to investigational use as provided in § 312.1 or § 511.1 of this chapter.

§ 201.125 Drugs and devices for use in teaching, law enforcement, research, and analysis.

A drug or device subject to §§ 201.100, 201.105, or 201.109 shall be exempt from section 502(f)(1) of the act if shipped or sold to, or in the possession of, persons regularly and lawfully engaged in instruction in pharmacy, chemistry, or medicine not involving clinical use, or engaged in law enforcement, or in research not involving clinical use, or in chemical analysis, or physical testing, and is to be used only for such instruction, law enforcement, research, analysis, or testing.

§ 201.127 Drugs and devices; expiration of exemptions.

(a) If a shipment or delivery, or any part thereof, of a drug or device which is exempt under the regulations in this section is made to a person in whose possession the article is not exempt, or is made for any purpose other than those specified, such exemption shall expire, with respect to such shipment or delivery or part thereof, at the beginning of that shipment or delivery. The causing of an exemption to expire shall be considered an act which results in such drug or device being misbranded unless it is disposed of under circumstances in which it ceases to be a drug or device.

(b) The exemptions conferred by §§ 201.117, 201.119, 201.120, 201.122, and 201.125 shall continue until the drugs or devices are used for the purposes for which they are exempted, or until they are relabeled to comply with section 502 (f) (1) of the act. If, however, the drug is converted, compounded, or manufactured into a dosage form limited to prescription dispensing, no exemption shall thereafter apply to the article unless the dosage form is labeled as required by section 503(b) and §§ 201.100, 201.105, or 201.109.

§ 201.128 eManing of "Intended uses".

The words "intended uses" or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, and 201.122 refer to the objective intent of the persons legally responsible for the labeling of drugs and devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer. If, for example, a packer, distributor, or seller intends an article for different uses than those intended by the person from whom he received the drug, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug or device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.

(Secs. 201(n), 502, 505, 507, 701, 52 Stat. 1041, 1050–53 as amended, 1055–56 as amended by 70 Stat. 919 and 72 Stat. 948, 59 Stat. 463 as amended; 21 U.S.C. 321(n), 352, 355, 357, 701)

Subpart E—Other Exemptions

§ 201.150 Drugs and devices; processing, labeling, or repacking.

(a) Except as provided by paragraphs (b) and (c) of this section, a shipment or other delivery of a drug or device which is, in accordance with the practice of the trade, to be processed, labeled, or repacked in substantial quantity at an establishment other than that where originally processed or packed, shall be exempt, during the time of introduction into and movement in interstate commerce and the time of holding in such establishment, from compliance with the labeling and packaging requirements of sections 501(b) and 502 (b), (d), (e), (f), and (g) of the act if:

(1) The person who introduced such shipment or delivery into interstate commerce is the operator of the establishment where such drug or device is to be processed, labeled, or repacked; or

(2) In case such person is not such operator, such shipment or delivery is made to such establishment under a written agreement, signed by and containing the post-office addresses of such person and such operator, and containing such specifications for the processing, labeling, or repacking, as the case may be, of such drug or device in such establishment as will insure, if such specifications are followed, that such drug or device will not be adulterated or misbranded within the meaning of the act upon completion of such processing, labeling, or repacking. Such person and such operator shall each keep a copy of such agreement until 2 years after the final shipment or delivery of such drug or device from such establishment, and shall make such copies available for inspection at any reasonable hour to any officer or employee of the Department who requests them.

(b) An exemption of a shipment or other delivery of a drug or device under paragraph (a) (1) of this section shall, at the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment, become void ab initio if the drug or device comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed.

(c) An exemption of a shipment or other delivery of a drug or device under paragraph (a) (2) of this section shall become void ab initio with respect to the person who introduced such shipment or delivery into interstate commerce upon refusal by such person to make available for inspection a copy of the agreement, as required by such subparagraph.

(d) An exemption of a shipment or other delivery of a drug or device under paragraph (a) (2) of this section shall expire:

(1) At the beginning of the act of removing such shipment or delivery, or any part thereof, from such establishment if the drug or device comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed; or

(2) Upon refusal by the operator of the establishment where such drug or device is to be processed, labeled, or repacked, to make available for inspection a copy of the agreement, as required by such clause.

(e) Except as provided in paragraphs (g) and (h) of this section, a shipment or other delivery of a drug which is subject to section 507 of the act and which is, in accordance with the practice of the trade, to be processed or repacked in a substantial quantity at an establishment other than that where originally processed or packed shall be exempt from compliance with the labeling requirements of section 502 (f) of the act during the time such drug is also exempt from the requirements of section 502 (l) of the act or, in the case of a new animal drug, is exempt from certification under section 512(n) of the act under the provisions of § 433.15 or § 433.16 of this chapter.

(f) Except as provided by paragraphs (g) and (h) of this section, a shipment or other delivery of a drug which is subject to section 507 of the act and which is, in accordance with the practice of the trade, to be labeled in substantial quantity at an establishment other than that where originally processed or packed shall be exempt from compliance with the labeling requirements of section 502 (b), (e) and (f) of the act during the time such drug is also exempt from the requirements of section 502 (l) of the act or, in the case of a new animal drug, is exempt from certification under section 512(n) of the act under § 433.12 of this chapter, if the words, statements, and other information required by section 502 (b) and (e) of the act appear on each shipping container of such drug.

(g) In case the person who introduced such shipment or other delivery

into interstate commerce is the operator of the establishment where such drug is to be processed, labeled, or repacked, an exemption of such shipment or delivery under paragraph (e) or (f) of this section shall become void at the beginning of the act of removing such shipment or delivery or any part thereof from such establishment if the drug comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed.

(h) In case the person who introduced such shipment or delivery into interstate commerce is not the operator of the establishment where such drug is to be processed, labeled, or repacked, an exemption of a shipment or other delivery of such drug under paragraph (e) or (f) of this section shall expire at the beginning of the act of removing such shipment or delivery or any part thereof from such establishment if the drug comprising such shipment, delivery, or part is adulterated or misbranded within the meaning of the act when so removed.

(i) As it is a common industry practice to manufacture and/or assemble, package, and fully label a device as sterile at one establishment and then ship such device in interstate commerce to another establishment or to a contract sterilizer for sterilization, the Food and Drug Administration will initiate no regulatory action against the device as misbranded or adulterated when the nonsterile device is labeled sterile, provided all the following conditions are met:

(1) There is in effect a written agreement which:

(i) Contains the names and post office addresses of the firms involved and is signed by the person authorizing such shipment and the operator or person in charge of the establishment receiving the devices for sterilization.

(ii) Provides instructions for maintaining proper records or otherwise accounting for the number of units in each shipment to insure that the number of units shipped is the same as the number received and sterilized.

(iii) Acknowledges that the device is nonsterile and is being shipped for further processing, and

(iv) States in detail the sterilization process, the gaseous mixture or other media, the equipment, and the testing method or quality controls to be used by the contract sterilizer to assure that the device will be brought into full compliance with the Federal Food, Drug, and Cosmetic Act.

(2) Each pallet, carton, or other designated unit is conspicuously marked to show its nonsterile nature when it is introduced into and is moving in interstate commerce, and while it is being held prior to sterilization. Following sterilization, and until such time as it is established that the device is sterile and can be released from quarantine, each pallet, carton, or other designated unit is conspicuously marked to show that it has not been released from quarantine, e.g. "sterilized-awaiting test results" or an equivalent designation.

(Secs. 501(c), 502(a), 503, 701(a), 52 Stat. 1049, 1050, 1051, 1055; 21 U.S.C. 351(c), 352 (a), 371(a))

§ 201.160 Drugs; information commonly known.

(a) Section 201.100(c) of this chapter provides that in the case of certain drugs for which directions, hazards, warnings, and use information are commonly known to practitioners licensed by law, such information may be omitted from the dispensing package. Under this proviso, the Commissioner of Food and Drugs will offer an opinion, upon written request, stating reasonable grounds therefor, on a proposal to omit such information from the dispensing package.

(b) The Commissioner of Food and Drugs has considered submitted material covering a number of drug products and has offered the opinion that the following drugs, when intended for those human uses for which they are now generally employed by the medical profession, should be exempt from the requirements of § 201.100(c) of this chapter, provided that they meet the conditions prescribed in this paragraph. Preparations that are not in dosage unit form (for example, solutions) will be regarded as meeting the conditions with respect to the maximum quantity of drug per dosage unit if they are prepared in a manner that enables accurate and ready administration of a quantity of drug not in excess of the stated maximum per dosage unit:

Aminophylline. For oral use, not in excess of 200 milligrams per dosage unit, with or without not in excess of 33 milligrams of phenobarbital.

Atropine methyl nitrate. For oral use, not in excess of 1.0 milligram per dosage unit.

Atropine sulfate. For oral use, not in excess of 0.54 milligram per dosage unit; for injection, not in excess of 0.54 milligram ($\frac{1}{120}$-grain) per dosage unit.

Barbiturates. For oral use, not in excess of 100 milligrams per dosage unit; for use as suppositories, not in excess of 130 milligrams per suppository.

Chloral hydrate. For oral use, not in excess of 500 milligrams per dosage unit; for use as suppositories, not in excess of 1.0 gram per suppository.

Codeine phosphate. For oral use, not in excess of 65 milligrams per dosage unit; for injection, not in excess of 65 milligrams per dosage unit.

Codeine sulfate. For oral use, not in excess of 65 milligrams per dosage unit; for injection, not in excess of 65 milligrams per dosage unit.

Digitalis. Preparations of whole leaf digitalis including forms such as digitalis tincture. For oral use, containing the equivalent of not more than 1 U.S.P. digitalis unit per dosage unit.

Dihydrocodeinone bitartrate. For oral use, not in excess of 10 milligrams per dosage unit.

Dihydromorphinone hydrochloride. For oral use, not in excess of 4 milligrams per dosage unit.

Epinephrine injection, 1: 1,000.

Erythrityl tetranitrate. For oral use, not in excess of 30 milligrams per dosage unit.

Homatropine methylbromide. For oral use, not in excess of 5 milligrams per dosage unit.

Hyoscyamine hydrobromide. For oral use, not in excess of 1 milligram per dosage unit.

Hyoscyamine sulfate. For oral use, not in excess of 1 milligram per dosage unit.

Hyoscyamus tincture. For oral use, not in excess of 2 milliliters per dosage unit.

Mannitol hexanitrate. For oral use, not in excess of 32 milligrams per dosage unit.

Methenamine. For oral use, not in excess of 1 gram per dosage unit.

Morphine phosphate. For oral use, not in excess of 33 milligrams per dosage unit; for injection, not in excess of 33 milligrams per dosage unit.

Morphine sulfate. For oral use, not in excess of 33 milligrams per dosage unit; for injection, not in excess of 33 milligrams per dosage unit.

Nitroglycerin. For oral use, not in excess of 0.65 milligram per dosage unit.

Pentaerythritol tetranitrate. For oral use, not in excess of 20 milligrams per dosage unit.

Pentaerythritol tetranitrate with phenobarbital. For oral use, not in excess of 20 milligrams of pentaerythritol tetranitrate and 35 milligrams of phenobarbital.

Quinidine sulfate. For oral use, not in excess of 325 milligrams per dosage unit.

Scopolamine methylbromide. For oral use, not in excess of 2.5 milligrams per dosage unit.

Sodium chloride injection.

Sodium nitrite. For oral use, not in excess of 60 milligrams per dosage unit.

Theobromine. For oral use, not in excess of 325 milligrams per dosage unit.

Thyroid. For oral use, not in excess of 220 milligrams per dosage unit.

Water for injection, sterile.

§ 201.161 Carbon dioxide and certain other gases.

(a) Carbon dioxide, cyclopropane, ethylene, helium, and nitrous oxide gases intended for drug use are exempted from the requirements of § 201.100(b)(2), (3), and (c)(1) provided the labeling bears, in addition to any other information required by the Federal Food, Drug, and Cosmetic Act, the following:

(1) The warning statement "Warning—Administration of (name of gas) may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of (name of gas) and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and the precautions to be taken"; and

(2) Any needed directions concerning the conditions for storage and warnings against the inherent dangers in the handling of the specific compressed gas.

(b) This labeling exemption does not apply to mixtures of any one or more of these gases with oxygen or with each other.

(c) Regulatory action may be initiated with respect to any article shipped within the jurisdiction of the Act contrary to the provisions of this section after 60 days following publication of this section in the FEDERAL REGISTER.

(Sec. 502(f), 52 Stat. 1051; 21 U.S.C. 352(f))

Subpart F—Labeling Claims for Drugs in Drug Efficacy Study

§ 201.200 Disclosure of drug efficacy study evaluations in labeling and advertising.

(a) (1) The National Academy of Sciences-National Research Council, Drug Efficacy Study Group, has completed an exhaustive review of labeling claims made for drugs marketed under new-drug and antibiotic drug procedures between 1938 and 1962. The results are compiled in "Drug Efficacy Study, A Report to the Commissioner of Food and Drugs from the National Academy of Sciences (1969)." As the report notes, this review has made "an audit of the state of the art of drug usage that has been uniquely extensive in scope and uniquely intensive in time" and is applicable to more than 80 percent of the currently marketed drugs. The report further notes that the quality of the evidence of efficacy, as well as the quality of the labeling claims, is poor. Labeling and other promotional claims have been evaluated as "effective," "probably effective," "possibly effective," "ineffective," "ineffective as a fixed combination," and "effective but," and a report for each drug in the study has been submitted to the Commissioner.

(2) The Food and Drug Administration is processing the reports, seeking voluntary action on the part of the drug manufacturers and distributors in the elimination or modification of unsupported promotional claims, and initiating administrative actions as necessary to require product and labeling changes.

(3) Delays have been encountered in bringing to the attention of the prescribers of prescription items the conclusions of the expert panels that reviewed the promotional claims.

(b) The Commissioner of Food and Drugs concludes that:

(1) The failure to disclose in the labeling of a drug and in other promotional material the conclusions of the Academy experts that a claim is "ineffective," "possibly effective," "probably effective," or "ineffective as a fixed combination," while labeling and promotional material bearing any such claim are being used, is a failure to disclose facts that are material in light of the representations made and causes the drug to be misbranded.

(2) The Academy classification of a drug as other than "effective" for a claim for which such drug is recommended establishes that there is a material weight of opinion among qualified experts contrary to the representation made or suggested in the labeling, and failure to reveal this fact causes such labeling to be misleading.

(c) Therefore, after publication in the FEDERAL REGISTER of a Drug Efficacy Study Implementation notice on a prescription drug, unless exempted or otherwise provided for in the notice, all package labeling (other than the immediate container or carton label, unless such labeling contains information required by § 201.100(c)(1) in lieu of a package insert), promotional labeling, and advertisements shall include, as part of the information for practitioners under which the drug can be safely and effectively used, an appropriate qualification of all claims evaluated as other than "effective" by a panel of the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, if such claims continue to be included in either the labeling or advertisements. However, this qualifying information will be required in advertisements only if promotional material is included therein for claims evaluated as less than "effective" or if such claims are included in the indications section of the portion of the advertisement containing the information required in brief summary by § 202.1(e)(1) of this chapter. When, however, the Food and Drug Administration classification of such claim is "effective" (for example, on the basis of revision of the language of the claim or submission or existence of adequate data), such qualification is not necessary. When the Food and Drug Administration classification of the claim, as stated in the implementation notice, differs from that of the Academy but is other than "effective," the qualifying statement shall refer to this classification in lieu of the Academy's classification.

(d) For new drugs and antibiotics, supplements to provide for revised labeling in accord with paragraph (c) of this section shall be submitted under the provisions of § 314.8 (d) and (e) and § 514.50 of this chapter within 90 days after publication of the implementation notice in the FEDERAL REGISTER or by May 15, 1972, for those drugs for which notices have been published and such labeling shall be put into use as soon as possible but not later than the end of the time period allowed for submitting supplements to provide for revised labeling.

(e) Qualifying information required in drug labeling by paragraph (c) of this section in order to advise prescribers of a drug of the findings made by a panel of the Academy in evaluating a claim as other than "effective" shall be at least of the same size and color and degree of prominence as other printing in the labeling and shall be presented in a prominent box using one of the following formats and procedures:

(1) In drug labeling the box statement may entirely replace the indications section and be in the following format:

> INDICATIONS
>
> Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indication(s) as follows:
>
> Effective: (list or state in paragraph form).
>
> "Probably" effective: (list or state in paragraph form).
>
> "Possibly" effective: (list or state in paragraph form).
>
> Final classification of the less-than-effective indications requires further investigation.

(2) Or the indication(s) for which the drug has been found effective may appear outside the boxed statement and be followed immediately by the following boxed statement:

> Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the other indication(s) as follows:
>
> "Probably" effective: (list or state in paragraph form).
>
> "Possibly" effective: (list or state in paragraph form).
>
> Final classification of the less-than-effective indications requires further investigation.

(3) In drug labeling (other than that which is required by § 201.100(c)(1) which may contain a promotional message, the promotional message shall be keyed to the boxed statement by the same means as those provided for advertisements in paragraph (f)(2) of this section.

(f) Qualifying information required in prescription drug advertising by paragraph (c) of this section shall contain a prominent boxed statement of the advertised indication(s) and of the limitations of effectiveness using the same format, language, and emphasis as that required in labeling by paragraph (e) of this section.

(1) The boxed statement shall appear in (or next to) the information required in brief summary by § 202.1(e)(1) of this chapter and shall have prominence at least equal to that provided for other information presented in the brief summary and shall have type size, captions, color, and other physical characteristics comparable to the information required in the brief summary.

(2) Less-than-effective indication(s) in the promotional message of an advertisement which is a single page or less shall be keyed to the boxed statement by asterisk, by an appropriate statement, or by other suitable means providing adequate emphasis on the boxed statement. On each page where less-than-effective indication(s) appear in a mutiple page advertisement, an asterisk shall be placed after the most prominent mention of the indication(s); if the degree of prominence does not vary, an asterisk shall be

placed after the first mention of the indication. The asterisk shall refer to a notation at the bottom of the page which shall state "This drug has been evaluated as probably effective (or possibly effective whichever is appropriate) for this indication" and "See Brief Summary" or "See Prescribing Information," the latter legend to be used only if the advertisement carries the required information for professional use as set forth in § 201.100 (c)(1).

(3) For less-than-effective indications which are included in the advertisement only as a part of the information required in brief summary, the disclosure information shall appear in this portion of the advertisement in the same manner as is specified for labeling in paragraph (e) of this section.

(g) The Commissioner may find circumstances are such that, while the elimination of claims evaluated as other than effective will generally eliminate the need for disclosure about such claims, there will be instances in which the change in the prescribing or promotional profile of the drug is so substantial as to require a disclosure of the reason for the change so that the purchaser or prescriber is not misled by being left unaware through the sponsor's silence that a basic change has taken place. The Food and Drug Administration will identify these situations in direct correspondence with the drug promoters, after which the failure to make the disclosure will be regarded as misleading and appropriate action will be taken.

(Secs. 201(n), 502, 505, 507, 52 Stat. 1041, 1050–53 as amended, 1056, as amended by 70 Stat. 919 and 72 Stat. 948, 59 Stat. 463 as amended; 21 U.S.C. 321(n), 352, 355, 357, 701)

Subpart G—Specific Labeling Requirements for Specific Drug Products

§ 201.300 Notice to manufacturers, packers, and distributors of glandular preparations.

(a) Under date of December 4, 1941, in a notice to manufacturers of glandular preparations, the Food and Drug Administration expressed the opinion that preparations of inert glandular materials intended for medicinal use should, in view of the requirement of section 201(n) of the Federal Food, Drug, and Cosmetic Act (52 Stat. 1041; 21 U.S.C. 321(n)), be labeled with a statement of the material fact that there is no scientific evidence that the articles contain any therapeutic or physiologically active constituents. Numerous preparations of such inert glandular materials were subsequently marketed with disclaimers of the type suggested. The term "inert glandular materials" means preparations incapable of exerting an action or effect of some significant or measurable benefit in one way or another, i.e., in the diagnosis, cure, mitigation, treatment, or prevention of disease, or in affecting the structure or any function of the body.

(b) Manufacturers have heretofore taken advantage of § 201.100 permitting omission of directions for use when the label bears the prescription legend. Section 201.100(c) requires that the labeling of the drug, which may include brochures readily available to licensed practitioners, bear information as to the use of the drug by practitioners licensed by law to administer it. Obviously, information adequate for the use of an inert glandular preparation is not available to practitioners licensed by law.

(c) The Department of Health, Education, and Welfare is of the opinion that inert glandular materials may not be exempted from the requirements of section 502 (f) (1) of the act that they bear adequate directions for use; and, accordingly, that their labeling must include, among other things, representations as to the conditions for which such articles are intended to be used or as to the structure or function of the human body that they are intended to affect. Since any such representations offering these articles for use as drugs would be false or misleading, such articles will be considered to be misbranded if they are distributed for use as drugs.

(d) The amended regulations provide also that in the case of drugs intended for parenteral administration there shall be no exemption from the requirement that their labelings bear adequate directions for use. Such inert glandular materials for parenteral use are therefore subject to the same comment as applies to those intended for oral administration.

§ 201.301 Notice to manufacturers, packers, and distributors of estrogenic hormone preparations.

Some drug preparations fabricated wholly or in part from estradiol and labeled as to potency in terms of international units or in terms of international units of estrone activity have been marketed. The international unit of the estrus-producing hormone was established by the International Conference on the Standardization of Sex Hormones at London, England, on August 1, 1932. This unit was defined as "the specific estrus-producing activity contained in 0.1 gamma (=0.0001 mg.) of the standard" hydroxyketonic hormone found in urine (estrone). The International Conference declared that it did not recommend the determination of the activity of nonhydroxyketonic forms of estrogenic hormones in units of estrone because of the varying ratios between the activity of such nonhydroxyketonic estrogenic hormones and estrone, when measured by different methods on test animals. There is no international unit for measuring the activity of estradiol and no accepted relationship between its activity and that of estrone, either in test animals or in humans. The declaration of potency of estradiol in terms of international units or in terms of international units of estrone activity is therefore considered misleading, within the meaning of 21 U.S.C. 352(a). The declaration of the estradiol content of an estrogenic hormone preparation in terms of weight is considered appropriate.

§ 201.302 Notice to manufacturers, packers, and distributors of drugs for internal use which contain mineral oil.

(a) In the past few years research studies have altered medical opinion as to the usefulness and harmfulness of mineral oil in the human body. These studies have indicated that when mineral oil is used orally near mealtime it interferes with absorption from the digestive tract of provitamin A and the fat-soluble vitamins A, D, and K, and consequently interferes with the utilization of calcium and phosphorus, with the result that the user is left liable to deficiency diseases. When so used in pregnancy it predisposes to hemorrhagic disease of the newborn.

(b) There is accumulated evidence that the indiscriminate administration of mineral oil to infants may be followed by aspiration of the mineral oil and subsequent "lipoid pneumonia."

(c) In view of these facts, the Department of Health, Education, and Welfare will regard as misbranded under the provisions of the Federal Food, Drug, and Cosmetic Act a drug for oral administration consisting in whole or in part of mineral oil, the labeling of which encourages its use in pregnancy or indicates or implies that such drug is for administration to infants.

(d) It is also this Department's view that the act requires the labelings of such drugs to bear a warning against consumption other than at bedtime and against administration to infants. The following form of warning is suggested: "Caution: To be taken only at bedtime. Do not use at any other time or administer to infants, except upon the advice of a physician."

(e) This statement of interpretation does not in any way exempt mineral oil or preparations containing mineral oil from complying in all other respects with the requirements of the Federal Food, Drug, and Cosmetic Act.

§ 201.303 Labeling of drug preparations containing significant proportions of wintergreen oil.

(a) Because methyl salicylate (wintergreen oil) manifests no toxicity in the minute amounts in which it is used as a flavoring, it is mistakenly regarded by the public as harmless even when taken in substantially larger amounts. Actually, it is quite toxic when taken in quantities of a teaspoonful or more. Wintergreen oil and preparations containing it have caused a number of deaths through accidental misuse by both adults and children. Children are particularly attracted by the odor and are likely to swallow these products when left within reach.

(b) To safeguard against fatalities from this cause, the Department of Health, Education, and Welfare will regard as misbranded under the provisions of the Federal Food, Drug, and Cosmetic Act any drug containing more than 5 percent methyl salicylate (wintergreen

oil), the labeling of which fails to warn that use otherwise than as directed therein may be dangerous and that the article should be kept out of reach of children to prevent accidential poisoning.

(c) This statement of interpretation in no way exempts methyl salicylate (wintergreen oil) or its preparations from complying in all other respects with the requirements of the Federal Food, Drug, and Cosmetic Act.

(Sec. 502, 52 Stat. 1050, as amended; 21 U.S.C. 352)

§ 201.304 Tannic acid and barium enema preparations.

(a) It has become a widespread practice for tannic acid to be added to barium enemas to improve X-ray pictures. Tannic acid is capable of causing diminished liver function and severe liver necrosis when absorbed in sufficient amounts. The medical literature reports a number of deaths associated with the addition of tannic acid to barium enemas. There is a lack of scientific evidence to establish the conditions, if any, under which tannic acid is safe and effective for use in enemas. Tannic acid for rectal use to enhance X-ray visualization is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(b) In view of the hazards involved when tannic acid is used in barium enemas, any shipments of tannic acid labeled to come within the exemptions under 502(f) of the Act containing such phrases as: "Caution: For manufacturing, processing, or repackaging," "For prescription compounding," or "Diagnostic reagent—For professional use only" will be regarded by the Commissioner of Food and Drugs as misbranded within the meaning of section 502(f) of the Federal Food, Drug, and Cosmetic Act unless the label and the labeling bear conspicuously a warning to the effect: "Warning—Not for use in enemas."

(c) Any tannic acid intended for use by man and found within the jurisdiction of the Federal Food, Drug, and Cosmetic Act labeled contrary to this section after 60 days from the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

(Sec. 502, 52 Stat. 1050, as amended; 21 U.S.C. 352)

§ 201.305 Isoproterenol inhalation preparations (pressurized aerosols, nebulizers, powders) for human use; warnings.

(a) Accumulating reports have been received by the Food and Drug Administration and have appeared in the medical literature of severe paradoxical bronchoconstriction associated with repeated, excessive use of isoproterenol inhalation preparations in the treatment of bronchial asthma and other chronic bronchopulmonary disorders. The cause of this paradoxical reaction is unknown; it has been observed, however, that patients have not responded completely to other forms of therapy until use of the isoproterenol inhalation preparation was discontinued. In addition, sudden unexpected deaths have been associated with the excessive use of isoproterenol inhalation preparations. The mechanism of these deaths and their relationship, if any, to the cases of severe paradoxical bronchospasm are not clear. Cardiac arrest was noted in several of these cases of sudden death.

(b) On the basis of the above information and after discussion with and concurrence of the Respiratory and Anesthetic Drugs Advisory Committee for Food and Drug Administration, the Commissioner of Food and Drugs concludes that in order for the labeling of such drugs to bear adequate information for their safe use, as required by § 201.100, such labeling must include the following:

Warning: Occasional patients have been reported to develop severe paradoxical airway resistance with repeated, excessive use of isoproterenol inhalation preparations. The cause of this refractory state is unknown. It is advisable that in such instances the use of this preparation be discontinued immediately and alternative therapy instituted, since in the reported cases the patients did not respond to other forms of therapy until the drug was withdrawn.

Deaths have been reported following excessive use of isoproterenol inhalation preparations and the exact cause is unknown. Cardiac arrest was noted in several instances.

(c) (1) The Commissioner also concludes that in view of the manner in which these preparations are self-administered for relief of attacks of bronchial asthma and other chronic bronchopulmonary disorders, it is necessary for the protection of users that warning information to patients be included as a part of the label and as part of any instructions to patients included in the package dispensed to the patient as follows:

Warning: Do not exceed the dose prescribed by your physician. If difficulty in breathing persists, contact your physician immediately.

(2) The warning on the label may be accomplished (i) by including it on the immediate container label with a statement directed to pharmacists not to remove the label or (ii) by including in the package a printed warning with instructions to pharmacists to place the warning on the container prior to dispensing.

(d) The marketing of isoproterenol inhalation preparations may be continued if all the following conditions are met:

(1) Within 30 days following the date of publication of this section in the FEDERAL REGISTER:

(i) The label and labeling of such preparations shipped within the jurisdiction of the act are in accordance with paragraphs (b) and (c) of this section.

(ii) The holder of an approved new-drug application for such preparation submits a supplement to his new-drug application to provide for appropriate labeling changes as described in paragraphs (b) and (c) of this section.

(2) Within 90 days following the date of publication of this section in the FEDERAL REGISTER, the manufacturer, packer, or distributor of any drug containing isoproterenol intended for inhalation for which a new-drug approval is not in effect submits a new-drug application containing satisfactory information of the kinds required by items 4, 5, 6, 7, 8, and 9 of the new-drug application form (form FD–356H set forth in § 314.1(c)(2) of this chapter), including appropriate labeling as described in paragraphs (b) and (c) of this section.

(3) The applicant submits additional information required for the approval of the application as may be specified in a written communication from the Food and Drug Administration.

(e) After 270 days following expiration of said 90 days, regulatory proceedings based on section 505(a) of the Federal Food, Drug, and Cosmetic Act may be initiated with regard to any such drug shipped within the jurisdiction of the act for which an approved new-drug application is not in effect.

(Secs. 502 (f), (j), 505, 52 Stat. 1051–53, as amended; 21 U.S.C. 352 (f), (j), 355)

§ 201.306 Potassium salt preparations intended for oral ingestion by man.

(a) The Food and Drug Administration will initiate no regulatory action with respect to the continued marketing of coated tablets containing potassium chloride or other potassium salts which supply 100 milligrams or more of potassium per tablet provided all the following conditions are met:

(1) Within 30 days from the date of publication of this statement of policy in the FEDERAL REGISTER:

(i) The labeling of the drug bears the prescription caution statement quoted in section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act;

(ii) The labeling on or within the package from which the drug is to be dispensed bears adequate information for its use by practitioners in accord with the "full disclosure" labeling requirements of § 201.100 of this chapter, including the following warning statement: "Warning—There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required and deaths have occurred. Based on a large survey of physicians and hospitals, both United States and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Coated potassium tablets should be used only when adequate dietary supplementation is not practicable."

(Although the warning statement includes references to enteric-coated potassium salt preparations, it applies to any capsule or coated tablet of a potassium salt intended for oral ingestion without prior dilution with an adequate volume of liquid to preclude gastrointestinal injury.)

(iii) Any other labeling or additional advertising for the drug conforms to the labeling described in paragraph (a)(1)(ii) of this section, in accordance with §§ 202.1 and 201.100 of this chapter.

(2) Within 90 days from the date of publication of this statement of policy in the FEDERAL REGISTER, the manufacturer, packer, or distributor of the drug shall submit a new-drug application containing satisfactory information of the kind required by Items 2, 3, 4, 6, 7, and 9 of the new-drug application form contained in § 314.1(c) of this chapter, with appropriate labeling as described in this paragraph.

(b) The Food and Drug Administration may initiate regulatory proceedings after 30 days from the date of publication of this section, with respect to the marketing of uncoated tablets containing potassium chloride or other potassium salts which supply 100 milligrams or more of potassium per tablet or with respect to liquid preparations containing potassium chloride or other potassium salts which supply 20 milligrams or more of potassium per milliliter, labeled or intended for human use, unless all the following conditions are met:

(1) The labeling of the drug bears the prescription caution statement quoted in section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act; and

(2) The labeling on or within the package from which the drug is to be dispensed bears adequate information for its use by practitioners in accord with the "full disclosure" labeling requirements of § 201.100 of this chapter, including a recommendation that patients be directed to dissolve any such tablets in an appropriate amount of liquid and to dilute any such liquid preparations adequately to assure against gastrointestinal injury associated with the oral ingestion of concentrated potassium salt preparations.

(Secs. 502(f), 503(b)(4), 505; 52 Stat. 1051, 1052; 21 U.S.C. 352(f), 353(b), 355)

§ 201.307 Chlorcyclizine, cyclizine, meclizine; warnings; labeling requirements.

(a) The Food and Drug Administration, pursuant to its responsibility for the safety and effectiveness of drugs, has conducted active investigations of reports of available animal data which reveal that chlorcyclizine hydrochloride, cyclizine hydrochloride and lactate, and meclizine hydrochloride exert a teratogenic response in animals such as the rat, mouse, rabbit, pig, and dog. While clinical studies to date are inconclusive, scientific experts are of the opinion that these drugs may possess a potential for adverse effects on the human fetus. Investigations have led to the conclusion that there exists sufficient evidence of teratogenicity in animals administered these drugs to justify warnings against their use in pregnancy except on advice of a physician. An Ad Hoc Advisory Committee on the Teratogenic Effect of Certain Drugs, comprised of scientists in various branches of medicine concerned with the problem, has submitted its findings and conclusions to the Commissioner of Food and Drugs and has recommended that all over-the-counter preparations containing chlorcyclizine, cyclizine, or meclizine or their salts bear a warning.

(b) On the basis of studies made by the Food and Drug Administration and on the recommendations of the Advisory Committee, the Commissioner of Food and Drugs has concluded that it is necessary for the protection of users that the label and labeling of all over-the-counter preparations containing chlorcyclizine, cyclizine, or meclizine or their salts bear a statement to the following effect: "*Warning*—Not for use by women who are pregnant or who may possibly become pregnant, unless directed by a physician, since this drug may have the potentiality of injuring the unborn child."

(c) The marketing of oral and parenteral drugs containing chlorcyclizine, cyclizine, or meclizine or their salts may be continued provided that all the following conditions are met:

(1) Within 30 days from the date of publication of this statement in the FEDERAL REGISTER,

(i) The label and applicable labeling of drugs containing chlorcyclizine, cyclizine, or meclizine or their salts at acceptable levels for over-the-counter distribution, shall prominently and conspicuously display the statement: "*Warning*—Not for use by women who are pregnant or who may possibly become pregnant, unless directed by a physician, since this drug may have the potentiality of injuring the unborn child."

(ii) The package labeling and other labeling providing professional use information concerning prescription drugs containing chlorcyclizine, cyclizine, or meclizine or their salts and not contraindicated for use in pregnancy because of some other ingredient, shall bear, in accordance with § 201.100* of this chapter, a section under "Adverse Reactions" headed "Use in Pregnancy," as follows:

The following information should be taken into account in determining whether the potential benefits of [chlorcyclizine, cyclizine, meclizine, or their salts] outweigh the risks of their use in women of childbearing age and particularly during pregnancy. A review of available animal data reveals that this drug exerts a teratogenic response in the [rat, mouse, rabbit, pig, dog]. While available clinical data are inconclusive, scientific experts are of the opinion that this drug may possess a potential for adverse effects on the human fetus. Consequently, consideration should be given to initial use of a nonphenothiazine agent that is not suspected of having a teratogenic potential. In any case, the dosage and duration of treatment should be kept to a minimum.

This statement shall be followed with an appropriate summary of the pertinent animal studies and adverse clinical experiences, with adequate references to the scientific literature. Also, the labeling shall contain, in juxtaposition with any representation for use in the treatment of nausea and vomiting in pregnancy, the following statement:

The effectiveness of ------ for the prevention and treatment of nausea and vomiting of pregnancy has not been established, and the decision to use ------ should be based on the seriousness of the situation, remembering that while this drug has been used clinically for a decade, there are yet no controlled studies to demonstrate its usefulness in an objective fashion. In most cases, nausea and vomiting of pregnancy may be unpleasant but do not present a serious threat to the health of the patient or to the progress of her pregnancy. In view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, management by physiologic means such as proper nutrition and by psychologic support is preferable to antiemetic therapy.

(2) Within 30 days from the date of publication of this statement of policy in the FEDERAL REGISTER, the applicant under an approved new-drug application for a drug containing chlorcyclizine, cyclizine, or meclizine or their salts shall submit a supplement to his new-drug application, providing for appropriate labeling changes as described in paragraph (c)(1)(i) or (ii) of this section.

(3) Within 90 days from the date of publication of this statement of policy in the FEDERAL REGISTER, the manufacturer, packer, or distributor of any drug containing chlorcyclizine, cyclizine, or meclizine or their salts for which a new-drug approval is not in effect shall submit a new-drug application containing satisfactory information of the kinds required in the new-drug application form contained in § 314.1(c) of this chapter, including appropriate labeling as described in paragraph (c)(1)(i) or (ii) of this section.

(d) In view of the fact that no substantial evidence has been offered for the effectiveness of chlorcyclizine, cyclizine, and meclizine or their salts in the prevention and treatment of nausea and vomiting of pregnancy, but mindful of the fact that some practicing physicians believe that these drugs exert a beneficial effect upon this condition, the Food and Drug Administration will permit a modified claim in indications for this use for a period not exceeding 2 years. However, this modified indication for use of these drugs in the prevention and treatment of nausea and vomiting of pregnancy will be deleted from the labeling unless substantial evidence is offered before the expiration of this period of time. The Food and Drug Administration will also continue to follow the large-scale surveys of clinical experience and any reports of adverse reaction that may be due to the use of these drugs under the revised labeling.

*Section 202.1 will require that prescription drug advertising contain this warning.

§ 201.308 Ipecac syrup; warnings and directions for use for over-the-counter sale.

(a) It is estimated that each year about 500,000 accidental poisonings occur in the United States and result in approximately 1,500 deaths, of which over 400 are children. In the emergency treatment of these poisonings, ipecac syrup is considered the emetic of choice. The immediate availability of this drug for use in such situations is critical, since rapid treatment may be the difference between life and death. The restriction of this drug to prescription sale limits its availability in emergencies. On the other hand, it is the consensus of informed medical opinion that ipecac syrup should be used only under medical supervision in the emergency treatment of poisonings. In view of these facts, the question of whether ipecac syrup labeled as an emergency treatment for use in poisonings should be available over the counter has been controversial.

(b) In connection with its study of this problem, the Food and Drug Administration has obtained the views of medical authorities. It is the unanimous recommendation of the American Academy of Pediatrics, the American Association of Poison Control Centers, the American Medical Association, and the Medical Advisory Board of the Food and Drug Administration that ipecac syrup in 1 fluid ounce containers be permitted to be sold without prescription so that it will be readily available in the household for emergency treatment of poisonings, under medical supervision, and that the drug be appropriately packaged and labeled for this purpose.

(c) In view of the above recommendations, the Commissioner of Food and Drugs has determined that it is in the interest of the public health for ipecac syrup to be available for sale without prescription, provided that it is packaged in a quantity of 1 fluid ounce (30 milliliters), and its label bears, in addition to other required label information, the following, in a prominent and conspicuous manner:

(1) A statement conspicuously boxed and in red letters, to the effect: "For emergency use to cause vomiting in poisoning. Before using, call physician, the Poison Control Center, or hospital emergency room immediately for advice."

(2) A warning to the effect: "Warning—Keep out of reach of children. Do not use in unconscious persons. Ordinarily, this drug should not be used if strychnine, corrosives such as alkalies (lye) and strong acids, or petroleum distillates such as kerosine, gasoline, coal oil, fuel oil, paint thinner, or cleaning fluid have been ingested."

(3) Usual dosage: 1 tablespoon (15 milliliters) in persons over 1 year of age.

§ 201.309 Acetophenetidin (phenacetin)-containing preparations; necessary warning statement.

(a) In 1961, the Food and Drug Administration, pursuant to its statutory responsibility for the safety and effectiveness of drugs shipped in interstate commerce, began an active investigation of reports of possible toxic effects and renal damage due to misuse of the drug acetophenetidin. This study led to the decision that there was probable cause to conclude that misuse and prolonged use of the drug were in fact responsible for kidney lesions and disease. The Commissioner of Food and Drugs, in December 1963, appointed an ad hoc Advisory Committee of Inquiry on Possible Nephrotoxicity Associated With the Abuse of Acetophenetidin (Phenacetin)-Containing Preparations. This committee, composed of scientists in the fields of pharmacology and medicine, on April 23, 1964, submitted its findings and conclusions in the matter and recommended that all acetophenetidin (phenacetin)-containing preparations bear a warning as provided in section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act.

(b) On the basis of the studies made by the Food and Drug Administration and the report of the Advisory Committee, the Commissioner of Food and Drugs has concluded that it is necessary for the protection of users that the label and labeling of all acetophenetidin (phenacetin)-containing preparations bear a warning statement to the following effect: "Warning—This medication may damage the kidneys when used in large amounts or for a long period of time. Do not take more than the recommended dosage, nor take regularly for longer than 10 days without consulting your physician."

§ 201.310 Phenindione; labeling of drug preparations intended for use by man.

(a) Reports in the medical literature and data accumulated by the Food and Drug Administration indicate that phenindione, a synthetic anticoagulant drug, has caused a number of cases of agranulocytosis (with two fatalities). There are also reports implicating the drug in cases of hepatitis and hypersensitivity reactions. In view of the potentially serious effects found to be associated with preparations of this drug intended for use by man, the Commissioner of Food and Drugs will regard such preparations as misbranded within the meaning of section 502(f)(1) and (2) of the Federal Food, Drug, and Cosmetic Act, unless the label and labeling on or within the package from which the drug is to be dispensed, and any other labeling furnishing or purporting to furnish information for use of the drug, bear a conspicuous warning statement to the following effect: "Warning: Agranulocytosis and hepatitis have been associated with the use of phenindione. Patients should be instructed to report promptly prodromal symptoms such as marked fatigue, chill, fever, and sore throat. Periodic blood studies and liver function tests should be performed. Use of the drug should be discontinued if leukopenia occurs or if evidence of hypersensitivity, such as dermatitis or fever, appears."

(b) Regulatory action may be initiated with respect to preparations of phenindione intended for use by man found within the jurisdiction of the act on or after November 25, 1961, unless such preparations are labeled in accordance with paragraph (a) of this section.

(Secs. 502(f), 52 Stat. 1051, 21 U.S.C. 352(f))

§ 201.311 Aminopyrine or dipyrone drug preparations for human use; directions and warnings.

(a) Because of the increasing number of reports of fatal agranulocytosis associated with the use of aminopyrine (4-dimethylamino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) and dipyrone (1-phenyl-2,3-dimethyl-5-pyrazolone-4-methylaminomethanesulfonate sodium), the Commissioner of Food and Drugs convened an ad hoc Committee on Aminopyrine and Dipyrone. The members of the committee consisted of authorities in the fields of hematology, internal medicine, neurology, pediatrics, and pharmacology. This committee considered the questions of safety and effectiveness of aminopyrine and dipyrone and reported its findings and recommendations to the Commissioner of Food and Drugs. Copies of the committee's report and recommendations are available upon request, directed to the office of the Assistant Commissioner for Public Affairs, 5600 Fishers Lane, Rockville, MD 20852. The committee found:

(1) Aminopyrine and dipyrone, a derivative of aminopyrine, are capable of causing and have caused fatal agranulocytosis.

(2) Relatively small amounts of these drugs given intermittently over a period of time, as well as regular and continued administration, can precipitate the reaction of agranulocytosis.

(3) In most instances, other antipyretics and analgesics that are much safer should be used in preference to aminopyrine or dipyrone.

(4) The only conditions in which aminopyrine or dipyrone are known to be possibly indicated are febrile convulsions in children, where a parenteral antipyretic may be needed, and in rare instances of Hodgkin's disease and similar malignant diseases in which the fever cannot be controlled by any other means.

(b) The committee summarized its recommendations as follows:

1. It is recommended that aminopyrine and dipyrone for the present be retained on the market, but that the following statements be included in the labeling of the drugs:

All brochures, mailing pieces, detail pieces, advertising, and other labeling should contain the following paragraphs, in this order:

Warning—THIS DRUG MAY CAUSE FATAL AGRANULOCYTOSIS. (This should immediately follow the name of the drug.)

Caution—This drug should be used only in those conditions in which it is specifically indicated and in which other less toxic drugs have proved ineffective or are not tolerated. The potential benefit accruing from the use of this drug must be weighed against the possibility of fatal agranulocytosis.

Indications for use. Aminopyrine and aminopyrine derivates (dipyrone preparations) should be restricted for use in serious or life-threatening situations where salicylates or similar drugs are known to be ineffective or are contraindicated or not tolerated.

Duration of administration. Fatal agranulocytosis has been reported after short-term use, intermittent use, and after long-term administration. Therefore, the use of these agents should be as brief as possible.

Precautions. Frequent white blood cell and differential counts should be carried out. However, it is emphasized that agranulocytosis may occur precipitously without prior warning. The drug should be discontinued at the first evidence of any alteration of the blood count or sign of agranulocytosis, and the patient should be instructed to discontinue use of the drug at the first indication of sore throat or sign of other infection in the mouth or throat (pain, swelling, tenderness, ulceration).

Dosage. Adults: The usual antipyretic dose should not exceed ½ to 1 gram per dose, nor should more than 3 grams total daily dosage be used. If the desired effect is not achieved within a very few days, use of the drug should be discontinued.

Children: 250 to 500 milligrams per dose, repeated in 3 to 4 hours if necessary. Use of the drug should be as brief as possible.

2. It is recommended that every effort be made through educational media to emphasize the identical nature of aminopyrine and dipyrone insofar as toxicity is concerned.

3. It is further recommended that the official name of dipyrone be changed to aminopyrinesulfonate sodium, if possible. The purpose of this is to achieve the objective of Item 2 above.

4. The committee suggests that the panel be recalled by the Commissioner of the Food and Drug Administration within approximately one year after these recommendations have been fully implemented. The purpose of such a meeting would be to ascertain whether the use of dipyrone and aminopyrine and the cases of fatal agranulocytosis associated with the use of these drugs had been noticeably reduced by the method proposed. If the recommended labeling changes do not have the desired effect, other recommendations would need to be considered at that time.

(c) The committee also decided that a letter should be sent to all physicians to remind them of the close similarity and toxicity of aminopyrine and dipyrone.

(d) On the basis of the available evidence, including the findings and recommendations of the committee, the Commissioner of Food and Drugs finds and determines with respect to any drug preparation intended for administration to man that contains aminopyrine or dipyrone:

(1) Such drugs are unsafe and are regarded as misbranded within the meaning of section 502(f) (1) and (2) and (j) of the Federal Food, Drug, and Cosmetic Act when labeled or advertised for routine use as antipyretics or analgesics.

(2) Regulatory proceedings may be initiated with regard to the continued marketing of any such preparations with labeling or advertising offering such drugs for routine use as antipyretics or analgesics.

(3) Such preparations may be approved as safe and effective for marketing on the basis of new-drug applications containing labeling to the following effect, which labeling differs substantially from the labeling that has been commonly employed for many years in the marketing of such drugs:

(i) The label and labeling of the drug contains prominently and conspicuously, immediately following the trade name of the drug, without any intervening written, printed or graphic matter, the following:

(*a*) A quantitative declaration of the aminopyrine content; or

(*b*) A quantitative declaration of the dipyrone content with the name "dipyrone" followed immediately and conspicuously in parentheses by the declaration "aminopyrine derivative"; and

(c) The statement "Warning:—This drug may cause fatal agranulocytosis."

(ii) Labeling on or within the package from which the drug is to be dispensed and any other labeling for the drug that furnishes or purports to furnish information for use, or which prescribes, recommends, or suggests a dosage for the use of the drug, bears, in addition to the information required in this subparagraph, information to the following effect:

WARNING—THIS DRUG MAY CAUSE FATAL AGRANULOCYTOSIS.

CAUTION: This drug should be used only in those conditions in which it is specifically indicated and in which other less toxic drugs have proved ineffective or are not tolerated. The potential benefit accruing from the use of this drug must be weighed against the possibility of fatal agranulocytosis.

Indications for use. Aminopyrine and aminopyrine derivatives (dipyrone preparations) should be restricted to use for their antipyretic effect in serious or life-threatening situations where salicylates or similar drugs are known to be ineffective or are contraindicated or not tolerated.

Duration of administration. Fatal agranulocytosis has been reported after short-term use, intermittent use, and after long-term administration. Therefore, the use of these agents should be as brief as possible.

Precautions. Frequent white blood cell and differential counts should be carried out. However, it is emphasized that agranulocytosis may occur precipitously without prior warning. The drug should be discontinued at the first evidence of any alteration of the blood count or sign of agranulocytosis, and the patient should be instructed to discontinue use of the drug at the first indication of sore throat or sign of other infection in the mouth or throat (pain, swelling, tenderness, ulceration).

Dosage. Adults: The usual antipyretic dose should not exceed ½ to 1 gram per dose, nor should more than 3 grams total daily dosage be used. If the desired effect is not achieved within a very few days, use of the drug should be discontinued.

Children: 250 to 500 milligrams per dose, repeated in 3 to 4 hours if necessary. Use of the drug should be as brief as possible.

(4) A new-drug application for such a preparation should include a commitment that all advertising for the drug will bear the information required by paragraph (d)(3)(i) of this section, and that any advertisement that provides any information regarding indications or dosage recommendations will include the information required to appear in the package labeling by paragraph (d)(3)(ii) of this section and will not recommend or suggest use of the drug under any other conditions.

(5) A new-drug application will be regarded as approvable if it contains satisfactory information of the kinds required by items 4, 5, 6, 7, and 8 of the new-drug application form set forth in § 314.1(c)(2) of this chapter.

(6) Regulatory proceedings may be initiated with regard to the interstate shipment of any such preparations for which a new-drug application is not approved or which is labeled or advertised contrary to the labeling approved in such application consistent with this statement of policy.

(Sec. 502 (f), (j); 52 Stat. 1051; 21 U.S.C. 352 (f), (j))

§ 201.312 Magnesium sulfate heptahydrate; label declaration on drug products.

Magnesium sulfate heptahydrate should be listed on the label of a drug product as epsom salt, which is its common or usual name.

(Sec. 502, 52 Stat. 1051; 21 U.S.C. 352)

§ 201.313 Estradiol labeling.

The article presently recognized in The National Formulary under the heading "Estradiol" and which is said to be "17-cis-beta estradiol" is the same substance formerly recognized in the United States Pharmacopeia under the designation "Alpha Estradiol." The substance should no longer be referred to in drug labeling as "Alpha Estradiol." The Food and Drug Administration would not object to label references to the article as simply "Estradiol"; nor would it object if the label of a preparation containing this substance referred to the presence of "Estradiol (formerly known as Alpha Estradiol)."

(Secs. 201, 502, 52 Stat. 1040, 1051; 21 U. S. C. 321, 352)

§ 201.314 Labeling of drug preparations containing salicylates.

(a) The label of any oral drug preparation intended for sale without prescription and which contains any salicylate ingredient (including aspirin, salicylamide, other salicylates, and combinations) must bear a conspicuous warning statement in heavy block type on clearly contrasting background, such as: "Warning—Keep this and all medicines out of children's reach. In case of accidental overdose, contact a physician immediately," or "Warning—Keep out of the reach of children," except that if the article is an aspirin preparation, it shall bear the first of these warning statements. Such a warning statement is required for compliance with section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act and is intended to guard against accidental poisonings. Safety closures that prevent access to the drug by young children are also recommended to guard against accidental poisonings.

(b) Effervescent preparations and preparations containing para-aminosalicylate as the only salicylate ingredient are exempted from this labeling requirement.

(c) Aspirin tablets sold as such and containing no other active ingredients, except tablets which cannot be readily subdivided into a child's dose because of their coating or size, should always bear

dosage directions for each age group down to 3 years of age, with a statement such as "For children under 3 years of age, consult your physician." It is recommended that:

(1) Aspirin tablets especially made for pediatric use be produced only in 1¼-grain size to reduce the hazard of errors in dosage;

(2) By June 1, 1967, manufacturers and distributors of 1¼-grain size aspirin tablets discontinue the distribution of such tablets in retail containers containing more than 36 tablets, to reduce the hazard of accidental posoning;

(3) The flavoring of 5-grain aspirin tablets or other "adult aspirin tablets" be discontinued; and

(4) Labeling giving undue emphasis to the pleasant flavor of flavored aspirin tablets be discontinued.

(d) Salicylate preparations other than aspirin tablets sold as such may, at the option of the distributor, be labeled for use by adults only. If their labeling and advertising clearly offer them for administration to adults only.

(e) (1) It is the obligation of the distributor who labels a salicylate preparation for administration to children to make certain that the article is suitable for such use and labeled with adequate directions for use in the age group for which it is offered, but in no case should such an article bear directions for use in children under 3 years of age. If the directions provide for administration to children as young as 3 years of age, the label should bear the statement, "For children under 3 years of age consult your physician." However, if the directions provide for administration to children only of an age greater than 3 years (for example, the dosage instructions provide for administration of the article to children only down to age 6), the label should bear a statement such as, "For younger children consult your physician."

(2) A statement such as, "For children under 3 years of age consult your physician" or "For younger children consult your physician" is not required on the label of an article clearly offered for administration to adults only.

(f) If the labeling or advertising of a salicylate preparation offers it for use in arthritis or rheumatism, the label and labeling should clearly state that the beneficial effects claimed are limited to: "For the temporary relief of minor aches and pains of arthritis and rheumatism." The qualifying phrase "for the temporary relief of minor aches and pains" should appear with the same degree of prominence and conspicuousness as the phrase "arthritis and rheumatism". The label and labeling should bear in juxtaposition with such directions for use conspicuous warning statements to the effect: "Caution: If pain persists for more than 10 days, or redness is present, or in conditions affecting children under 12 years of age, consult a physician immediately." The salicylate dosage should not exceed 60 grains in a 24-hour period or 10 grains in a 4-hour period. If the article contains other analgesics, the salicylate dosage should be appropriately reduced.

(g) (1) The label of any drug containing more than 5 percent methyl salicylate (wintergreen oil) should bear a conspicuous warning such as: "Warning: Do not use otherwise than as directed. Keep out of the reach of children to avoid accidental poisoning."

(2) If the preparation is a counter-irritant or rubefacient, it should also bear a caution such as, ""Caution: Discontinue use if excessive irritation of the skin develops. Avoid getting into the eyes or on mucous membranes." (See also § 201.303.)

(Sec. 502, 52 Stat. 1051; 21 U.S.C. 352)

§ 201.315 Over-the-counter drugs for minor sore throats; suggested warning.

The Food and Drug Administration has studied the problem of the labeling of lozenges or troches containing a local anesthetic, chewing gum containing aspirin, various mouth washes and gargles and other articles sold over the counter for the relief of minor irritations of the mouth or throat. It will not object to the labeling of suitable articles of this type "For the temporary relief of minor sore throats", provided this is immediately followed in the labeling with a warning statement in prominent type essentially as follows: "Warning—Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult physician promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by physician."

(Sec. 502, 52 Stat. 1051; 21 U.S.C. 352)

Subpart H—Special Requirements for Specific Devices

§ 201.405 Labeling of articles intended for lay use in the repairing and/or refitting of dentures.

(a) The American Dental Association and leading dental authorities have advised the Food and Drug Administration of their concern regarding the safety of denture reliners, repair kits, pads, cushions, and other articles marketed and labeled for lay use in the repairing, refitting, or cushioning of ill-fitting, broken, or irritating dentures. It is the opinion of dental authorities and the Food and Drug Administration that to properly repair and properly refit dentures a person must have professional knowledge and specialized technical skill. Layman cannot be expected to maintain the original vertical dimension of occlusion and the centric relation essential in the proper repairing or refitting of dentures. The continued wearing of improperly repaired or refitted dentures may cause acceleration of bone resorption, soft tissue hyperplasia, and other irreparable damage to the oral cavity. Such articles designed for lay use should be limited to emergency or temporary situations pending the services of a licensed dentist.

(b) The Food and Drug Administration therefore regards such articles as unsafe and misbranded under the Federal Food, Drug, and Cosmetic Act, unless the labeling:

(1) (i) Limits directions for use for denture repair kits to emergency repairing pending unavoidable delay in obtaining professional reconstruction of the denture;

(ii) Limits directions for use for denture reliners, pads, and cushions to temporary refitting pending unavoidable delay in obtaining professional reconstruction of the denture;

(2) Contains in a conspicuous manner the word "emergency" preceding and modifying each indication-for-use statement for denture repair kits and the word "temporary" preceding and modifying each indication-for-use statement for reliners, pads, and cushions; and

(3) Includes a conspicuous warning statement to the effect:

(i) For denture repair kits: *"Warning—For emergency repairs only.* Long-term use of home-repaired dentures may cause faster bone loss, continuing irritation, sores, and tumors. This kit for emergency use only. See Dentist Without Delay."

(ii) For denture reliners, pads, and cushions: *"Warning—For temporary use only.* Long-term use of this product may lead to faster bone loss, continuing irritation, sores, and tumors. For Use Only Until a Dentist Can Be Seen."

(c) Adequate directions for use require full information of the temporary and emergency use recommended in order for the layman to understand the limitations of usefulness, the reasons therefor, and the importance of adhering to the warnings. Accordingly, the labeling should contain substantially the following information:

(1) For denture repair kits: Special training and tools are needed to repair dentures to fit properly. Home-repaired dentures may cause irritation to the gums and discomfort and tiredness while eating. Long-term use may lead to more troubles, even permanent changes in bones, teeth, and gums, which may make it impossible to wear dentures in the future. For these reasons, dentures repaired with this kit should be used only in an emergency until a dentist can be seen. Dentures that don't fit properly cause irritation and injury to the gums and faster bone loss, which is permanent. Dentures that don't fit properly cause gum changes that may require surgery for correction. Continuing irritation and injury may lead to cancer in the mouth. You must see your dentist as soon as possible.

(2) For denture reliners, pads, and cushions: Use of these preparations or devices may temporarily decrease the discomfort; however, their use will not make the denture fit properly. Special training and tools are needed to repair a denture to fit properly. Dentures that do not fit properly cause irritation and injury to the gums and faster bone loss, which is permanent and may require a a completely new denture. Changes in the gums caused by dentures that do not fit properly may require surgery for correction. Continuing irritation and injury

may lead to cancer in the mouth. You must see your dentist as soon as possible.

(3) If the denture relining or repairing material forms a permanent bond with the denture, a warning statement to the following effect should be included: "This reliner becomes fixed to the denture and a completely new denture may be required because of its use."

(d) Labeling claims exaggerating the usefulness or the safety of the material or failing to disclose all facts relevant to the claims of usefulness will be regarded as false and misleading under sections 201(n) and 502(a) of the Federal Food, Drug, and Cosmetic Act.

(e) Regulatory action may be initiated with respect to any article found within the jurisdiction of the act contrary to the provisions of this policy statement after 90 days following the date of publication of this section in the FEDERAL REGISTER.

§ 201.410 Use of impact-resistant lenses in eyeglasses and sunglasses.

(a) Examination of data available on the frequency of eye injuries resulting from the shattering of ordinary crown glass lenses indicate that the use of such lenses constitutes an avoidable hazard to the eye of the wearer.

(b) The consensus of the ophthalmic community is that the number of eye injuries would be substantially reduced by the use in eyeglasses and sunglasses of either plastic lenses, heat-treated crown glass lenses, or lenses made impact-resistant by other methods.

(c) To protect the public more adequately from potential eye injury, eyeglasses and sunglasses must be fitted with impact-resistant lenses, except in those cases where the physician or optometrist finds that such lenses will not fulfill the visual requirements of the particular patient, directs in writing the use of other lenses and gives written notification thereof to the patient.

(d) The physician or optometrist shall have the option of ordering heat-treated glass lenses, plastic lenses, laminated glass lenses, or glass lenses made impact resistant by other methods; however, all such lenses must be capable of withstanding an impact test in which a ⅝-inch steel ball weighing approximately 0.56 ounces is dropped from a height of 50 inches upon the horizontal upper surface of the lens. The ball shall strike within a ⅝-inch diameter circle located at the geometric center of the lens. The ball may be guided, but not restricted, in its fall by being dropped through a tube extending to within approximately 4 inches of the lens. In order to pass the test, the lens must not fracture (for the purpose of this section, a lens will be considered to have fractured if it cracks through its entire thickness, including a laminar layer, if any, and across a complete diameter into two or more separate pieces or if any lens material visable to the naked eye becomes detached from the ocular surface). The test shall be conducted with the lens supported by a tube (1-inch inside diameter, 1¼-inch outside diameter, and approximately 1-inch high) affixed to a rigid iron or steel base plate. The total weight of the base plate and its rigidly attached fixtures shall be not less than 27 pounds. For lenses of small minimum diameter, a support tube having an outside diameter of less than 1¼ inches may be used. The support tube shall be made of rigid acrylic plastic, steel or other suitable substance and shall have securely bonded on the top edge a ⅛- by ⅛-inch neoprene gasket having a hardness of 40±5, as determined by ASTM Method D 1415; a minimum tensile strength of 1,200 pounds, as determined by ASTM Method D 412; and a minimum ultimate elongation of 400 percent, as determined by ASTM Method D 412. The diameter and/or contour of the lens support may be modified as necessary so that the ⅛- by ⅛-inch neoprene gasket supports the lens at its periphery. Each finished impact-resistant glass lens for prescription use shall be subjected to the impact test prescribed by this paragraph. Raised ledge multifocal lenses must be impact-resistant but need not be tested beyond initial design testing. To demonstrate that all other types of impact-resistant lenses (including impact-resistant laminated glass lenses) are capable of withstanding this impact test, the manufacturer of such lenses shall subject to the impact test a statistically significant sampling of lenses from each production batch, and the lenses so tested shall be representative of the finished forms as worn by the wearer (including finished forms that are of minimal lens thickness and have been subjected to any treatment used to impart impact resistance). Plastic prescription and all nonprescription lenses, tested on the basis of statistical significance, may be tested in uncut finished or semifinished form at the point of original manufacture. This statement of policy will be appropriately amended to provide for use of alternate methods of testing the impact resistance of lenses if it can be shown that the alternate method is equal to or superior to the method prescribed in this paragraph.

(e) Copies of invoice(s), shipping document(s), and records of sale or distribution of all impact resistant lenses (including finished eyeglasses and sunglasses) shall be kept and maintained for a period of 3 years; however, the names and addresses of individuals purchasing nonprescription eyeglasses and sunglasses at the retail level need not be kept and maintained by the retailer. The records kept in compliance with this paragraph shall be made available upon request at all reasonable hours by any officer or employee of the Food and Drug Administration or by any other officer or employee acting on behalf of the Secretary of Health, Education, and Welfare and such officer or employee shall be permitted to inspect and copy such records, to make such inventories of stock as he deems necessary, and otherwise to check the correctness of such inventories.

(f) In addition, those persons conducting impact tests in accordance with paragraph (d) of this section, shall keep and maintain the results thereof for a period of 3 years. Such records and results shall be made available, upon request at all reasonable hours by any officer or employee acting on behalf of the Secretary of Health, Education, and Welfare and shall permit such officer or employee to inspect and copy such records, to make such inventories of stock as he deems necessary, and otherwise to check the correctness of such inventories.

(g) For the purpose of this section, the term "manufacturer" includes an importer for resale. Such importer may have the tests required by paragraph (d) of this section conducted in the country of origin but must make the results thereof available, upon request, to the Food and Drug Administration, as soon as practicable.

(h) The transition to impact-resistant lenses must be completed as promptly as possible; however, to provide for the development of an adequate supply of impact-resistant lenses and to facilitate an orderly changeover to these lenses, all lenses manufactured after January 31, 1972, must be impact-resistant, except when the physician or optometrist finds that impact-resistant lenses will not fulfill the visual requirements of a particular patient.

(i) This statement of policy does not apply to contact lenses.

(Secs. 502(j), 52 Stat. 1051; 21 U.S.C. 352(j))

PART 202—PRESCRIPTION DRUG ADVERTISING

Sec.
202.1 Prescription-drug advertisements.

AUTHORITY: Secs. 201(n), 502, 505, 507, 701, 52 Stat. 1041, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948, 59 Stat. 463 as amended (21 U.S.C. 321(n), 352, 355, 357, 701).

§ 202.1 Prescription drug advertisements.

(a) (1) The ingredient information required by section 502(n) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter, except the proprietary names of ingredients, which may be included with the listing of established names.

(2) The order of listing of ingredients in the advertisement shall be the same as the order of listing of ingredients on the label of the product, and the information presented in the advertisement concerning the quantity of each such ingredient shall be the same as the corresponding information on the label of the product.

(3) The advertisement shall not employ a fanciful proprietary name for the drug or any ingredient in such a manner as to imply that the drug or ingredient has some unique effectiveness or composition, when, in fact, the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name.

(4) The advertisement shall not feature inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation.

(5) The advertisement shall not designate a drug or ingredient by a proprie-

tary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.

(b) (1) If an advertisement for a prescription drug bears a proprietary name or designation for the drug or any ingredient thereof, the established name, if such there be, corresponding to such proprietary name or designation shall accompany such proprietary name or designation each time it is featured in the advertisement for the drug; but, except as provided below in this subparagraph, the established name need not be used with the proprietary name or designation in the running text of the advertisement. On any page of an advertisement in which the proprietary name or designation is not featured but is used in the running text, the established name shall be used at least once in the running text in association with such proprietary name or designation and in the same type size used in the running text: *Provided, however,* That if the proprietary name or designation is used in the running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such running text. If any advertisement includes a column with running text containing detailed information as to composition, prescribing, side effects, or contraindications and the proprietary name or designation is used in such column but is not featured above or below the column, the established name shall be used at least once in such column of running text in association with such proprietary name or designation and in the same type size used in such column of running text: *Provided, however,* That if the proprietary name or designation is used in such column of running text in larger size type, the established name shall be used at least once in association with, and in type at least half as large as the type used for, the most prominent presentation of the proprietary name or designation in such column of running text. Where the established name is required to accompany or to be used in association with the proprietary name or designation, the established name shall be placed in direct conjunction with the proprietary name or designation, and the relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as "brand of" preceding the established name, by brackets surrounding the established name, or by other suitable means.

(2) The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

(c) In the case of a prescription drug containing two or more active ingredients, if the advertisement bears a proprietary name or designation for such mixture and there is no established name corresponding to such proprietary name or designation, the quantitative ingredient information required in the advertisement by section 502(n) of the act shall be placed in direct conjunction with the most prominent display of the proprietary name or designation. The prominence of the quantitative ingredient information shall bear a reasonable relationship to the prominence of the proprietary name.

(d) (1) If the advertisement employs one proprietary name or designation to refer to a combination of active ingredients present in more than one preparation (the individual preparations differing from each other as to quantities of active ingredients and/or the form of the finished preparation) and there is no established name corresponding to such proprietary name or designation, a listing showing the established names of the active ingredients shall be placed in direct conjunction with the most prominent display of such proprietary name or designation. The prominence of this listing of active ingredients shall bear a reasonable relationship to the prominence of the proprietary name and the relationship between such proprietary name or designation, and the listing of active ingredients shall be made clear by use of such phrase as "brand of", preceding the listing of active ingredients.

(2) The advertisement shall prominently display the name of at least one specific dosage form and shall have the quantitative ingredient information required by section 502(n) of the act in direct conjunction with such display. If other dosage forms are listed in the advertisement, the quantitative ingredient information for such dosage forms shall appear in direct conjunction and in equal prominence with the most prominent listing of the names of such dosage forms.

(e) True statement of information in brief summary relating to side effects, contraindications, and effectiveness:

(1) *When required.* All advertisements for any prescription drug ("prescription drug" as used in this section means drugs defined in section 503(b)(1) of the act and § 201.105, applicable to drugs for use by man and veterinary drugs, respectively), except advertisements described in paragraph (e)(2) of this section, shall present a true statement of information in brief summary relating to side effects, contraindications (when used in this section "side effects, contraindications" include side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc.) and effectiveness. Advertisements broadcast through media such as radio, television, or telephone communications systems shall include information relating to the major side effects and contraindications of the advertised drugs in the audio or audio and visual parts of the presentation and unless adequate provision is made for dissemination of the approved or permitted package labeling in connection with the broadcast presentation shall contain a brief summary of all necessary information related to side effects and contraindications.

(2) *Exempt advertisements.* The following advertisements are exempt from the requirements of paragraph (e)(1) of this section under the conditions specified:

(i) *Reminder advertisements.* Reminder advertisements if they contain only the properietary or trade name of a drug (which necessitates declaring the established name, if any, and furnishing the formula showing quantitatively each ingredient of the drug to the extent required for labels) and, optionally, information relating to dosage form, quantity of package contents, price, the name and address of the manufacturer, packer, or distributor or other written, printed, or graphic matter containing no representation or suggestion relating to the advertised drug: *Provided, however,* That if the Commissioner finds that there is evidence of significant incidence of fatalities or serious damage associated with the use of a particular prescription drug, he may notify the manufacturer, packer, or distributor of the drug by mail that this exemption does not apply to such drug by reason of such finding: *And provided, however,* That reminder advertisements are not permitted for a drug for which an announcement has been published pursuant to a review of the labeling claims for the drug by the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, and for which no claim has been evaluated as higher than "possibly effective." If the Commissioner finds the circumstances are such that a reminder advertisement may be misleading to prescribers of drugs subject to NAS–NRC evaluation such advertisements will not be allowed and the manufacturer, packer, or distributor will be notified either in the publication of the conclusions on the effectiveness of the drug or by letter.

(ii) *Advertisements of bulk-sale drugs.* Advertisements of bulk-sale drugs that promote sale of the drug in bulk packages in accordance with the practice of the trade solely to be processed, manufactured, labeled, or repackaged in substantial quantities and that contain no claims for the therapeutic safety or effectiveness of the drug.

(iii) *Advertisements of prescription-compounding drugs.* Advertisements of prescription-compounding drugs that promote sale of a drug for use as a prescription chemical or other compound for use by registered pharmacists in compounding prescriptions if the drug otherwise complies with the conditions for the labeling exemption contained in § 201.120 and the advertisement contains no claims for the therapeutic safety or effectiveness of the drug.

(3) *Scope of information to be included; applicability to the entire advertisement.* (i) The requirement of a true statement of information relating

to side effects, contraindications, and effectiveness applies to the entire advertisement. Untrue or misleading information in any part of the advertisement will not be corrected by the inclusion in another distinct part of the advertisement of a brief statement containing true information relating to side effects, contraindications, and effectiveness of the drug. If any part or theme of the advertisement would make the advertisement false or misleading by reason of the omission of appropriate qualification or pertinent information, that part or theme shall include the appropriate qualification or pertinent information, which may be concise if it is supplemented by a prominent reference on each page to the presence and location elsewhere in the advertisement of a more complete discussion of such qualification or information.

(ii) The information relating to effectiveness is not required to include information relating to all purposes for which the drug is intended but may optionally be limited to a true statement of the effectiveness of the drug for the selected purpose(s) for which the drug is recommended or suggested in the advertisement. The information relating to effectiveness shall include specific indications for use of the drug for purposes claimed in the advertisement; for example, when an advertisement contains a broad claim that a drug is an antibacterial agent, the advertisement shall name a type or types of infections and microorganisms for which the drug is effective clinically as specifically as required, approved, or permitted in the drug package labeling.

(iii) The information relating to side effects and contraindications shall disclose each specific side effect and contraindication (which include side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc.; see paragraph (e)(1) of this section) contained in required, approved, or permitted labeling for the advertised drug dosage form(s): *Provided, however,*

(*a*) The side effects and contraindications disclosed may be limited to those pertinent to the indications for which the drug is recommended or suggested in the advertisement to the extent that such limited disclosure has previously been approved or permitted in drug labeling conforming to the provisions of §§ 201.100 or 201.105; and

(*b*) The use of a single term for a group of side effects and contraindications (for example, "blood dyscrasias" for disclosure of "leukopenia," "agranulocytosis," and "neutropenia") is permitted only to the extent that the use of such a single term in place of disclosure of each specific side effect and contraindication has been previously approved or permitted in drug labeling conforming to the provisions of §§ 201.100 or 201.105.

(4) *Substance of information to be included in brief summary.* (i) (*a*) An advertisement for a prescription drug covered by a new-drug application approved pursuant to section 505 of the act after October 10, 1962 or section 512 of the act after August 1, 1969, or any approved supplement thereto, shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement. The advertisement shall present information from labeling required, approved, or permitted in a new-drug application relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

(*b*) If a prescription drug was covered by a new-drug application or a supplement thereto that became effective prior to October 10, 1962, an advertisement may recommend or suggest:

(*1*) Uses contained in the labeling accepted in such new-drug application and any effective, approved, or permitted supplement thereto.

(*2*) Additional uses contained in labeling in commercial use on October 9, 1962, to the extent that such uses did not cause the drug to be an unapproved "new drug" as "new drug" was defined in section 201(p) of the act as then in force, and to the extent that such uses would be permitted were the drug subject to paragraph (e)(4)(iii) of this section.

(*3*) Additional uses contained in labeling in current commercial use to the extent that such uses do not cause the drug to be an unapproved "new drug" as defined in section 201(p) of the act as amended or a "new animal drug" as defined in section 201(w) of the act as amended.

The advertisement shall present information from labeling required, approved, or permitted in a new-drug application relating to each specific side effect and contraindication in such labeling that relates to the uses of the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

(ii) An advertisement for a prescription drug subject to certification under section 507 or 512 of the act shall not recommend or suggest any use that is not in the labeling covered by the certification or the applicable certification regulations or regulations providing for exemption from certification. The advertisement shall present information from such labeling covered by the certification or the applicable certification regulations or regulations providing for exemption from certification, relating to each specific side effect and contraindication in such labeling and such regulations for the advertised drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

(iii) In the case of an advertisement for a prescription drug other than a drug the labeling of which causes it to be an unapproved "new drug" and other than drugs covered by paragraph (e)(4)(i) and (ii) of this section, an advertisement may recommend and suggest the drug only for those uses contained in the labeling thereof:

(*a*) For which the drug is generally recognized as safe and effective among experts qualified by scientific training and experience to evaluate the safety and effectiveness of such drugs; or

(*b*) For which there exists substantial evidence of safety and effectiveness, consisting of adequate and well-controlled investigations, including clinical investigations (as used in this section "clinical investigations," "clinical experience," and "clinical significance" mean in the case of drugs intended for administration to man, investigations, experience, or significance in humans, and in the case of drugs intended for administration to other animals, investigations, experience, or significance in the specie or species for which the drug is advertised), by experts qualified by scientific training and experience to evaluate the safety and effectiveness of the drug involved, on the basis of which it can fairly and responsibly be concluded by such experts that the drug is safe and effective for such uses; or

(*c*) For which there exists substantial clinical experience (as used in this section this means substantial clinical experience adequately documented in medical literature or by other data (to be supplied to the Food and Drug Administration, if requested)), on the basis of which it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective for such uses; or

(*d*) For which safety is supported under any of the preceding clauses in paragraph (e)(4)(iii) (*a*), (*b*), and (*c*) of this section and effectiveness is supported under any other of such clauses.

The advertisement shall present information relating to each specific side effect and contraindication that is required, approved, or permitted in the package labeling by §§ 201.100 or 201.105 of this chapter of the drug dosage form(s) or shall otherwise conform to the provisions of paragraph (e)(3)(iii) of this section.

(5) *"True statement" of information.* An advertisement does not satisfy the requirement that it present a "true statement" of information in brief summary relating to side effects, contraindications, and effectiveness if:

(i) It is false or misleading with respect to side effects, contraindications, or effectiveness; or

(ii) It fails to present a fair balance between information relating to side effects and contraindications and information relating to effectiveness of the drug in that the information relating to effectiveness is presented in greater scope, depth, or detail than is required by section 502(n) of the act and this information is not fairly balanced by a presentation of a summary of true information relating to side effects and contraindications of the drug; *Provided, however,* That no advertisement shall be considered to be in violation of this section if the presentation of true information relating to side effects and contraindications is comparable in depth and de-

tail with the claims for effectiveness or safety.

(iii) It fails to reveal facts material in the light of its representations or material with respect to consequences that may result from the use of the drug as recommended or suggested in the advertisement.

(6) *Advertisements that are false, lacking in fair balance, or otherwise misleading.* An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act, among other reasons, if it:

(i) Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients (as used in this section "patients" means humans and in the case of veterinary drugs, other animals), safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience (as described in paragraph (e)(4)(iii) (*b*) and (*c*) of this section) whether or not such representations are made by comparison with other drugs or treatments, and whether or not such a representation or suggestion is made directly or through use of published or unpublished literature, quotations, or other references.

(ii) Contains a drug comparison that represents or suggests that a drug is safer or more effective than another drug in some particular when it has not been demonstrated to be safer or more effective in such particular by substantial evidence or substantial clinical experience.

(iii) Contains favorable information or opinions about a drug previously regarded as valid but which have been rendered invalid by contrary and more credible recent information, or contains literature references or quotations that are significantly more favorable to the drug than has been demonstrated by substantial evidence or substantial clinical experience.

(iv) Contains a representation or suggestion that a drug is safer than it has been demonstrated to be by substantial evidence or substantial clinical experience, by selective presentation of information from published articles or other references that report no side effects or minimal side effects with the drug or otherwise selects information from any source in a way that makes a drug appear to be safer than has been demonstrated.

(v) Presents information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does.

(vi) Contains references to literature or studies that misrepresent the effectiveness of a drug by failure to disclose that claimed results may be due to concomitant therapy, or by failure to disclose the credible information available concerning the extent to which claimed results may be due to placebo effect (information concerning placebo effect is not required unless the advertisement promotes the drug for use by man).

(vii) Contains favorable data or conclusions from nonclinical studies of a drug, such as in laboratory animals or in vitro, in a way that suggests they have clinical significance when in fact no such clinical significance has been demonstrated.

(viii) Uses a statement by a recognized authority that is apparently favorable about a drug but fails to refer to concurrent or more-recent unfavorable data or statements from the same authority on the same subject or subjects.

(ix) Uses a quote or paraphrase out of context to convey a false or misleading idea.

(x) Uses literature quotations or references that purport to support an advertising claim but in fact do not support the claim or have relevance to the claim.

(xi) Uses literature, quotations, or references for the purpose of recommending or suggesting conditions of drug use that are not approved or permitted in the drug package labeling.

(xii) Offers a combination of drugs for the treatment of patients suffering from a condition amenable to treatment by any of the components rather than limiting the indications for use to patients for whom concomitant therapy as provided by the fixed combination drug is indicated, unless such condition is included in the uses permitted under paragraph (e)(4) of this section.

(xiii) Uses a study on normal individuals without disclosing that the subjects were normal, unless the drug is intended for use on normal individuals.

(xiv) Uses "statistics" on numbers of patients, or counts of favorable results or side effects, derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such "statistics" are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case.

(xv) Uses erroneously a statistical finding of "no significant difference" to claim clinical equivalence or to deny or conceal the potential existence of a real clinical difference.

(xvi) Uses statements or representations that a drug differs from or does not contain a named drug or category of drugs, or that it has a greater potency per unit of weight, in a way that suggests falsely or misleadingly or without substantial evidence or substantial clinical experience that the advertised drug is safer or more effective than such other drug or drugs.

(xvii) Uses data favorable to a drug derived from patients treated with dosages different from those recommended in approved or permitted labeling if the drug advertised is subject to section 505, 507, or 512 of the act, or, in the case of other drugs, if the dosages employed were different from those recommended in the labeling and generally recognized as safe and effective. This provision is not intended to prevent citation of reports of studies that include some patients treated with dosages different from those authorized, if the results in such patients are not used.

(xviii) Uses headline, subheadline, or pictorial or other graphic matter in a way that is misleading.

(xix) Represents or suggests that drug dosages properly recommended for use in the treatment of certain classes of patients or disease conditions are safe and effective for the treatment of other classes of patients or disease conditions when such is not the case.

(xx) Presents required information relating to side effects or contraindications by means of a general term for a group in place of disclosing each specific side effect and contraindication (for example employs the term "blood dyscrasias" instead of "leukopenia," "agranulocytosis," "neutropenia," etc.) unless the use of such general term conforms to the provisions of paragraph (e)(3)(iii) of this section.

Provided, however, That any provision of this paragraph shall be waived with respect to a specified advertisement as set forth in a written communication from the Food and Drug Administration on a petition for such a waiver from a person who would be adversely affected by the enforcement of such provision on the basis of a showing that the advertisement is not false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act. A petition for such a waiver shall set forth clearly and concisely the petitioner's interest in the advertisement, the specific provision of this paragraph from which a waiver is sought, a complete copy of the advertisement, and a showing that the advertisement is not false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act.

(7) *Advertisements that may be false, lacking in fair balance, or otherwise misleading.* An advertisement may be false, lacking in fair balance, or otherwise misleading or otherwise violative of section 502(n) of the act if it:

(i) Contains favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions.

(ii) Uses the concept of "statistical significance" to support a claim that has not been demonstrated to have clinical significance or validity, or fails to reveal the range of variations around the quoted average results.

(iii) Uses statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations.

(iv) Uses tables or graphs to distort or misrepresent the relationships, trends, differences, or changes among the variables or products studied; for example, by failing to label abscissa and ordinate

so that the graph creates a misleading impression.

(v) Uses reports or statements represented to be statistical analyses, interpretations, or evaluations that are inconsistent with or violate the established principles of statistical theory, methodology, applied practice, and inference, or that are derived from clinical studies the design, data, or conduct of which substantially invalidate the application of statistical analyses, interpretations, or evaluations.

(vi) Contains claims concerning the mechanism or site of drug action that are not generally regarded as established by scientific evidence by experts qualified by scientific training and experience without disclosing that the claims are not established and the limitations of the supporting evidence.

(vii) Fails to provide sufficient emphasis for the information relating to side effects and contraindications, when such information is contained in a distinct part of an advertisement, because of repetition or other emphasis in that part of the advertisement of claims for effectiveness or safety of the drug.

(viii) Fails to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis.

(ix) Fails to provide adequate emphasis (for example, by the use of color scheme, borders, headlines, or copy that extends across the gutter) for the fact that two facing pages are part of the same advertisement when one page contains information relating to side effects and contraindications.

(x) In an advertisement promoting use of the drug in a selected class of patients (for example, geriatric patients or depressed patients), fails to present with adequate emphasis the significant side effects and contraindications or the significant dosage considerations, when dosage recommendations are included in an advertisement, especially applicable to that selected class of patients.

(xi) Fails to present on a page facing another page (or on another full page) of an advertisement on more than one page, information relating to side effects and contraindications when such information is in a distinct part of the advertisement.

(xii) Fails to include on each page or spread of an advertisement the information relating to side effects and contraindications or a prominent reference to its presence and location when it is presented as a distinct part of an advertisement.

(xiii) Contains information from published or unpublished reports or opinions falsely or misleadingly represented or suggested to be authentic or authoritative.

(f) through (i) [Reserved]

(j)(1) No advertisement concerning a particular prescription drug may be disseminated without prior approval by the Food and Drug Administration if:

(i) The sponsor or the Food and Drug Administration has received information that has not been widely publicized in medical literature that the use of the drug may cause fatalities or serious damage;

(ii) The Commissioner (or in his absence the officer acting as Commissioner), after evaluating the reliability of such information, has notified the sponsor that the information must be a part of the advertisements for the drug; and

(iii) The sponsor has failed within a reasonable time as specified in such notification to present to the Food and Drug Administration a program, adequate in light of the nature of the information, for assuring that such information will be publicized promptly and adequately to the medical profession in subsequent advertisements.

If the Commissioner finds that the program presented is not being followed, he will notify the sponsor that prior approval of all advertisements for the particular drug will be required. Nothing in this paragraph is to be construed as limiting the Commissioner's or the Secretary's rights, as authorized by law, to issue publicity, to suspend any new-drug application, to decertify any antibiotic, or to recomend any regulatory action.

(2) Within a reasonable time after information concerning the possibility that a drug may cause fatalities or serious damage has been widely publicized in medical literature, the Food and Drug Administration shall notify the sponsor of the drug by mail that prior approval of advertisements for the drug is no longer necessary.

(3) Dissemination of an advertisement not in compliance with this paragraph shall be deemed to be an act that causes the drug to be misbranded under section 502(n) of the act.

(4) Any advertisement may be submitted to the Food and Drug Administration prior to publication for comment. If the advertiser is notified that the submitted advertisement is not in violation and, at some subsequent time, the Food and Drug Administration changes its opinion, the advertiser will be so notified and will be given a reasonable time for correction before any regulatory action is taken under this section. Notification to the advertiser that a proposed advertisement is or is not considered to be in violation shall be in written form.

(k) An advertisement issued or caused to be issued by the manufacturer, packer, or distributor of the drug promoted by the advertisement and which is not in compliance with section 502(n) of the act and the applicable regulations thereunder shall cause stocks of such drug in possession of the person responsible for issuing or causing the issuance of the advertisement, and stocks of the drug distributed by such person and still in the channels of commerce, to be misbranded under section 502(n) of the act.

(l) (1) Advertisements subject to section 502(n) of the act include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.

(2) Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the "Physicians Desk Reference") for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act.

PART 207—REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

Subpart A—Definitions

Sec.
207.3 Definitions.

Subpart B—Procedures for Domestic Drug Establishments

207.20 Who must register and submit a drug list.
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207.22 How and where to register and list drugs.
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Subpart C—Procedures for Foreign Drug Establishments

207.40 Drug listing requirements for foreign drug establishments.

Subpart D—Exemptions

207.65 Exemptions for domestic establishments.

AUTHORITY: Secs. 201, 502, 505, 506, 507; 510, 512, 701(a), 704; 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055, 1057 as amended; 21 U.S.C. 321, 352, 355, 356, 357, 360, 360b, 371(a), 374; sec. 351, 58 Stat. 702 as amended; 42 U.S.C. 262; the Drug Listing Act of 1972, Pub. L. 92–387; 86 Stat. 559–562 (21 U.S.C. 360 note) unless otherwise noted.

Subpart A—Definitions

§ 207.3 Definitions.

(a) The term "act" means the Federal Food, Drug, and Cosmetic Act approved June 25, 1938 (52 Stat. 1040 et seq., as amended, 21 U.S.C. 301–392).

(b) "Establishment" means a place of business under one management at one general physical location. The term includes, among others, independent laboratories that engage in control activities for registered drug establishment (e.g.,

"consulting" laboratories), manufacturers of medicated feeds and of vitamin products that are "drugs" within the meaning of section 201(g) of the act, human blood donor centers, and animal facilities used for the production or control testing of licensed biologicals.

(c) Manufacture, preparation, propagation, compounding, or processing of a drug or drugs means the making by chemical, physical, biological, or other procedures of any articles which meet the definition of drugs as defined in section 201(g) of the act, and including manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package in furtherance of the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.

(d) "Commercial distribution" means any distribution of a human drug except pursuant to the investigational use provisions of § 312.1 of this chapter, and any distribution of an animal drug or an animal feed bearing or containing an animal drug for noninvestigational uses but does not include internal or interplant transfer of a bulk drug substance between registered domestic establishments within the same parent, subsidiary, and/or affiliate company.

(e) "Representative sampling of advertisements" means typical advertising material (excluding labeling as determined in § 202.1(l)(2) of this chapter) which gives a balanced picture of the promotional claims being used for the drug (e.g., if more than one medical journal advertisement is used but their promotional content is essentially identical, only one need be submitted).

(f) "Representative sampling of any other labeling" as used in this part means typical labeling material (excluding labels and package inserts) which gives a balanced picture of the promotional claims being used for the drug (e.g., if more than one brochure is used but their promotional content is essentially identical, only one need be submitted).

(g) "Any material change" includes but is not limited to any change in the name of the drug, in the quantity or identity of the active ingredient(s) or in the quantity or identity of the inactive ingredient(s) where quantitative listing of all ingredients is required pursuant to § 207.31(a)(2), any significant change in the labeling of a prescription drug, and any significant change in the label or package insert of an over-the-counter drug. Changes that are not significant include changes in arrangement or printing or changes of an editorial nature.

(h) "Bulk drug substance" means any substance that is represented for use in a drug and when used in the manufacturing, processing, or packaging of a drug becomes an active ingredient or a finished dosage form of such drug, but does not include intermediates used in the synthesis of such substances.

(i) "Advertising" and "labeling" include the promotional material described in § 202.1(l)(1) and (2) of this chapter respectively.

(j) The definitions and interpretations contained in sections 201 and 510 of the act shall be applicable to such terms when used in this Part 207.

Subpart B—Procedures for Domestic Drug Establishments

§ 207.20 Who must register and submit a drug list.

(a) Owners or operators of all drug establishments, not exempt under section 510(g) of the act or Subpart D of this Part 207, that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register and to submit a list of every drug in commercial distribution (except that listing information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments). Such owners or operators are required to register and to submit a list of every drug in commercial distribution (except that listing information may be submitted by the parent, subsidiary, and/or affiliate company for all establishments when operations are conducted at more than one establishment and there exists joint ownership and control among all the establishments), whether or not the output of such establishment or any particular drug so listed enters interstate commerce, except that drug listing is not required at this time for the manufacturing, preparation, propagation, compounding, or processing of an animal feed (including a feed concentrate, a feed supplement, and a complete animal feed) bearing or containing an animal drug.

(b) Distributors which are not otherwise required to register under section 510 of the act, may submit drug listing information directly to the Food and Drug Administration for those drugs which they distribute under their own label or trade name but which are manufactured, prepared, propagated, compounded, or processed by a registered establishment. Where drug listing information is submitted by a distributor, the registration number of the drug establishment which manufactured, prepared, propagated, compounded, or processed the drug shall be included for each drug listed. If a distributor does not elect to obtain a "Labeler Code" the registered establishment shall submit the drug listing information. Such submissions and requests for Labeler Codes shall be made on Form FD-2658 (Registered Establishments' Report of Private Label Distributors). All distributors submitting drug listing information to the Food and Drug Administration assume full responsibility for compliance with all of the requirements of this part. Each distributor at the time of each submission of drug listing information or updating as required under § 207.30 shall so certify to the registered establishment that such submission has been made by providing a signed copy of Form FD-2656 (Registration of Drug Establishment) to the registered establishment which manufactures, prepares, propagates, compounds, or processes the drug. The original of Form FD-2656 (Registration of Drug Establishment) showing such certification shall be submitted to the Food and Drug Administration. Such certification shall be accompanied by a list showing the National Drug Code number assigned to each drug product by the distributor.

(c) Preparatory to engaging in the manufacture, preparation, propagation, compounding, or processing of a drug, owners or operators of establishments who are submitting new drug applications, new animal drug applications, Form FD-1800 (Medicated Feed Application), antibiotic Forms 5 and 6, or an establishment license application in order to manufacture biological products are required to register before the new drug application, new animal drug application, Form FD-1800, antibiotic Form 5 or 6, or establishment license application is approved.

(d) No registration fee is required. Registration and listing do not constitute an admission or agreement or determination that a product is a "drug" within the meaning of section 201(g) of the act.

§ 207.21 Times for registration and drug listing.

The owner or operator of an establishment entering into an operation defined in § 207.3(c) shall register such establishment within 5 days after the beginning of such operation and submit a list of every drug in commercial distribution at that time. If the owner or operator of the establishment defined in § 207.3(c) has not previously entered into such operation, registration shall follow within 5 days after the submission of a new drug application, new animal drug application, Form FD-1800, antibiotic Form 5 or 6, or an establishment license application in order to manufacture biological products. Owners or operators of all establishments so engaged shall register annually between November 15 and December 31 and shall update their drug listing information every June and December.

§ 207.22 How and where to register and list drugs.

(a) The first registration of an establishment shall be on Form FD-2656 (Registration of Drug Establishment) obtainable on request from the Department of Health, Education, and Welfare, Food and Drug Administration, Bureau of Drugs, Registration Section, 5600 Fishers Lane, Rockville, MD 20852, or from Food and Drug Administration district offices. Subsequent annual registration shall also be accomplished on Form FD-2656 (Registration of Drug Establishment), which will be furnished by the Food and Drug Administration before November 15 of each year to estab-

lishments whose drug registration for that year was validated pursuant to § 207.35. The completed form shall be mailed to the above address before December 31 of that year.

(b) The first list of drugs and subsequent June and December updatings shall be on Form FD–2657 (Drug Product Listing), obtainable upon request as described in paragraph (a) of this section. In lieu of Form FD–2657 (Drug Product Listing), tapes for computer inputs may be submitted if equivalent in all elements of information as specified in Form FD–2657 (Drug Product Listing). All formats proposed for such use will require initial review and approval by the Food and Drug Administration.

§ 207.25 Information required in registration and drug listing.

(a) Form FD–2656 (Registration of Drug Establishment) requires furnishing or confirming information required by the act. This information includes the name and street address of the drug establishment, including post office ZIP code; all trade names used by the establishment; the kind of ownership or operation (that is, individually owned partnership, or corporation); and the name of the owner or operator of such establishment. The term "name of the owner or operator" shall include in the case of a partnership the name of each partner, and in the case of a corporation the name and title of each corporate officer and director and the name of the State of incorporation. The information required shall be given separately for each establishment, as defined in § 207.3(b).

(b) Form FD–2657 (Drug Product Listing) requires furnishing information required by the act as follows:

(1) A list of drugs, including bulk drug substances and drug premixes for use in the manufacture of animal feeds as well as finished dosage forms, by established name as defined in section 502(e) of the act and by proprietary name, which are being manufactured, prepared, propagated, compounded, or processed for commercial distribution and which have not been included in any list previously submitted on Form FD–2657 (Drug Product Listing) or in conjunction with the Food and Drug Administration voluntary inventory on Form FD–2422 (Survey Report of Marketed Drugs), or Form FD–2250 (National Drug Code Directory Input).

(2) For each drug so listed which is regarded by the registrant as subject to section 505, 506, 507, or 512 of the act, the new drug application number, abbreviated new drug application number, new animal drug application number, or Form 5 or Form 6 number, and a copy of all current labeling, except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement.

(3) For each drug so listed which is regarded by the registrant as subject to section 351 of the Public Health Service Act, the license number of the manufacturer.

(4) For each human drug so listed which is subject to section 503(b)(1) of the act and regarded by the registrant as not subject to section 505, 506, or 507 of the act or 351 of the Public Health Service Act, and which is not manufactured by a registered blood bank, a copy of all current labeling except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement and a representative sampling of advertisements.

(5) For each human over-the-counter drug or each animal drug so listed which is regarded by the registrant as not subject to section 505, 506, 507, or 512 of the act, or 351 of the Public Health Service Act, a copy of the label except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement; package insert, and a representative sampling of any other labeling.

(6) For each prescription or over-the-counter drug so listed which is regarded by the registrant as not subject to section 505, 506, 507, or 512 of the act, or 351 of the Public Health Service Act, and which is not manufactured by a registered blood bank, quantitative listing of the active ingredient(s). If the drug is in unit dosage form the statements of the quantity of ingredient shall express the amount, not the percent, of such ingredient in each such unit, unless the quantitative listing is expressed as a percentage in the official compendium. If the drug is not in unit dosage form, the statement of the quantity of an ingredient shall express the amount, not the percent, of such ingredient in a specific unit of weight or measure of the drug unless the quantitative listing is expressed as a percentage in the official compendium, except that for drug premixes for use in the manufacture of animal feeds such ingredient which is not an antibiotic may be expressed in terms of percent. If a drug premix has been assigned a Product Code as provided for in § 207.35(b)(2)(iii), the quantitative listing of ingredients may be limited to each variation of level of active drug ingredient.

(7) For each drug listed, the registration number of every drug establishment within the parent company at which it is manufactured, prepared, propagated, compounded, or processed.

(8) For each drug so listed, the National Drug Code (NDC) number. If no NDC Labeler Code number has been assigned, the Product Code and Package Code will be included and a Labeler Code will be assigned as described in § 207.35(b)(2)(i).

§ 207.26 Amendments to registration.

Changes in individual ownership, corporate or partnership structure location or drug-handling activity, shall be submitted by Form FD–2656 (Registration of Drug Establishment) as amendment to registration within 5 days of such changes. Changes in the names of officers and directors of the corporations do not require such amendment but must be shown at time of annual registration.

§ 207.30 Updating drug listing information.

(a) After submission of the initial drug listing information, every person who is required to list drugs pursuant to § 207.20 shall submit on Form FD–2657 (Drug Product Listing) during each subsequent June and December, or at the discretion of the registrant at the time the change occurs, the following information:

(1) A list of each drug introduced by the registrant for commercial distribution which has not been included in any list previously submitted. All of the information required by § 207.25(b) shall be provided for each such drug.

(2) A list of each drug formerly listed pursuant to § 207.25(b) for which commercial distribution has been discontinued, including for each drug so listed the NDC number, the identity by established name and proprietary name, and date of discontinuance. It is requested but not required that the reason for discontinuance of distribution be included with this information.

(3) A list of each drug for which a notice of discontinuance was submitted pursuant to paragraph (a)(2) of this section and for which commercial distribution has been resumed, including for each drug so listed the NDC number, the identity by established name as defined in section 502(e) of the act and by any proprietary name, the date of resumption, and any other information required by § 207.25(b) not previously submitted.

(4) Any material change in any information previously submitted.

(b) When no changes have occurred since the previously submitted list, no report is required.

§ 207.31 Additional drug listing information.

(a) In addition to the information routinely required by §§ 207.25 and 207.30, the Commissioner may require submission of the following information by letter or by FEDERAL REGISTER notice:

(1) For a particular drug so listed which is subject to section 503(b)(1) of the act and regarded by the registrant as not subject to section 505, 506, or 507 of the act, upon request made by the Commissioner for good cause, a copy of all advertisements.

(2) For a particular drug product so listed which is regarded by the registrant as not subject to section 505, 506, 507, or 512 of the act, upon a finding by the Commissioner that it is necessary to carry out the purposes of the act, a quantitative listing of all ingredients.

(3) For a particular drug product upon request by the Commissioner, a brief statement of the basis upon which the registrant has determined that the drug product is not subject to section 505, 506, 507, or 512 of the act.

(4) For each registrant, upon a finding by the Commissioner that it is necessary to carry out the purposes of the act, a list of each listed drug product containing a particular ingredient.

(b) It is requested but not required that information concerning the quantity

of drug distributed be submitted in conjunction with the annual registration in the format prescribed in a section of Form FD–2656A (Optional Distribution Data), for each drug currently listed.

(c) It is requested but not required that a qualitative listing of the inactive ingredients be submitted for all listed drugs in the format prescribed in Form FD–2657 (Drug Product Listing).

(d) It is requested but not required that a quantitative listing of the active ingredients be submitted for all drugs listed which are subject to section 505, 506, 507, or 512 of the act or section 351 of the Public Health Service Act.

§ 207.35 Notification of registrant; drug establishment registration number and drug listing number.

(a) The Commissioner will provide to the registrant a validated copy of Form FD–2656 (Registration of Drug Establishment) as evidence of registration. This validated copy will be sent only to the location shown for the registering establishment. A permanent registration number will be assigned to each drug establishment registered in accordance with these regulations.

(b) A drug listing number will be assigned, using the National Drug Code numbering system, to each drug or class of drugs listed as follows:

(1) If a drug is already listed in the National Drug Code System or in the National Health Related Items Code System, the number will be the same as that assigned pursuant to those codes. A lead zero will be added by the Food and Drug Administration to the first three characters of the code, which identifies the manufacturer or distributor, to expand the "Labeler Code" segment to four characters. The National Drug Code, Product Code and Package Code configurations used to describe such drugs, or any new drugs added to the product line, will remain the same (i.e., a four-character Product Code and a two-character Package Code). Alphanumeric characters where already used in the Product Code and Package Code segments of the National Drug Code may be retained; however, these alphanumeric characters may be converted to all numeric digits. The manufacturer or distributor shall inform the Food and Drug Administration of such changes.

(2) If a registered establishment or distributor has not previously participated in the National Drug Code system, or in the National Health Related Items Code system, the National Drug Code numbering system will be used in assigning a number, as follows (only numerics will be used):

(i) The first five numeric characters of the 10-character code identify the manufacturer or distributor and are known as the Labeler Code. The Food and Drug Administration will expand the Labeler Code from five to six numeric characters when the available five-character code combinations are exhausted. These code numbers are assigned by the Food and Drug Administration and provided to the registrant along with the validated copy of Form FD–2656 (Registration of Drug Establishment). Any registered firm that does not have an assigned "Labeler Code" will be assigned one when registration and listing information is submitted.

(ii) The last five numeric characters of the 10-character code identify the drug and the trade package size and type. The segment which identifies the drug formulation is known as the Product Code and the segment which identifies the trade package size and type is known as the Package Code. The Product Code and the Package Code shall be assigned by the manufacturer or distributor prior to drug listing and included in Form FD–2657 (Drug Product Listing). Either of two methods may be used by the manufacturer or distributor in assigning the Product and Package Codes; a 3–2 Product-Package Code configuration (i.e., 542–12) or a 4–1 Product-Package Code configuration (i.e., 5421–2). Only one such Product-Package Code configuration may be used by a manufacturer or distributor with a given Labeler Code and this same configuration shall be used in assigning the Product-Package Codes for all drugs included in the drug listing. The manufacturer or distributor shall report to the Food and Drug Administration the Product-Package Code configuration he used in assigning these codes. Once a Product Code has been assigned to a specific drug, this same code may never again be used for any other drug regardless whether the drug has been discontinued.

(iii) If the drug formulation is a custom premix intended for use in the manufacture of an animal feed, a separate Product Code is required only for each variation of level of active drug ingredient.

(3) The NDC number is requested but not required to appear on all drug labels and in all drug labeling, including the label of any prescription drug container furnished to a consumer. If the NDC number is shown on a drug label it shall be placed as follows:

(i) The NDC number shall be placed prominently in the top third of the center panel of the label of the immediate container and of the outside container or wrapper if such there be.

(ii) The NDC number shall be preceded by the initials NDC, in a different color or different type style (font) than that used to print the number if the label is printed rather than typewritten, whenever it is used on a label or in labeling.

(iii) The Product-Package Code configuration shall be indicated and the segments of the number shall be separated by a dash (i.e., NDC 15643–542–12 or NDC 15643–5421–2).

(iv) All 10 characters shall appear and the leading zeros in any segment of the NDC number shall be shown: *Provided, however,* That when the NDC number is used for product identification by direct imprinting on dosage forms, leading zeros may be dropped from the Product Code segment of the NDC number.

(v) The placing of the assigned NDC number on a label or in labeling does not require the submission of a supplemental new drug application, supplemental new animal drug application, or supplemental antibiotic Form 5 or 6.

(4) If any material change occurs in product characteristics (including but not limited to a change in dosage form, active ingredient(s) or active ingredient(s) strength or concentration, route of administration, or product name, etc.) a new NDC number shall be assigned by the registrant to the new product version and the information submitted to the Food and Drug Administration. If a change in packaging only is involved the trade package code can be revised without the necessity of assigning a new product code segment, but the Food and Drug Administration shall be informed about the new trade package code and characteristics.

(c) Although registration and drug listing are required to engage in the drug activities described in § 207.20, validation of registration and the assignment of a drug listing number do not, in themselves, establish that the holder of the registration is legally qualified to deal in such drugs.

NOTE: The provisions of § 207.35(b)(3) shall not be effective until printing plates are revised or until July 1, 1975 (38 FR 27593).

§ 207.37 Inspection of registrations and drug listings.

(a) A copy of the Form FD–2656 (Registration of Drug Establishment) filed by the registrant will be available for inspection pursuant to section 510(f) of the act, at the Department of Health, Education, and Welfare, Food and Drug Administration, Bureau of Drugs, Registration Section, 5600 Fishers Lane, Rockville, MD 20852. In addition, there will be available for inspection at each of the Food and Drug Administration district offices the same information for firms within the geographical area of such district office. Upon request and receipt of a self-addressed stamped envelope, vertification of registration number, or location of a registered concern will be provided.

(1) The following information submitted pursuant to the drug listing requirements is illustrative of the type of information that will be available for public disclosure when it is compiled:

(i) A list of all drug products.

(ii) A list of all drug products broken down by labeled indications or pharmacological category.

(iii) A list of all drug products, broken down by manufacturer.

(iv) A list of a drug product's active ingredients.

(v) A list of drug products newly marketed or where marketing is resumed.

(vi) A list of drug products discontinued.

(vii) All labeling.

(viii) All advertising.

(ix) All data or information that has already become a matter of public knowledge.

(2) The following information submitted pursuant to the drug listing requirement is illustrative of the type of

information that will not be available for public disclosure:

(i) Any data or information submitted as the basis upon which it has been determined that a particular drug product is not subject to section 505, 506, 507, or 512 of the act.

(ii) A list of a drug product's inactive ingredients.

(iii) A list of drugs containing a particular ingredient.

(iv) *Provided,* That any of the above information will be available for public disclosure if it has already become a matter of public knowledge or if the Commissioner finds that confidentiality would be inconsistent with protection of the public health.

(b) Requests for information about registrations and drug listings should be directed to the Department of Health, Education, and Welfare, Food and Drug Administration, Bureau of Drugs, Registration Section, 5600 Fishers Lane, Rockville, MD 20852.

§ 207.39 Misbranding by reference to registration or to registration number.

Registration of a drug establishment or drug wholesaler or assignment of a registration number or assignment of a NDC number does not in any way denote approval of the firm or its products. Any representation that creates an impression of official approval because of registration or possession of registration number or NDC number is misleading and constitutes misbranding.

Subpart C—Procedures for Foreign Drug Establishments

§ 207.40 Drug listing requirements for foreign drug establishments.

(a) Every foreign drug establishment shall comply with the drug listing requirements contained in Subpart B of this part, unless exempt under Subpart D of this part, whether or not it is also registered.

(b) No drug may be imported from a foreign drug establishment into the United States except a drug imported or offered for import pursuant to the investigational use provisions of § 312.1 of this chapter, unless it is first the subject of a drug listing as required in Subpart B of this part. The drug listing information shall be in the English language.

(c) Foreign drug establishments shall submit as part of the drug listing, the name and address of the establishment and the name of the individual responsible for submitting drug listing information. Any changes in this information shall be reported to the Food and Drug Administration at the intervals specified for updating drug listing information in § 207.30(a).

Subpart D—Exemptions

§ 207.65 Exemptions for domestic establishments.

The following classes of persons are exempt from registration and drug listing in accordance with this Part 207 under the provisions of section 510(g), (1), (2), and (3) of the act, or because the Commissioner has found, under section 510(g)(4), that such registration is not necessary for the protection of the public health.

(a) Pharmacies that are operating under applicable local laws regulating dispensing of prescription drugs and that do not manufacture, prepare, propagate, compound, or process drugs for sale other than in the regular course of the practice of the profession of pharmacy including the business of dispensing and selling drugs at retail. The supplying by such pharmacies of prescription drugs to a practitioner licensed to administer such drugs for his use in the course of his professional practice or to other pharmacies to meet temporary inventory shortages are not acts which require such pharmacies to register.

(b) Hospitals, clinics, and public health agencies which maintain establishments in conformance with any applicable local laws regulating the practices of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs, other than human blood or blood products, upon prescription of practitioners licensed by law to administer such drug for patients under the care of such practitioners in the course of their professional practice.

(c) Practitioners who are licensed by law to prescribe or administer drugs and who manufacture, prepare, propagate, compound, or process drugs solely for use in the course of their professional practice.

(d) Persons who manufacture, prepare, propagate, compound, or process drugs solely for use in research, teaching, or chemical analysis and not for sale.

(e) Manufacturers of harmless inactive ingredients which are excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs, and who otherwise would not be required to register under the provisions of this Part 207.

(f) Any person who uses drugs to prepare feed for his own animals: *Provided,* That under the act and its regulations such person would not be required to hold an approved new animal drug application (or supplement thereto) or a Form FD–1800 in order to possess and use the drug.

(g) Any manufacturer of a virus, serum, toxin, or analogous product intended for treatment of domestic animals, who holds an unsuspended and unrevoked license issued by the Secretary of Agriculture under the animal virus-serum-toxin law of March 4, 1913 (37 Stat. 832; 21 U.S.C. 151 et seq.): *Provided,* That such exemption from registration shall apply only with respect to the manufacture of such animal virus, serum, toxin, or analogous product.

(h) Carriers, by reason of their receipt, carriage, holding, or delivery of drugs in the usual course of business as carriers.

(i) Persons who are engaged solely in the manufacture, preparation, propagation, compounding, or processing of a general purpose laboratory reagent (as described in § 328.10(d) of this chapter) intended for use in in vitro diagnostic procedures in the diagnosis of disease or in the determination of the state of health in order to cure, mitigate, treat, or prevent disease or its sequelae.

PART 210—CURRENT GOOD MANUFACTURING PRACTICES IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS: GENERAL

Sec.
210.3 Definitions.

AUTHORITY: Secs. 501, 701, 52 Stat. 1049–1050 as amended, 1055–1056 as amended (21 U.S.C. 351, 371).

§ 210.3 Definitions.

(a) As used in this part, "act" means the Federal Food, Drug, and Cosmetic Act, sections 201–902, 52 Stat. 1052 (21 U.S.C. 321–392) with all the amendments thereto.

(b) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in the regulations in this part.

(c) As used in this part:

(1) The term "medicated feed" means any "complete feed," "feed additive supplement," or "feed additive concentrate," as defined in § 121.200 of this chapter, which feed contains one or more drugs as defined in section 201(g) of the act. Medicated feeds are subject to §§ 225.1 through 225.115 of this chapter, inclusive.

(2) The term "medicated premix" means a substance that meets the definition in § 121.200 of this chapter for a "feed additive premix," except that it contains one or more drugs as defined in section 201(g) of the act and is intended for manufacturing use in the production of a medicated feed. Medicated premixes are subject to §§ 226.1 through 226.115 of this chapter, inclusive.

(d) As used in §§ 211.1 through 211.115 of this chapter, inclusive:

(1) The term "component" means any ingredient intended for use in the manufacture of drugs in dosage form, including those that may not appear in the finished product.

(2) The term "batch" means a specific quantity of a drug that has uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) The term "lot" means a batch or any portion of a batch of a drug or, in the case of a drug produced by a continuous process, an amount of drug produced in a unit of time or quantity in a manner that assures its uniformity, and in either case which is identified by a distinctive lot number and has uniform character and quality within specified limits.

(4) The terms "lot number" or "control number" mean any distinctive combination of letters or numbers, or both, from which the complete history of the manufacture, control, packaging, and distribution of a batch or lot of drug can be determined.

(5) The term "active ingredient" means any component which is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term shall include those components which may undergo chemical change in the manufacture of the drug and be present in the finished drug product in a modified form intended to furnish the specified activity or effect.

(6) The term "inactive ingredient" means any component other than an "active ingredient" present in a drug.

(7) The term "materials approval unit" means any organizational element having the authority and responsibility to approve or reject components, in-process materials, packaging components, and final products.

(8) The term "strength" means:

(i) The concentration of the drug substance (for example, w/w, w/v, or unit dose/volume basis) and/or

(ii) The potency, that is, the therapeutic activity of the drug substance as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

PART 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

AUTHORITY: Secs. 501, 701, 52 Stat. 1049–1050 as amended, 1055–1056 as amended (21 U.S.C. 351, 371).

Subpart A—General Provisions

§ 211.1 Finished pharmaceuticals; manufacturing practice.

(a) The criteria in §§ 211.20–211.115, inclusive, shall apply in determining whether the methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of a drug conform to or are operated or administered in conformity with current good manufacturing practice to assure that a drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics which it purports or is represented to possess as required by section 501(a)(2)(B) of the act.

(b) The regulations in this part permit the use of precision automatic, mechanical, or electronic equipment in the production and control of drugs when adequate inspection and checking procedures are used to assure proper performance.

§ 211.10 Personnel.

(a) The personnel responsible for directing the manufacture and control of the drug shall be adequate in number and background of education, training, and experience, or combination thereof, to assure that the drug has the safety, identity, strength, quality, and purity that it purports to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing or control operations they perform, the necessary training or experience, and adequate information concerning the reason for application of pertinent provisions of this part to their respective functions.

(b) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drugs shall be excluded from direct contact with drug products until the condition is corrected. All employees shall be instructed to report to supervisory personnel any conditions that may have such an adverse effect on drug products.

Subpart B—Construction and Maintenance of Facilities and Equipment

§ 211.20 Buildings.

Buildings shall be maintained in a clean and orderly manner and shall be of suitable size, construction, and location to facilitate adequate cleaning, maintenance, and proper operations in the manufacturing, processing, packing, labeling, or holding of a drug. The buildings shall:

(a) Provide adequate space for:

(1) Orderly placement of equipment and materials to minimize any risk of mixups between different drugs, drug components, in-process materials, packaging materials, or labeling, and to minimize the possibility of contamination.

(2) The receipt, storage, and withholding from use of components pending sampling, identification, and testing prior to release by the materials approval unit for manufacturing or packaging.

(3) The holding of rejected components prior to disposition to preclude the possibility of their use in manufacturing or packaging procedures for which they are unsuitable.

(4) The storage of components, containers, packaging materials, and labeling.

(5) Any manufacturing and processing operations performed.

(6) Any packaging or labeling operations.

(7) Storage of finished products.

(8) Control and production-laboratory operations.

(b) Provide adequate lighting, ventilation, and screening and, when necessary for the intended production or control purposes, provide facilities for adequate air-pressure, microbiological, dust, humidity, and temperature controls to:

(1) Minimize contamination of products by extraneous adulterants, including cross-contamination of one product by dust or particles of ingredients arising from the manufacture, storage, or handling of another product.

(2) Minimize dissemination of microorganisms from one area to another.

(3) Provide suitable storage conditions for drug components, in-process materials, and finished drugs in conformance with stability information as derived under § 211.60.

(c) Provide adequate locker facilities and hot and cold water washing facilities, including soap or detergent, air drier or single service towels, and clean toilet facilities near working areas.

(d) Provide an adequate supply of potable water (§ 1250.82 of this chapter) under continuous positive pressure in a plumbing system free of defects that could cause or contribute to contamination of any drug. Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent back-siphonage.

(e) Provide suitable housing and space for the care of all laboratory animals.

(f) Provide for safe and sanitary disposal of sewage, trash, and other refuse within and from the buildings and immediate premises.

§ 211.30 Equipment.

Equipment used for the manufacture, processing, packing, labeling, holding, testing, or control of drugs shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction, and location to facilitate cleaning, maintenance, and operation for its intended purpose. The equipment shall:

(a) Be so constructed that all surfaces that come into contact with a drug product shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug or its components beyond the official or other established requirements.

(b) Be so constructed that any substances required for operation of the equipment, such as lubricants or coolants, do not contact drug products so as to alter the safety, identity, strength, quality, or purity of the drug or its components beyond the official or other established requirements.

(c) Be constructed and installed to facilitate adjustment, disassembly cleaning and maintenance to assure the reliability of control procedures uniformity of production and exclusion from the drugs of contaminants from previous and current operations that might

affect the safety, identity, strength, quality, or purity of the drug or its components beyond the official or other established requirements.

(d) Be of suitable type, size, and accuracy for any testing, measuring, mixing, weighing, or other processing or storage operations.

Subpart C—Product Quality Control

§ 211.40 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the drugs produced have the safety, identity, strength, quality, and purity they purport to possess:

(a) Each significant step in the process, such as the selection, weighing, and measuring of components, the addition of ingredients during the process, weighing and measuring during various stages of the processing, and the determination of the finished yield, shall be performed by a competent and responsible individual and checked by a second competent and responsible individual; or if such steps in the processing are controlled by precision automatic, mechanical, or electronic equipment, their proper performance is adequately checked by one or more competent and responsible individuals. The written record of the significant steps in the process shall be identified by the individual performing these tests and by the individual charged with checking these steps. Such identifications shall be recorded immediately following the completion of such steps.

(b) All containers, lines, and equipment used during the production of a batch of a drug shall be properly identified at all times to accurately and completely indicate their contents and, when necessary, the stage of processing of the batch.

(c) To minimize contamination and prevent mixups, equipment, utensils, and containers shall be thoroughly and appropriately cleaned and properly stored and have previous batch identification removed or obliterated between batches or at suitable intervals in continuous production operations.

(d) Appropriate precautions shall be taken to minimize microbiological and other contamination in the production of drugs purporting to be sterile or which by virtue of their intended use should be free from objectionable microorganisms.

(e) Appropriate procedures shall be established to minimize the hazard of cross-contamination of any drugs while being manufactured or stored.

(f) To assure the uniformity and integrity of products, there shall be adequate in-process controls, such as checking the weights and disintegration times of tablets, the adequacy of mixing, the homogeneity of suspensions, and the clarity of solutions. In-process sampling shall be done at appropriate intervals using suitable equipment.

(g) Representative samples of all dosage form drugs shall be tested to determine their conformance with the specifications for the product before distribution.

(h) Procedures shall be instituted whereby review and approval of all production and control records, including packaging and labeling, shall be made prior to the release or distribution of a batch. A thorough investigation of any unexplained discrepancy or the failure of a batch to meet any of its specifications shall be undertaken whether or not the batch has already been distributed. This investigation shall be undertaken by a competent and responsible individual and shall extend to other batches of the same drug and other drugs that may have been associated with the specific failure. A written record of the investigation shall be made and shall include the conclusions and followup.

(i) Returned goods shall be identified as such and held. If the conditions under which returned goods have been held, stored, or shipped prior to or during their return, or the condition of the product, its container, carton, or labeling as a result of storage or shipping, cast doubt on the safety, identity, strength, quality, or purity of the drug, the returned goods shall be destroyed or subjected to adequate examination or testing to assure that the material meets all appropriate standards or specifications before being returned to stock for warehouse distribution or repacking. If the product is neither destroyed nor returned to stock, it may be reprocessed provided the final product meets all its standards and specifications. Records of returned goods shall be maintained and shall indicate the quantity returned, date, and actual disposition of the product. If the reason for returned goods implicates associated batches, an appropriate investigation shall be made in accordance with the requirements of paragraph (h) of this section.

(j) Use of asbestos-containing or other fiber-releasing filters: (1) Filters used in the manufacture, processing or packaging of components of drug products for parenteral injection in humans shall not release fibers into such products. No asbestos-containing or other fiber-releasing filter may be used in the manufacture, processing or packaging of such products unless it is not possible to manufacture that drug product or component without the use of such a filter. Filtration, as needed, shall be through a non-fiber-releasing filter. For the purposes of this regulation a non-fiber-releasing filter is defined as a nonasbestos, nonglass fiber filter which, after any appropriate pretreatment such as washing or flushing, will not continue to release fibers into the drug product or component which is being filtered. A fiber is defined as any particle with length at least three times greater than its width.

(2) If use of a fiber-releasing filter is required, an additional non-fiber-releasing filter of maximum pore size of 0.22 microns (0.45 microns if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of any asbestos-form particles in the drug product or component. Use of an asbestos-containing filter with or without subsequent use of a specific non-fiber-releasing filter is permissible only upon submission of proof to the appropriate bureau of the Food and Drug Administration that use of a non-fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the drug.

(3) Substitution for a fiber-releasing filter shall be achieved on or before September 14, 1976. If such substitution is not achieved on or before March 14, 1976, the manufacturer of the drug product for parenteral injection who requires the additional 6 months to develop new manufacturing procedures so as to utilize non-fiber-releasing filters in place of fiber-releasing filters shall submit monthly reports to the appropriate bureau of the Food and Drug Administration indicating progress in substituting the new filters. Such a substitution shall be shown to have been effected without loss of the safety or effectiveness of the drug.

Paragraph (j) is effective April 14, 1975.

§ 211.42 Components.

All components and other materials used in the manufacture, processing, and packaging of drug products, and materials necessary for building and equipment maintenance, upon receipt shall be stored and handled in a safe, sanitary, and orderly manner. Adequate measures shall be taken to prevent mixups and cross-contamination affecting drugs and drug products. Components shall be withheld from use until they have been identified, sampled, and tested for conformance with established specifications and are released by a materials approval unit. Control of components shall include the following:

(a) Each container of component shall be examined visually for damage or contamination prior to use, including examination for breakage of seals when indicated.

(b) An adequate number of samples shall be taken from a representative number of component containers from each lot and shall be subjected to one or more tests to establish the specific identity.

(c) Representative samples of components liable to contamination with filth, insect infestation, or other extraneous contaminants shall be appropriately examined.

(d) Representative samples of all components intended for use as active ingredients shall be tested to determine their strength in order to assure conformance with appropriate specifications.

(e) Representative samples of components liable to microbiological contamination shall be subjected to microbiological tests prior to use. Such components shall not contain microorganisms that are objectionable in view of their intended use.

(f) Approved components shall be appropriately identified and retested as necessary to assure that they conform to appropriate specifications of identity,

strength, quality, and purity at time of use. This requires the following:

(1) Approved components shall be handled and stored to guard against contaminating or being contaminated by other drugs or components.

(2) Approved components shall be rotated in such a manner that the oldest stock is used first.

(3) Rejected components shall be identified and held to preclude their use in manufacturing or processing procedures for which they are unsuitable.

(g) Appropriate records shall be maintained, including the following:

(1) The identity and quantity of the component, the name of the supplier, the supplier's lot number, and the date of receipt.

(2) Examinations and tests performed and rejected components and their disposition.

(3) An individual inventory and record for each component used in each batch of drug manufactured or processed.

(h) An appropriately identified reserve sample of all active ingredients consisting of at least twice the quantity necessary for all required tests, except those for sterility and determination of the presence of pyrogens, shall be retained for at least 2 years after distribution of the last drug lot incorporating the component has been completed or 1 year after the expiration date of this last drug lot, whichever is longer.

§ 211.55 Product containers and their components.

Suitable specifications, test methods, cleaning procedures, and when indicated, sterilization procedures shall be used to assure that containers, closures, and other component parts of drug packages are suitable for their intended use. Containers for parenteral drugs, drug products or drug components shall be cleansed with water which has been filtered through a non-fiber-releasing filter equivalent to that indicated in § 211.40(j)(2). Product containers and their components shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug or its components beyond the official or established requirements and shall provide adequate protection against external factors that can cause deterioration or contamination of the drug.

Effective date. This section effective April 14, 1975.

(Secs. 501, 502, 701, 52 Stat. 1049–1051, 1055–1056, as amended; (21 U.S.C. 351, 352, 371))

§ 211.58 Laboratory controls.

Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, and test procedures to assure that components, in-processed drugs, and finished products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications for the acceptance of each lot of drug components, product containers, and their components used in drug production and packaging and a description of the sampling and testing procedures used for them. Said samples shall be representative and adequately identified. Such records shall also provide for appropriate retesting of drug components, product containers, and their components subject to deterioration.

(b) A reserve sample of all active ingredients as required by § 211.42(h).

(c) The establishment of master records, when needed, containing specifications and a description of sampling and testing procedures for in-process drug preparations. Such samples shall be adequately representative and properly identified.

(d) The establishment of master records containing a description of sampling procedures and appropriate specifications for finished drug products. Such samples shall be adequately representative and properly identified.

(e) Adequate provisions for checking the identity and strength of drug products for all active ingredients and for assuring:

(1) Sterility of drugs purported to be sterile and freedom from objectionable microorganisms for those drugs which should be so by virtue of their intended use.

(2) The absence of pyrogens for those drugs purporting to be pyrogen-free.

(3) Minimal contamination of ophthalmic ointments by foreign particles and harsh or abrasive substances.

(4) That the drug release pattern of sustained release products is tested by laboratory methods to assure conformance to the release specifications.

(f) Adequate provision for auditing the reliability, accuracy, precision, and performance of laboratory test procedures and laboratory instruments used.

(g) A properly identified reserve sample of the finished product (stored in the same immediate container-closure system in which the drug is marketed) consisting of at least twice the quantity necessary to perform all the required tests, except those for sterility and determination of the absence of pyrogens, and stored under conditions consistent with product labeling shall be retained for at least 2 years after the drug distribution has been completed or at least 1 year after the drug's expiration date, whichever is longer.

(h) Provision for retaining complete records of all laboratory data relating to each batch or lot of drug to which they apply. Such records shall be retained for at least 2 years after distribution has been completed or 1 year after the drug's expiration date, whichever is longer.

(i) Provision that animals shall be maintained and controlled in a manner that assures suitability for their intended use. They shall be identified and appropriate records maintained to determine the history of use.

(j) Provision that firms which manufacture nonpenicillin products (including certifiable antibiotic products) on the same premises or use the same equipment as that used for manufacturing penicillin products, or that operate under any circumstances that may reasonably be regarded as conducive to contamination of other drugs by penicillin, shall test such nonpenicillin products to determine whether any have become cross-contaminated by penicillin. Such products shall not be marketed if intended for use in man and the product is contaminated with an amount of penicillin equivalent to 0.05 unit or more of penicillin G per maximum single dose recommended in the labeling of a drug intended for parenteral administration, or an amount of penicillin equivalent to 0.5 unit or more of penicillin G per maximum single dose recommended in the labeling of a drug intended for oral use.

§ 211.60 Stability.

There shall be assurance of the stability of finished drug products. This stability shall be:

(a) Determined by reliable, meaningful, and specific test methods.

(b) Determined on products in the same container-closure systems in which they are marketed.

(c) Determined on any dry drug product that is to be reconstituted at the time of dispensing (as directed in its labeling), as well as on the reconstituted product.

(d) Recorded and maintained in such manner that the stability data may be utilized in establishing product expiration dates.

§ 211.62 Expiration dating.

To assure that drug products liable to deterioration meet appropriate standards of identity, strength, quality, and purity at the time of use, the label of all such drugs shall have suitable expiration dates which relate to stability tests performed on the product.

(a) Expiration dates appearing on the drug labeling shall be justified by readily available data from stability studies such as described in § 211.60.

(b) Expiration dates shall be related to appropriate storage conditions stated on the labeling wherever the expiration date appears.

(c) When the drug is marketed in the dry state for use in preparing a liquid product, the labeling shall bear expiration information for the reconstituted product as well as an expiration date for the dry product.

Subpart D—Packaging and Labeling

§ 211.80 Packaging and labeling.

Packaging and labeling operations shall be adequately controlled: To assure that only those drug products that have met the standards and specifications established in their master production and control records shall be distributed; to prevent mixups between drugs during filling, packaging, and labeling operations; to assure that correct labels and labeling are employed for the drug; and to identify the finished product with a lot or control number that permits determination of the history of the manufacture and control of the batch. An hour, day, or shift code is appropriate as a lot or control number for drug products manufactured or processed in continuous production equipment. Packaging and labeling operations shall:

(a) Be separated (physically or spatially) from operations on other drugs in a manner adequate to avoid mixups and minimize cross-contamination. Two or more packaging or labeling operations having drugs, containers, or labeling similar in appearance shall not be in process simultaneously on adjacent or nearby lines unless these operations are separated either physically or spatially.

(b) Provide for an inspection of the facilities prior to use to assure that all drugs and previously used packaging and labeling materials have been removed.

(c) Include the following labeling controls:

(1) The holding of labels and package labeling upon receipt pending review and proofing against an approved final copy by a competent and responsible individual to assure that they are accurate regarding identity, content, and conformity with the approved copy before release to inventory.

(2) The maintenance and storage of each type of label and package labeling representing different products, strength, dosage forms, or quantity of contents in such a manner as to prevent mixups and provide proper identification.

(3) A suitable system for assuring that only current labels and package labeling are retained and that stocks of obsolete labels and package labeling are destroyed.

(4) Restriction of access to labels and package labeling to authorized personnel.

(5) Avoidance of gang printing of cut labels, cartons, or inserts when the labels, cartons, or inserts are for different products or different strengths of the same products or are of the same size and have identical or similar format and/or color schemes. If gang printing is employed, packaging and labeling operations shall provide for added control procedures. These added controls should consider sheet layout, stacking, cutting, and handling during and after printing.

(d) Provide strict control of the package labeling issued for use with the drug. Such issue shall be carefully checked by a competent and responsible person for identity and conformity to the labeling specified in the batch production record. Said record shall identify the labeling and the quantities issued and used and shall reasonably reconcile any discrepancy between the quantity of drug finished and the quantities of labeling issued. All excess package labeling bearing lot or control numbers shall be destroyed. In event of any significant unexplained discrepancy, an investigation should be carried out according to § 211.40(h).

(e) Provide for adequate examination or laboratory testing of representative samples of finished products after packaging and labeling to safeguard against any errors in the finishing operations and to prevent distribution of any batch until all specified tests have been met.

Subpart E—Records and Reports

§ 211.101 Master production and control records; batch production and control records.

(a) To assure uniformity from batch to batch, a master production and control record for each drug product and each batch size of drug product shall be prepared, dated, and signed or initialed by a competent and responsible individual and shall be independently checked, reconciled, dated, and signed or initialed by a second competent and responsible individual. The master production and control record shall include:

(1) The name of the product, description of the dosage form, and a specimen or copy of each label and all other labeling associated with the retail or bulk unit, including copies of such labeling signed or initialed and dated by the person or persons responsible for approval of such labeling.

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the finished drug, and a statement of the total weight or measure of any dosage unit.

(3) A complete list of ingredients designated by names or codes sufficiently specific to indicate any special quality characteristic; an accurate statement of the weight or measure of each ingredient regardless of whether it appears in the finished product, except that reasonable variations may be permitted in the amount of components necessary in the preparation in dosage form provided that provisions for such variations are included in the master production and control record; an appropriate statement concerning any calculated excess of an ingredient; an appropriate statement of theoretical weight or measure at various stages of processing; and a statement of the theoretical yield.

(4) A description of the containers, closures, and packaging and finishing materials.

(5) Manufacturing and control instructions, procedures, specifications, special notations, and precautions to be followed.

(b) The batch production and control record shall be prepared for each batch of drug produced and shall include complete information relating to the production and control of each batch. These records shall be retained for at least 2 years after the batch distribution is complete or at least 1 year after the batch expiration date, whichever is longer. These records shall identify the specific labeling and lot or control numbers used on the batch and shall be readily available during such retention period. The batch record shall include:

(1) An accurate reproduction of the appropriate master formula record checked, dated, and signed or initialed by a competent and responsible individual.

(2) A record of each significant step in the manufacturing, processing, packaging, labeling, testing, and controlling of the batch, including: Dates; individual major equipment and lines employed; specific identification of each batch of components used; weights and measures of components and products used in the course of processing; in-process and laboratory control results; and identifications of the individual(s) actively performing and the individual(s) directly supervising or checking each significant step in the operation.

(3) A batch number that identifies all the production and control documents relating to the history of the batch and all lot or control numbers associated with the batch.

(4) A record of any investigation made according to § 211.40(h).

§ 211.110 Distribution records.

(a) Finished goods warehouse control and distribution procedures shall include a system by which the distribution of each lot of drug can be readily determined to facilitate its recall if necessary. Records within the system shall contain the name and address of the consignee, date and quantity shipped, and lot or control number of the drug. Records shall be retained for at least 2 years after the distribution of the drug has been completed or 1 year after the expiration date of the drug, whichever is longer.

(b) To assure the quality of the product, finished goods warehouse control shall also include a system whereby the oldest approved stock is distributed first whenever possible. (See 21 CFR 1304 for regulations relating to manufacturing and distribution records of drugs subject to the Drug Abuse Control Amendments of 1965; Public Law 89–74.)

§ 211.115 Complaint files.

Records shall be maintained of all written and oral complaints regarding each product. An investigation of each complaint shall be made in accordance with § 211.40(h). The record of each investigation shall be maintained for at least 2 years after distribution of the drug has been completed or 1 year after the expiration date of the drug, whichever is longer.

PART 225—CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICATED FEEDS

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Subpart B—Construction and Maintenance of Facilities and Equipment

Subpart C—Product Quality Control

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225.80 Packaging and labeling.

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225.115 Complaint files.

AUTHORITY: Secs. 501, 701, 52 Stat. 1049–1050 as amended, 1055–1056 as amended (21 U.S.C. 351, 371).

Subpart A—General Provisions

§ 225.1 Current good manufacturing practice.

The criteria in §§ 225.10 through 225.115, inclusive, shall apply in determining whether the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or holding of a medicated feed conform to or are operated or administered in conformity with current good manufacturing practice to assure that a medicated feed meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess, as required by section 501(a)(2)(B) of the act. The regulations in this Part 225 permit the use of precision, automatic, mechanical, or electronic equipment in the production of a medicated feed when adequate inspection and checking procedures are used to assure proper performance.

§ 225.10 Personnel.

The key employees and/or consultants responsible for the formulation, manufacture, and control of the medicated feed shall have a background of education or experience or a combination thereof that is adequate to assure proper composition and labeling of the medicated feeds.

Subpart B—Construction and Maintenance of Facilities and Equipment

§ 225.20 Buildings.

Buildings in which medicated feeds are manufactured, processed, packaged, labeled, or held shall be maintained in a reasonably clean and orderly manner and shall be of suitable size, construction, and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. The buildings shall:

(a) Provide adequate space for the orderly placement of equipment and materials used in any of the following operations for which they are employed, to minimize any risk of mixups between different medicated feeds, their components, packaging, or labeling:

(1) The receipt, control, and storage of components.

(2) Any manufacturing and processing operations performed on the medicated feed.

(3) Any packaging and labeling operations.

(4) Storage of containers, packaging materials, labeling, and finishing products.

(b) Provide adequate lighting and other physical facilities necessary to prevent unsafe contamination of raw materials and finished products before, during, and after production.

(c) Provide for adequate washing, cleaning, toilet, and locker facilities.

Work areas and equipment used for the production of medicated feeds or for the storage of the components of medicated feeds shall not be used for the production, mixing, or storage of finished or unfinished insecticides, fungicides, or rodenticides or their components.

§ 225.30 Equipment.

Equipment used for the manufacture, processing, packaging, bulk shipment, labeling, holding or control of medicated feeds or their components shall be maintained in a reasonably clean and orderly manner and shall be of suitable design, size, construction, and location in relation to surroundings to facilitate maintenance and operation for its intended purpose. The equipment shall:

(a) Be so constructed that any surfaces that come into contact with medicated feeds are suitable, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the medicated feed or its components.

(b) Be so constructed that any substance required for the operation of the equipment, such as lubricants, coolants, etc., may be employed without hazard of becoming an unsafe additive to the medicated feed.

(c) Be constructed to facilitate adjustment, cleaning, and maintenance, and to assure uniformity of production and reliability of control procedures and to assure the exclusion from medicated feeds of unsafe contamination, including cross-examination from manufacturing operations.

(d) Be suitably grounded electrically to prevent lack of uniform mixing due to electrically charged particles.

(e) Be of suitable size and accuracy for use in any intended measuring, mixing or weighing operations.

Subpart C—Product Quality Control

§ 225.40 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the medicated feeds produced are of proper composition and labeling:

(a) Each critical step in the process, such as the selection, weighing, and measuring of components; the addition of drugs or components during the process; the control of mixing times; the adjustment of the equipment involved in continuous production processes; and the determination of the finished yield, shall be performed in a manner that has been determined by appropriate methods, including laboratory testing of the medicated feed, to be adequate to assure the integrity of the final product. If such steps in the processing are controlled by precision, automatic, mechanical, or electronic equipment, provision shall be made to adequately check its performance.

(b) All containers to be used for undiluted drugs, drug components, intermediate mixtures, and finished feeds shall be received, adequately identified, and properly stored and handled in a manner adequate to prevent mixups or contamination.

(c) Equipment, including dust-control and other equipment, such as that used for holding and returning recovered or flush-out materials back into production, shall be maintained and operated in such a manner as to prevent unsafe contamination of the medicated feed.

(d) The steps used to prevent unsafe contamination of medicated feed include one or more of the following, or other equally effective procedures:

(1) Cleaning of those parts of storage, mixing, conveying, and any other equipment coming in contact with the drug component of the medicated feed for the purpose of cleaning out of the equipment any drug, drug component, or medicated feed prior to the use of the same equipment for the production of a different medicated feed.

(2) The cleaning of the equipment as required in paragraph (d)(1) of this section, may be achieved by flushing all feed-contacting surfaces of such equipment used in the production of a medicated feed with a quantity of an appropriate drug-free feedstuff that has been found sufficient to remove any significant quantity of a drug component or an intermediate mix or complete medicated feed prior to the production of a different medicated feed. The yield from any such flushing operation may be incorporated in appropriate amounts in the subsequent production of a medicated feed intended to contain the same drug component (or components) to produce a complete medicated feed conforming to its composition and labeling specifications.

(e) If there is sequential production of batches of a medicated feed containing the same drug component (or components) at the same or lower levels, there shall be sufficient safeguards to avoid any buildup above the specified levels of the drug components in any of the batches of the complete feed.

(f) A sampling and assay schedule on the finished medicated feed, or a schedule at least as reliable, for checking on the composition of the finished article shall be applied as follows:

(1) In the case of a medicated feed that requires an approved Form FD–1800 for its manufacture and marketing, the schedule of assays established in such application shall be used.

(2) In the case of a medicated feed that does not require an approved Form FD–1800 for its marketing, three appropriately drawn samples from each 400 tons of such medicated feeds produced shall be taken at appropriately spaced intervals over the production period, and, in any event, not less than three such

samples of each particular medicated feed during any 1 year shall be collected and analyzed. For the purposes of this subparagraph, the term "each particular medicated feed" shall be construed to include all feeds containing the same drug components) at different levels. The colponent (or the same mixture of components) at different levels. The collection and analysis of samples shall be from the medicated feed containing the highest level of the drug component (or mixture of components).

(3) A medicated feed covered by paragraph (f)(2) of this section shall be exempt from the prescribed sampling and analytical schedule under the following conditions:

(i) The manufacturing practices used in the production of the medicated feed were consistent with the regulations of this part; and

(ii) The manufacturer of the medicated feed has produced at least 3 batches of such feed conforming to composition and labeling specifications during the 1-year period immediately preceding the date of manufacture of the feed and during that period has not been notified by the Food and Drug Administration or any State regulatory official that his manufacturing practices were in conflict with section 501(a)(2)(B) of the act or the regulations of this part and has not distributed a medicated feed during that period which has been proceeded against under the act because of failure of such feed to comply with its composition or labeling requirements or which has been analyzed by any State official and found to be deficient; and

(iii) The medicated feed contains only, as the drug component (or components), a low-level growth-promotion antibiotic (or antibiotics) as provided by and in accordance with the regulations in Part 558 of this chapter; it was manufactured from a feed additive premix, feed additive concentrate, or feed additive supplement that, at the time of receipt by the medicated-feed manufacturer, bore a label, or was accompanied by labeling, containing a quantitative composition statement of its antibiotic content together with directions for its use in the manufacturing of a legal medicated feed; and the medicated-feed manufacturer, in good faith, relied upon and followed the feed additive premix, concentrate, or supplement label or labeling information and directions for use in the manufacturing of the medicated feed; or

(iv) The medicated feed contains only, as the drug component (or components), a drug (or drugs) as provided by and in accordance with the regulations in Part 558 of this chapter; it was manufactured from a feed additive concentrate or feed additive supplement that, at the time of receipt by the medicated-feed manufacturer, bore a label, or was accompanied by labeling, containing the quantitative composition of its drug content together with directions for its use in the manufacturing of a legal medicated feed; and the medicated-feed manufacturer, in good faith, relied upon and followed the feed additive concentrate or supplement label or labeling information and directions for use in the manufacturing of the medicated feed; or

(v) The medicated feed contains only drug components as provided by and in accordance with the regulations in Part 558 of this chapter and was manufactured from a feed additive supplement, a low level growth-promotion antibiotic premix, a low level growth-promotion antibiotic concentrate, a feed additive concentrate, or a combination of any two of these used in accordance with the conditions set forth in paragraph (f)(3) (ii), (iii), and (iv) of this section.

(g) Production and control procedures shall include provision for discontinuing distribution of any medicated feed found by the assay procedures, or any other controls preformed, to fail to conform to appropriate specifications. Distribution of subsequent production shall not begin until it has been determined that proper control produres have been established.

§ 225.42 Components.

(a) Drug components, including undiluted drugs and any intermediate mixes containing drugs used in the manufacture and processing of medicated feeds. shall be received, stored, handled, and otherwise controlled in a manner to maintain the integrity and identification of such articles. Appropriate receipt and inventory records shall be maintained for 1 year and such records shall show the origin of any drug components. the batches in which they were used, and the results of any testing of them by or on behalf of the medicated-feed manufacturer.

(b) Nondrug components shall be stored and otherwise handled in a manner to avoid unsafe contamination, including cross-contamination from manufacturing operations.

(c) Statements relating to the identification and the quantitative composition appearing on the labels of undiluted drugs or other drug components received by the medicated-feed manufacturer from other suppliers may be relied upon by the medicated-feed manufacturer as acceptable evidence of the identity and composition of the drug or drug components in lieu of actual testing of each such drug or drug component if such reliance is made in good faith.

§ 225.58 Laboratory controls.

Laboratory controls shall include the establishment of adequate specifications and test procedures to assure that the drug components and the finished medicated feeds conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications and a description of the test procedures used to check them for each kind of drug used in the manufacture of medicated feeds; this may consist of the manufacturer's or supplier's statement of specifications.

(b) The establishment of finished-product specifications for medicated feeds and a description of any necessary laboratory test procedures to check them, including methods of assay for the active drug ingredient.

(c) A determination that the drug components remain uniformly dispersed and stable in the medicated feed under ordinary conditions of shipment, storage, and use; this may consist of a supplier's or consultant's determination made on a feed of substantially the same formula.

(d) Adequate provision to check the reliability, accuracy, and precision of any laboratory test procedure used; the official Methods of Analysis of the Association of Official Agricultural Chemists, methods described in an official compendium, and any method, submitted as a part of a food additive petition or new-drug application, which has been accepted by the Food and Drug Administration shall be regarded as meeting this provision.

(e) Provision for the maintenance of the results of any assays, including dates and endorsement of analysts. Such records, together with records of analyses reported by any State feed control official shall be retained in the possession of the manufacturer or in the possession of a consulting laboratory operating in his behalf. Such records shall be maintained for a period of at least 1 year after distribution of the medicated feed has been completed.

Subpart D—Packaging and Labeling

§ 225.80 Packaging and labeling.

Packaging and labeling operations shall be adequately performed and controlled to assure that only those medicated feeds made in compliance with established formula records and manufacturing and control directions shall be distributed; to prevent mixups between the medicated feeds during the packaging and labeling operations; and to assure that correct labeling is employed for the medicated feed. In the case of medicated feeds distributed in bulk, complete labeling shall accompany the shipment and be supplied to the consignee at the time of delivery. Such labeling may consist of an invoice or placard identifying the medicated feed and bearing adequate information for the safe and effective use of the medicated feed. Labels and labeling shall be received, handled, and stored in a manner that avoids labeling mixups. Previously used containers shall be adequately cleaned and labeled before reuse to avoid adulteration or misbranding.

Subpart E—Records and Reports

§ 225.102 Formula and production records.

(a) For each medicated feed, a master formula record or card shall be prepared, checked, and maintained by a responsible key employee and retained for at least 1 year after production of the last batch. The formula record or card shall include at least the following:

(1) The name of the medicated feed, together with any other information necessary for the correct identification of the feed.

(2) The weight or measure of each ingredient, adequately identified, to be used in manufacturing a stated weight of the medicated feed.

(3) A copy, description, or notation adequately identifying the label, labeling, or placard necessary to be used on or with the complete medicated feed.

(4) Manufacturing instructions for each medicated feed produced on a batch or continuous operation basis, including mixing steps, mixing times, and batch formulas that have been determined to yield an adequately mixed medicated feed; and in the case of medicated feeds produced by continuous production run, any additional manufacturing directions including, when indicated, the settings of equipment that have been determined to yield an adequately mixed medicated feed of the specified formula.

(5) Appropriate control directions, including the manner and frequency with which any necessary samples of the medicated feed are to be taken for specified laboratory tests, the criteria for using laboratory test results to change formulations or manufacturing procedures, and the procedures to be observed to avoid unsafe contamination of the medicated feed with other medicated feeds or drug components.

(b) A production record shall be prepared for each batch or run of medicated feed produced, and shall be retained for at least 1 year. The production record shall include:

(1) Product identification, date of production, and endorsement by a responsible individual.

(2) A record of the quantity of drug components used.

(3) A record of the quantity of medicated feed produced.

(c) In the case of a customer-formula feed made to the specifications of a customer, the formula and production records required by this section may consist of copies of customers' purchase orders and sellers' invoices bearing the information required by this section.

§ 225.110 Distribution records.

Complete records shall be maintained for each shipment of medicated feeds in a manner that will facilitate the recall, diversion, or destruction of the medicated feed, if necessary. Such records shall be retained for at least 6 months after the date of the shipment, and shall include the name and address of the consignee, the date and quantity shipped, and the manufacturing dates, control numbers, or marks identifying the medicated feed shipped. If the medicated feed is held under control of the manufacturer for further shipment at establishments other than where produced, records as outlined in this section shall be maintained at these establishments.

§ 225.115 Complaint files.

The medicated-feed manufacturer shall evaluate by responsible key personnel each complaint received by him on a feed that is manufactured or distributed by him and, where indicated, make such further investigations or take such appropriate action as appears to be warranted in the circumstances. A record of complaints and the action taken by the feed manufacturer shall be maintained for a period of 2 years. If the medicated feed is the subject of an approved new-drug application held by the feed manufacturer, he shall make such reports as are required by § 510.301 of this chapter.

PART 226—CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICATED PREMIXES

Subpart A—General Provisions

Sec.

AUTHORITY: Secs. 501, 701, 52 Stat. 1049–1050 as amended; 1055–1056 as amended (21 U.S.C. 351, 371).

Subpart A—General Provisions

§ 226.1 Current good manufacturing practice.

The criteria in §§ 226.10 through 226.115, inclusive, shall apply in determining whether the methods used in, or the facilities and controls used for the manufacture, processing, packing, or holding of a medicated premix conform to or are operated or administered in conformity with current good manufacturing practice to assure that a medicated premix meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess, as required by section 501(a)(2)(B) of the act. The regulations in this Part 226 permit the use of precision, automatic, mechanical, or electronic equipment in the production of a medicated premix when adequate inspection and checking procedures or other quality control procedures are used to assure proper performance.

§ 226.10 Personnel.

The key personnel and any consultants involved in the manufacture and control of the medicated premix shall have a background of appropriate education or appropriate experience or combination thereof for assuming responsibility to assure that the medicated premix has the proper labeling and the safety, identity, strength, quality, and purity that it purports to possess.

Subpart B—Construction and Maintenance of Facilities and Equipment

§ 226.20 Buildings.

Buildings in which medicated premixes are manufactured, processed, packaged, labeled, or held shall be maintained in a clear and orderly manner and shall be of suitable size, construction and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. The building shall:

(a) Provide adequate space for the orderly placement of equipment and materials used in any of the following operations for which they are employed to minimize risk of mixups between different medicated premixes, their components, packaging, or labeling:

(1) The receipt, sampling, control, and storage of components.

(2) Manufacturing and processing operations performed on the medicated premix.

(3) Packaging and labeling operations.

(4) Storage of containers, packaging materials, labeling, and finished products.

(5) Control laboratory operations.

(b) Provide adequate lighting and ventilation, and when necessary for the intended production or control purposes, adequate screening, dust and temperature controls, to avoid contamination of medicated premixes, and to avoid other conditions unfavorable to the safety, identity, strength, quality, and purity of the raw materials and medicated premixes before, during, and after production.

(c) Provide for adequate washing, cleaning, toilet, and locker facilities.

Work areas and equipment used for the production of medicated premixes or for the storage of the components of medicated premixes shall not be used for the production, mixing or storage of finished or unfinished insecticides, fungicides, rodenticides, or other pesticides or their components unless such materials are recognized as approved drugs intended for use in animal feeds.

§ 226.30 Equipment.

Equipment used for the manufacture, processing, packaging, bulk shipment, labeling, holding, or control of medicated premixes or their components shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction, and location to facilitate maintenance and operation for its intended purpose. The equipment shall:

(a) Be so constructed that any surfaces that come into contact with medicated premixes are suitable, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the medicated premix or its components.

(b) Be so constructed that any substance required for the operation of the equipment, such as lubricants, coolants, etc., may be employed without hazard of becoming an unsafe additive to the medicated premix.

(c) Be constructed to facilitate adjustment, cleaning, and maintenance, and to assure uniformity of production and reliability of control procedures and to assure the exclusion from medicated premixes of contamination, including cross-contamination from manufacturing operations.

(d) Be suitably grounded electrically to prevent lack of uniform mixing due to electrically charged particles.

(e) Be of suitable size and accuracy for use in any intended measuring, mixing, or weighing operations.

Subpart C—Product Quality Control

§ 226.40 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the medicated premixes produced have the identity, strength, quality, and purity they purport to possess:

(a) Each critical step in the process, such as the selection, weighing, and measuring of components; the addition of drug components during the process; weighing and measuring during various stages of the processing; and the determination of the finished yield, shall be performed by one or more competent, responsible individuals. If such steps in the processing are controlled by precision, automatic, mechanical, or electronic equipment, their proper performance shall be adequately checked by one or more competent, responsible individuals.

(b) All containers to be used for undiluted drugs, drug components, intermediate mixtures thereof, and medicated premixes shall be received, adequately identified, and properly stored and handled in a maner adequate to avoid mixups and contamination.

(c) Equipment, including dust-control and other equipment, such as that used for holding and returning recovered or flush-out materials back into production, shall be maintained and operated in a manner to avoid contamination of the medicated premixes and to insure the integrity of the finished product.

(d) Competent and responsible personnel shall check actual against theoretical yield of a batch of medicated premix, and, in the event of any significant discrepancies, key personnel shall prevent distribution of the batch in question and other associated batches of medicated premixes that may have been involved in a mixup with it.

(e) Adequate procedures for cleaning of those parts of storage, mixing conveying and other equipment coming in contact with the drug component of the medicated premix shall be used to avoid contamination of medicated premixes.

(f) If there is sequential production of batches of a medicated premix containing the same drug component (or components) at the same or lower levels, there shall be sufficient safeguards to avoid any buildup above the specified levels of the drug components in any of the batches of the medicated premix.

(g) Production and control procedures shall include provision for discontinuing distribution of any medicated premix found by the assay procedures, or other controls performed to fail to conform to appropriate specifications. Distribution of subsequent production of such medicated premix shall not begin until it has been determined that proper control procedures have been established.

§ 226.42 Components.

(a) Drug components, including undiluted drugs and any intermediate mixes containing drugs used in the manufacture and processing of medicated premixes, shall be received, examined or tested, stored, handled, and otherwise controlled in a manner to maintain the integrity and identification of such articles. Appropriate receipt and inventory records shall be maintained for 2 years, and such records shall show the origin of any drug components, the manufacturer's control number (if any), the dates and batches in which they were used, and the results of any testing of them.

(b) Nondrug components shall be stored and otherwise handled in a manner to avoid contamination, including cross-contamination from manufacturing operations.

§ 226.58 Laboratory controls.

Laboratory controls shall include the establishment of adequate specifications and test procedures to assure that the drug components and the medicated premixes conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications and a description of the test procedures used to check them for each kind of drug component used in the manufacture of medicated premixes. This may consist of the manufacturer's or supplier's statement of specifications and methods of analyses.

(b) The establishment of specifications for medicated premixes and a description of necessary laboratory test procedures to check such specifications.

(c) Assays which shall be made of representative samples of finished medicated premixes in accordance with the following schedule:

(1) Each batch of a medicated premix manufactured from an undiluted drug shall be assayed for its drug component(s).

(2) In the case of medicated premixes which are manufactured by dilution of medicated premix(es) assayed in accordance with paragraph (c)(1) of this section, each batch shall be assayed for its drug component(s) with the first five consecutive batches assaying within the limitations, followed thereafter by assay of representative samples of not less than 5 percent of all batches produced. When any batch does not assay within limitations, each batch should again be assayed until five consecutive batches are within limitations.

(d) A determination establishing that the drug components remain uniformly dispersed and stable in the medicated premix under ordinary conditions of shipment, storage, and use. This may consist of a determination on a medicated premix of substantially the same formula and characteristics. Suitable expiration dates shall appear on the labels of the medicated premixes when needed to assure that the articles meet the appropriate standards of identity, strength, quality, and purity at the time of use.

(e) Adequate provision to check the reliability, accuracy, and precision of any laboratory test procedure used. The official methods in "Methods of Analysis of the Association of Official Analytical Chemists,"[1] methods described in an official compendium, and any method submitted as a part of a food additive petition or new-drug application that has been accepted by the Food and Drug Administration shall be regarded as meeting this provision.

(f) Provisions for the maintenance of the results of any assays, including dates and endorsement of analysts. Such records shall be retained in the possession of the manufacturer and shall be maintained for a period of at least 2 years after distribution by the manufacturer of the medicated premix has been completed.

Subpart D—Packaging and Labeling

§ 226.80 Packaging and labeling.

(a) Packaging and labeling operations shall be adequately controlled:

(1) To assure that only those medicated premixes that have met the specifications established in the master-formula records shall be distributed.

(2) To prevent mixups during the packaging and labeling operations.

(3) To assure that correct labeling is employed for each medicated premix.

(4) To identify medicated premixes with lot or control numbers that permit determination of the history of the manufacture and control of the batch of medicated premix.

(b) Packaging and labeling operations shall provide:

(1) For storage of labeling in a manner to avoid mixups.

(2) For careful checking of labeling for identity and conformity to the labeling specified in the batch-production records.

(3) For adequate control of the quantities of labeling issued for use with the medicated premix.

(c) Medicated premixes shall be distributed in suitable containers to insure the safety, identity, strength, and quality of the finished product.

Subpart E—Records and Reports

§ 226.102 Master-formula and batch-production records.

(a) For each medicated premix, master-formula records shall be prepared, endorsed, and dated by a competent and responsible individual and shall be independently checked, reconciled, endorsed, and dated by a second competent

[1] Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540; Ben Franklin Station, Washington, DC 20044.

and responsible individual. The record shall include:

(1) The name of the medicated premix and a specimen copy of its label.

(2) The weight or measure of each ingredient, adequately identified, to be used in manufacturing a stated weight of the medicated premix.

(3) A complete formula for each batch size, or of appropriate size in the case of continuous systems to be produced from the master-formula record, including a complete list of ingredients designated by names or codes sufficiently specific to indicate any special quality characteristics; an accurate statement of the weight or measure of each ingredient, except that reasonable variations may be permitted in the amount of ingredients necessary in the preparation of the medicated premix, provided that the variations are stated in the master formula; an appropriate statement concerning any calculated excess of an ingredient; and a statement of the theoretical yield.

(4) Manufacturing instructions for each type of medicated premix produced on a batch or continuous operation basis, including mixing steps and mixing times that have been determined to yield an adequately mixed medicated premix; and in the case of medicated premixes produced by continuous production run, any additional manufacturing directions including, when indicated, the settings of equipment that have been determined to yield an adequately mixed medicated premix of the specified formula.

(5) Control instructions, procedures, specifications, special notations, and precautions to be followed.

(b) A separate batch-production and control record shall be prepared for each batch or run of medicated premix produced and shall be retained for at least 2 years after distribution by the manufacturer has been completed. The batch-production and control record shall include:

(1) Product identification, date of production, and endorsement by a competent and responsible individual.

(2) Records of each step in the manufacturing, packaging, labeling, and controlling of the batch, including dates, specific identification of drug components used, weights or measures of all components, laboratory-control results, mixing times, and the endorsements of the individual actively performing or the individual actively supervising or checking each step in the operation.

(3) A batch number that permits determination of all laboratory-control procedures and results on the batch and all lot or control numbers appearing on the labels of the medicated premix.

§ 226.110 Distribution records.

Complete records shall be maintained for each shipment of medicated premixes in a manner that will facilitate the recall, diversion, or destruction of the medicated premix, if necessary. Such records shall be retained for at least 2 years after the date of the shipment by the manufacturer and shall include the name and address of the consignee, the date and quantity shipped, and the manufacturing dates, control numbers, or marks identifying the medicated premix shipped.

§ 226.115 Complaint files.

Records shall be maintained for a period of 2 years of all written or verbal complaints concerning the safety or efficacy of each medicated premix. Complaints shall be evaluated by competent and responsible personnel and, where indicated, appropriate action shall be taken. The record shall indicate the evaluation and the action.

PART 229—CURRENT GOOD MANUFACTURING PRACTICE FOR CERTAIN OTHER DRUG PRODUCTS

Sec.

229.25 Whole blood (human), red blood cells (human), and allergenic products; drugs subject to licensing by the Food and Drug Administration.

AUTHORITY: Secs. 501, 701, 52 Stat. 1049–1050 as amended, 1055–1056 as amended (21 U.S.C. 351, 371).

§ 229.25 Whole blood (human), red blood cells (human), and allergenic products; drugs subject to licensing by the Food and Drug Administration.

(a) The methods used in, or the facilities or controls used for, the manufacture, processing, packing, or holding of the drugs whole blood (human), red blood cells (human), and allergenic products do not conform to, or are not operated or administered in conformity with, current good manufacturing practice to assure that any such drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics, which it purports or is represented to possess, unless the manufacture, processing, packing, and holding of such drugs conform to the licensing and other requirements as to such drugs and the practices and standards of manufacture, processing, packing, and holding applicable to such drugs set forth in Part 640 of this chapter. Applications for licensing shall be submitted to the Director, Bureau of Biologics, Food and Drug Administration, Bldg. 29A, 9000 Rockville Pike, Bethesda, MD 20014.

PART 250—SPECIAL REQUIREMENTS FOR SPECIFIC HUMAN DRUGS

Subpart A—Drugs Regarded as Misbranded

Sec.

250.10 Oral prenatal drugs containing fluorides intended for human use.
250.11 Thyroid-containing drug preparations intended for treatment of obesity in humans.
250.12 Stramonium preparations labeled with directions for use in self-medication regarded as misbranded.

Subpart B—New Drug or Prescription Status of Specific Drugs

250.100 Amyl nitrite inhalant as a prescription drug for human use.
250.101 Amphetamine and methamphetamine inhalers regarded as prescription drugs.
250.102 Drug preparations intended for human use containing certain "coronary vasodilators."
250.103 Thorium dioxide for drug use.
250.104 Status of salt substitutes under the Federal Food, Drug, and Cosmetic Act.
250.105 Gelsemium-containing preparations regarded as prescription drugs.
250.106 Cobalt preparations intended for use by man.
250.107 Dimethylsulfoxide (DMSO) preparations; clinical testing and investigational use.
250.108 Potassium permanganate preparations as prescription drugs.
250.109 Vitamin A preparations for oral use as drugs.
250.110 Vitamin D preparations for oral use as drugs.

Subpart C—Requirements for Drugs and Foods

250.201 Preparations for the treatment of pernicious anemia.
250.203 Status of fluoridated water and foods prepared with fluoridated water.

Subpart D—Requirements for Drugs and Cosmetics

250.250 Hexachlorophene, as a component of drug and cosmetic products.

Subpart E—Special Packaging Requirements

250.300 Nitroglycerin for human use; packaging and warnings.

AUTHORITY: Sec. 701, 52 Stat. 1055–1056 (21 U.S.C. 371) unless otherwise noted.

Subpart A—Drugs Regarded as Misbranded

§ 250.10 Oral prenatal drugs containing fluorides intended for human use.

(a) The Food and Drug Administration finds that there is neither substantial evidence of effectiveness nor a general recognition by qualified experts that prenatal drug preparations containing fluorides promote tooth development in the fetus, prevent dental caries in the offspring, or prevent dental caries in pregnant women.

(b) Any such drug preparation that is so labeled, represented, or advertised will be regarded as misbranded and subject to regulatory proceedings unless such recommendations are covered by a new-drug application, including substantial evidence of effectiveness, approved pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act. Any such drug preparation that is labeled, represented, or advertised as containing fluorides as an active ingredient of the drug for prenatal use will similarly be regarded as misbranded and subject to regulatory proceedings.

(c) A completed and signed "Notice of Claimed Investigational Exception for a New Drug." Form FD–1571 set forth in § 312.1 of this chapter, must be submitted to cover clinical investigations designed to obtain evidence that such preparations are effective for such uses.

(d) Regulatory proceedings may be initiated with respect to drug preparations shipped within the jurisdiction of

the act that are contrary to provisions of this statement after 30 days from the date of publication of this statement in the FEDERAL REGISTER.

(Secs. 502 (a), (f), 505, 52 Stat. 1050, 1051, 1052, as amended; 21 U.S.C. 352 (a), (f), 355)

§ 250.11 Thyroid-containing drug preparations intended for treatment of obesity in humans.

(a) Investigation by the Food and Drug Administration has revealed that a large number of drug preparations containing thyroid or thyrogenic substances in combination with central nervous system stimulants, with or without one or more additional drug substances such as barbiturates or laxatives, are being marketed for or as adjuncts to the treatment, control, or management of obesity in humans. The Commissioner of Food and Drugs finds that the administration of such combinations for said purposes is without medical rationale except possibly in those relatively uncommon instances where the condition is directly related to hypothyroidism and there exists a concurrent need for appetite control (in such instances the safety and effectiveness of such combinations are not generally recognized). In particular, the Commissioner of Food and Drugs finds that neither the consensus of informed medical opinion nor clinical experience justifies any representation that such combinations are safe and effective in connection with the treatment, control, or management of obesity in patients having normal thyroid function.

(b) Combinations of thyroid or other thyrogenic drugs with central nervous system stimulants with or without other drug substances when offered for or as adjuncts to the treatment, control, or management of obesity not related to hypothyroidism are regarded as misbranded. Such combinations when offered for obesity in humans directly attributable to established hypothyroidism are regarded as new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act.

(Secs. 201(p), 502, 52 Stat. 1041–42, 1050, as amended; 21 U.S.C. 321(p), 352)

§ 250.12 Stramonium preparations labeled with directions for use in self-medication regarded as misbranded.

(a) Stramonium products for inhalation have been offered for use in the therapy of the acute attacks of bronchial asthma for many years although their reliability and effectiveness are questionable. Recently, a significantly increased number of reports have come to the attention of the Food and Drug Administration showing that such products have been subject to abuse and misuse on a fairly large scale, mostly by young people, through oral ingestion for the purpose of producing hallucinations. Reports of such use have been received from physicians and police and other law enforcement authorities. Reports have also appeared in the public press and in medical journals.

(b) Labeling these products with a warning that they are not for oral ingestion has not been effective in protecting the public. Misuse of stramonium preparations can cause serious toxic effects including toxic delirium, visual disturbances, fever, and coma. A number of serious reactions have already occurred from the oral ingestion of such products.

(c) On the basis of this information, the Commissioner of Food and Drugs has concluded that such articles have a potentiality for harmful effect through misuse and are not safe for use except under the supervision of a physician. In the interest of public health protection, therefore, the Food and Drug Administration adopts the following policy:

(1) Preparations containing stramonium supplied from the leaves, seeds, or any other part of the plant in the form of a powder, pipe mixture, cigarette, or any other form, with or without admixture of other ingredients, will be regarded as misbranded if they are labeled with directions for use in self-medication.

(2) The Food and Drug Administration will, on request, furnish comment on proposed labeling limiting any such preparation to prescription sale.

(d) The labeling or dispensing of stramonium preparations contrary to this statement after 60 days following the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

(Secs. 502 (a), (f), 503(b); 52 Stat. 1050–51, 1052, as amended; 21 U.S.C. 352 (a), (f), 353(b))

Subpart B—New Drug or Prescription Status of Specific Drugs

§ 250.100 Amyl nitrite inhalant as a prescription drug for human use.

(a) Amyl nitrite inhalant has been available over-the-counter for emergency use by the patient in the management of angina pectoris for a number of years. As a result of a proposed policy statement published August 25, 1967 (32 FR 12404), the Commissioner of Food and Drugs received reports of the abuse of this drug by those who do not require it for medical purposes. Additionally, comment included a great deal of concern expressed by individual physicians, medical associations, pharmaceutical associations, manufacturers, and State and local health authorities. Based on the information available, it is the opinion of the Commissioner of Food and Drugs, concurred in by the Food and Drug Administration Medical Advisory Board, that amyl nitrite inhalant is a drug with a potentiality for harmful effect and that it should be removed from over-the-counter status and restricted to sale on the prescription of a practitioner licensed by law to administer such drug.

(b) Therefore, amyl nitrite inhalant will be regarded as misbranded unless the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by physicians, in accordance with § 201.100(c) of this chapter, and its label bears the legend "Caution: Federal law prohibits dispensing without prescription."

(c) Regulatory proceedings may be initiated with regard to the interstate shipment of amyl nitrite inhalant that is labeled, advertised, or dispensed contrary to this statement of policy if such act occurs after July 1, 1969.

(Sec. 503(b), 52 Stat. 1052, as amended; 21 U.S.C. 353(b))

§ 250.101 Amphetamine and methamphetamine inhalers regarded as prescription drugs.

(a) Recurring reports of abuse and misuse of methamphetamine (also known as desoxyephedrine) inhalers show that they have a potentiality for harmful effect and that they should not be freely available to the public through over-the-counter sale. From complaints by law-enforcement officials, health officials, individual physicians, parents, and others as well as from Food and Drug Administration investigations, it is evident that the wicks from these inhalers are being removed and the methamphetamine they contain is being used as a substitute for amphetamine tablets. Amphetamine tablets and amphetamine inhalers have been restricted to prescription sale because of their potentiality for harm to the user.

(b) It is the considered opinion of the Food and Drug Administration that, in order to adequately protect the public health, inhalers containing methamphetamine or methamphetamine salts (d-desoxyephedrine, or dl-desoxyephedrine, or their salts), as well as amphetamine inhalers should be restricted to prescription sale and should be labeled with the legend "Caution: Federal law prohibits dispensing without prescription."

(Secs. 503(b)(1)(B), 52 Stat. 1052 as amended; 21 U.S.C. 353(b)(1)(B))

§ 250.102 Drug preparations intended for human use containing certain "coronary vasodilators."

(a)(1) The Food and Drug Administration finds that the following "coronary vasodilators" are extensively regarded by physicians as safe and useful as employed under medical supervision for the management of angina pectoris in some patients:

Amyl nitrite.
Erythrityl tetranitrate.
Mannitol hexanitrate.
Nitroglycerin.
Potassium nitrite.
Sodium nitrite.

(2) Additionally, new-drug applications have been approved for products containing:

Inositol hexanitrate.
Isosorbide dinitrate.
Octyl nitrite.
Pentaerythritol tetranitrate.
Triethanolamine trinitrate biphosphate (trolnitrate phosphate).

(b) The Food and Drug Administration also finds that there is neither substantial evidence of effectiveness nor a general recognition by qualified experts

that such drugs are effective for any of the other purposes for which some such drugs are promoted to the medical profession in labeling and advertising. In particular, neither clinical investigations nor clinical experience justify any representations that such drugs are effective in the management of hypertension; in the management of coronary insufficiency or coronary artery disease, except for their anginal manifestations; or in the management of the post coronary state, except angina pectoris present after coronary occlusion and myocardial infarction.

(c) Any preparation containing such drugs that is labeled or advertised for any use other than management of angina pectoris, or that is represented to be efficacious for any other purpose by reason of its containing such drug, will be regarded by the Food and Drug Administration as misbranded and subject to regulatory proceedings, unless such recommendations are covered by the approval of a new-drug application based on a showing of safety and effectiveness.

(d) Any such drug in long-acting dosage form is regarded as a new drug that requires an approved new-drug application before marketing.

(e) Any of the drugs listed in paragraph (a)(2) of this section is regarded as a new drug that requires an approved new-drug application. Articles for which new-drug approvals are now in effect should be covered by supplemental new-drug applications as necessary to provide for labeling revisions consistent with this policy statement.

(Secs. 502(f), 505; 52 Stat. 1051, 1052, 21 U.S.C. 352(f), 355)

§ 250.103 Thorium dioxide for drug use.

(a) Thorium dioxide is a source of naturally occurring radioactivity that has been used over a period of years as a radiopaque medium. When thorium dioxide is injected, it is permanently stored in the body. Because of its radioactivity, this storage causes scarring and carcinogenesis in the area of storage. There are reports in the medical literature of malignancy and deaths resulting from the injection of thorium dioxide. Therefore, the use in man of drugs containing thorium dioxide is justified only when this drug has a unique clinical usefulness and there is substantial evidence of limited life expectancy by reason of disease or advanced age. The administration of the drug to food-producing animals cannot be justified since it may result in residues of the drug in food.

(b) Drugs containing thorium dioxide are unsafe and are regarded as misbranded within the meaning of section 502 (f) (1), (2), and (j) of the Federal Food, Drug, and Cosmetic Act when labeled or advertised for administration to man except when they have a unique clinical usefulness and there is substantial evidence of limited life expectancy by reason of disease or advanced age.

(c) Drug preparations containing thorium dioxide may be approved for marketing on the basis of new-drug applications containing labeling bearing, in addition to other requirements, information to the following effect, which differs substantially from the labeling that has been employed in the past in the marketing of such drugs:

(1) *Warning.* For use only when this drug has a unique clinical usefulness and there is substantial evidence of limited life expectancy by reason of disease or advanced age. Not for administration to food-producing animals.

(2) *Precautions.* Special precautions should be taken to prevent soft tissue extravasation of the injected material. Precautions should be taken to prevent injection of thorium dioxide into the subarachnoid space.

(3) *Indications for use.* For demonstration of primary or secondary tumors in the liver; for the delineation of the wall of a cystic malignant brain tumor when such delineation is deemed advantageous for purposes of progressive monitoring in the course of therapy.

(4) *Dosage.* Minimum amount necessary for adequate visualization should be utilized.

(d) A new-drug application will be regarded as approvable if it contains appropriate labeling conforming to the provisions of paragraph (c) of this section and satisfactory information of the kinds required by items 2, 3, 4, 6, 7, and 9 of the new-drug application form contained in § 314.1(c) of this chapter.

(Secs. 502(f), 52 Stat. 1050 as amended; 21 U.S.C. 352(f); Secs. 402, 406, 52 Stat. 1046, as amended, 1049, as amended; 21 U.S.C. 342, 346)

§ 250.104 Status of salt substitutes under the Federal Food, Drug, and Cosmetic Act.

(a) As a result of reported poisonings from salt substitutes containing lithium chloride, under date of March 8, 1949, the Food and Drug Administration announced that it would regard each salt substitute as a new drug within the meaning of section 201 (p) of the Federal Food, Drug, and Cosmetic Act, and that interstate distribution of each salt substitute should be discontinued until a new-drug application had been filed and become effective. Substantial information concerning the safety of many of the ingredients used in salt substitutes has been developed and published since the announcement was made. It is now possible to evaluate the safety of many individual salt substitutes and to determine whether they are new drugs requiring effective applications prior to distribution in interstate commerce.

(b) The Food and Drug Administration no longer regards all salt substitutes as new drugs. Upon request, the Administration will express its opinion whether a new-drug application is necessary for any particular product if complete information concerning its composition and proposed labeling is submitted.

§ 250.105 Gelsemium-containing preparations regarded as prescription drugs.

It is the consensus of informed medical opinion that the margin of safety between the therapeutic and toxic concentration of gelsemium is narrow and it is difficult to predict the point at which the dose will be toxic. Very small doses may cause toxic symptoms. It is therefore the view of the Food and Drug Administration that gelsemium is not a proper ingredient in any product that is to be sold without prescription. Accordingly, any drug containing gelsemium will be regarded as misbranded under section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act if its label fails to bear in a prominent and conspicuous fashion the statement "Caution: Federal law prohibits dispensing without prescription."

§ 250.106 Cobalt preparations intended for use by man.

(a) On January 17, 1967 (21 CFR 3.48; 32 FR 449), the Commissioner of Food and Drugs issued a revised statement of policy with respect to the status of cobalt-containing drug preparations intended for use by man, which revision was to be modified as needed following consideration of such drugs by a panel of hematologists. A panel consisting of authorities in the field of hematology met on March 8, 1967, with representatives of the Medical Advisory Board for the Food and Drug Administration to consider the status of cobalt-containing drugs and the following findings and recommendations were made:

(1) Cobalt salts are not suitable for over-the-counter sale to the public for the treatment of iron-deficiency anemia. They are associated with toxic effects and offer no advantage over iron alone.

(2) Potential toxic effects of these salts includes liver damage, claudication, myocardial damage, thyroid hyperplasia, hypothyroidism, dermatitis, nausea, and anorexia.

(3) Cobalt salts are not generally recognized as safe or effective therapy for any disease condition.

(b) On the basis of the available evidence and the findings and recommendations of the representatives of the Medical Advisory Board, the Commissioner of Food and Drugs finds and determines with respect to cobalt-containing drug preparations intended for use by man, except radioactive forms of cobalt and its salts and cobalamin and its derivatives, that:

(1) Such articles, because of their potential for causing toxic effects, are not suitable for over-the-counter use in iron-deficiency anemia; any such article that is labeled, represented, or advertised for over-the-counter use in the prevention or treatment of iron-deficiency anemia will be regarded as subject to regulatory proceedings.

(2) Such articles are not generally recognized by qualified experts as safe or effective therapeutic agents for iron-

deficiency anemia or for any condition whether for over-the-counter sale or for prescription dispensing; any such article labeled, represented, or advertised for any condition will be regarded as subject to regulatory proceedings unless such recommendations are covered by a new-drug application approved pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act and based on a showing of safety and effectiveness.

(3) Cobalt salts added to drugs in small amounts are not effective for any purpose and should be removed.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug," Form FD-1571 set forth in § 312.1 of this chapter, must be submitted to cover clinical investigations to obtain evidence that such preparations are safe and effective for any purpose.

(d) (1) For such preparations for which new-drug approvals are in effect, supplemental new-drug applications may be submitted if changes consistent with this policy statement can be effected thereby. If the composition and labeling of an article are such that the cobalt is not significant in relation to the labeling claims, it will be permissible for the applicant to remove the cobalt salt from the formulation, delete all references to it in the labeling and resume marketing the reformulated drug, provided that a supplement is submitted within 30 days from the date of publication of this policy statement in the FEDERAL REGISTER furnishing full information regarding such changes, including the date on which such changes are being effected.

(2) Applicants holding other approved new-drug applications for such preparations should submit, within 30 days, a written statement waiving opportunity for a hearing preliminary to withdrawing approval of the application unless the applicant wishes to avail himself of the opportunity for a hearing.

(e) Regulatory proceedings may be initiated with respect to any drug within the jurisdiction of the act that is contrary to the provisions of:

(1) Paragraph (b) of this section and shipped after the date of publication of this policy statement in the FEDERAL REGISTER.

(2) Paragraphs (c) and (d) of this section and shipped after 30 days from the date of publication of this policy statement in the FEDERAL REGISTER.

(Secs. 502 (a), (f), (j), 505, 52 Stat. 1050–1053, as amended; 21 U.S.C. 352 (a), (f), (j), 355)

§ 250.107 Dimethylsulfoxide (DMSO) preparations; clinical testing and investigational use.

(a) (1) Chronic-toxicity studies with dimethylsulfoxide (DMSO) in animals, including dogs, rabbits, and swine, reported by a consulting laboratory in England and by a number of laboratories in the United States show that the administration of dimethylsulfoxide (DMSO) causes changes in the refractive index of the lens of the eyes of such animals. On the basis of these reports, clinical testing of dimethylsulfoxide (DMSO) preparations was discontinued for a time and later resumed under restricted conditions.

(2) An adequate, controlled human toxicity study (Phase I) involving short-term cutaneous application of 1 gram of dimethylsulfoxide (DMSO) per kilogram of body weight daily for 14 consecutive days has recently been completed. Data obtained, not previously available, show that when dimethylsulfoxide (DMSO) was applied topically to the skin of healthy volunteers, it did not produce adverse effects upon the eyes of the subjects. Mild, apparently reversible, changes were seen suggesting that the drug may have some effect upon the liver and upon the hemopoietic system in some subjects.

(b) A comprehensive evaluation of all available data on dimethylsulfoxide (DMSO) preparations justifies further clinical investigation of the drug in treating certain serious conditions. Although reports concerning the use of dimethylsulfoxide (DMSO) in relatively benign conditions are equivocal regarding its efficacy, short-term clinical use has been established as reasonably safe by adequate Phase I studies. Under appropriate protocols, further short-term clinical investigations in the treatment of such benign conditions can be justified.

(c) No person may ship dimethylsulfoxide (DMSO) within the jurisdiction of the Federal Food, Drug, and Cosmetic Act for clinical testing in man until a "Notice of Claimed Investigational Exemption for a New Drug," pursuant to § 312.1 of this chapter, is on file with the Food and Drug Administration and all the following conditions are met:

(1) Proposed long-term clinical studies (Phase II) are restricted to the use of DMSO to cutaneous application in serious conditions, such as the incapacitating arthropathies, scleroderma, dermatomyositis, and intractible pain due to malignancy, are to be conducted in medical centers having adequate facilities and well-trained, experienced medical personnel, and are to include the following essential conditions in the study protocol. All subjects will receive a full examination including:

(i) An eye evaluation by an ophthalmologist to include actual refractive error measurements and slit-lamp findings as well as other parameters of the ocular examination prior to receiving the drug, at intervals not exceeding 3 months during the study and 3 months after discontinuing the drug.

(ii) Liver function tests and a complete blood count (CBC) prior to receiving the drug, at intervals not exceeding 4 weeks during the study and 4 weeks after discontinuing the drug.

(2) Proposed short-term studies (Phase II) restrict the use of dimethylsulfoxide (DMSO) to cutaneous application for not more than 14 days in closely monitored investigations with appropriate control groups, that may include studies of use in such conditions as acute musculoskeletal conditions (acute arthritis, periarthritis, capsulitis, bursitis, tendonitis, synovitis, and post-traumatic lesions) and soft tissue injuries. The proposed studies shall provide for pretreatment liver function studies and a complete blood count (CBC), to be repeated within 7 days after commencing treatment and at the conclusion of the study. Routine monitoring of effects upon the eye is not required.

(3) All proposals must show that patient consent requirements will be carefully observed and shall include a commitment that patients will be fully informed of: The effects of dimethylsulfoxide (DMSO) in animals, the possibility that these may occur in humans, and the known possible effects of the drug in humans.

(d) Dimethylsulfoxide (DMSO) preparations may be shipped within the jurisdiction of the act.

(1) For tests in vitro and in laboratory research animals, in accord with § 312.9 (a) and § 511.1(a) of this chapter.

(2) For clinical investigations in animals in accord with § 511.1(b) of this chapter.

(Secs. 505, 512, 52 Stat. 1052, 1053, as amended; 82 Stat. 343–351; 21 U.S.C. 355, 360b)

§ 250.108 Potassium permanganate preparations as prescription drugs.

(a) There have been a number of reports in the medical literature of serious injuries to women resulting from the misuse of potassium permanganate in an effort to induce abortion. Reports from physicians who have treated such cases show that the injuries are commonly caused by introducing tablets or crystals of potassium permanganate into the vagina. Experience with these cases shows that such use of potassium permanganate is not effective in producing abortion, but that instead the drug produces serious and painful injury to the walls of the vagina, causing ulcers, massive hemorrhage, and infection. Such dangerous and useless employment of potassium permanganate is apparently encouraged among the misinformed by the mistaken idea that the vaginal bleeding caused by the corrosive action of the drug indicates a termination of pregnancy, which it does not.

(b) Potassium permanganate is a strong oxidizing agent, a highly caustic, tissue-destroying chemical, and a poison. There are no circumstances under which crystals and tablets of potassium permanganate constitute safe dosage forms for use in self-medication. It is the consensus of informed medical opinion that the only dosage forms of potassium permanganate known to be safe for use in self-medication are aqueous solutions containing not more than 0.04 percent potassium permanganate. Such solutions are safe for use in self-medication only by external application to the skin.

(c) In view of the very real potentiality for harmful effect, and the actual injuries caused by the misuse of potassium permanganate, the Food and Drug Administration believes that in order adequately to protect the public health:

(1) Potassium permanganate and potassium permanganate tablets intended

for human use are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and should be restricted to prescription sale. Such drugs will be regarded as misbranded if at any time prior to dispensing the label fails to bear the legend, "Caution: Federal law prohibits dispensing without prescription."

(2) Potassium permanganate labeled for use as a prescription component in human drugs under the exemption provided in § 201.120 of this chapter or labeled for manufacturing use under the exemption provided in § 201.122 of this chapter will be regarded as misbranded unless the label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

(3) These drugs will be regarded as misbranded when intended for veterinary use unless the label bears the legend, "Caution: Federal law restricts this drug to sale by or on the order of a licensed veterinarian"; *Provided, however,* That this shall not apply to a drug labeled and marketed for veterinary use if such drug contains not more than 50 percent of potassium permanganate and includes other ingredients which make it unsuitable for human use and unlikely that the article would be used in an attempt to induce abortion.

(4) Any preparation of potassium permanganate intended for over-the-counter sale for human use internally or by application to any mucous membranes or for use in the vagina will be regarded as misbranded under the provisions of section 502(f) (1) and (2) and section 502(j) of the act.

(5) Any other preparation of potassium permanganate intended for over-the-counter sale for human use will be regarded as misbranded under section 502(f)(1) and (2) and section 502(j) of the act unless, among other things, all of the following conditions are met:

(i) It is an aqueous solution containing not more than 0.04 percent potassium permanganate.

(ii) The label and labeling bear, in juxtaposition with adequate directions for use, clear warning statements designated as "Warning," and to the effect: "Warning—For external use on the skin only. Severe injury may result from use internally or as a douche. Avoid contact with mucous membranes."

(d) The labeling or dispensing of any potassium permanganate preparations intended for drug use within the jurisdiction of the Federal Food, Drug, and Cosmetic Act contrary to this statement after 60 days from the date of its publication in the FEDERAL REGISTER may be made the subject of regulatory proceedings.

(Secs. 502(f) (1), (2), (j), 503(b)(1), 705(b), 52 Stat. 1050, 1051, 1052, as amended, 1057; 21 U.S.C. 352(f) (1), (2), (j), 353(b)(1), 375(b))

§ 250.109 Vitamin A preparations for oral use as drugs.

(a) Vitamin A is an essental nutrient for humans. It is widely recognized that large amounts of vitamin A can cause adverse effects, some of which are serious. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin A is 1500 International Units, (IU) for infants, 2500 IU for children under 4 years of age, 5000 IU for adults and children 4 or more years of age, and 8000 IU for pregnant or lactating women.

(b) In view of the toxicity of excessive consumption of vitamin A, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin A in excess of 10,000 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 201.100(c) (1) of this chapter, and especially appropriate warnings regarding vitamin A toxicity.

(c) Preparations containing 10,000 or less IU of vitamin A per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 10,000 IU.

(Secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a))

§ 250.110 Vitamin D preparations for oral use as drugs.

(a) Vitamin D is an essential nutrient for humans. It is widely recognized that vitamin D, when ingested daily in large amounts, is toxic. The U.S. Recommended Daily Allowance (U.S. RDA) for vitamin D is 400 International Units (IU).

(b) In view of the toxicity of the excessive consumption of vitamin D, the Food and Drug Administration finds that, in order to protect the public health, oral preparations containing vitamin D in excess of 400 IU per dosage unit or recommended daily intake are drugs subject to section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act and shall be restricted to prescription sale. Such products will be regarded as misbranded if at any time prior to dispensing the following conditions are not met:

(1) The label bears the legend, "Caution: Federal law prohibits dispensing without a prescription"; and

(2) The labeling bears full disclosure information as required by § 201.100(c) (1) of this chapter, and especially appropriate warnings regarding vitamin D toxicity.

(c) Preparations containing 400 or less IU of vitamin D per dosage unit will be regarded as misbranded if their recommended daily intake exceeds 400 IU.

(d) Foods which are represented for use solely under medical supervision to meet nutritional requirements of persons with poor vitamin D absorption may contain vitamin D not in excess of 1000 IU per dosage unit or recommended daily intake.

(Secs. 502(a), (f), and (j), 503(b), 701(a), 52 Stat. 1050–1052, as amended, 1055; 21 U.S.C. 352(a), (f), and (j), 353(b), 371(a))

Subpart C—Requirements for Drugs and Foods

§ 250.201 Preparations for the treatment of pernicious anemia.

(a) The ninth announcement of the Anti-anemia Preparations Advisory Board of the United States Pharmacopeia is concerned with the status of the treatment of pernicious anemia. It clearly presents the following facts:

(1) The Sixteenth Revision of the Pharmacopeia of the United States, which became official on October 1, 1960, does not include preparations intended for the treatment of pernicious anemia by oral administration.

(2) The U.S.P. unit for anti-anemia preparations no longer has any significance.

(3) The U.S.P. Anti-anemia Preparations Advisory Board was disbanded.

(b) On the basis of the scientific evidence and conclusions summarized in the statement of the U.S.P. Anti-anemia Preparations Advisory Board as well as pertinent information from other sources, the Commissioner of Food and Drugs finds it is the consensus of well informed medical opinion that:

(1) The parenteral administration of cyanocobalamin or vitamin B_{12} is generally recognized as a fully effective treatment of pernicious anemia. Parenteral cyanocobalamin preparations have not been and are not authorized for use except by or on the prescription of a duly licensed medical practitioner.

(2) Some patients afflicted with pernicious anemia do not respond to orally ingested products. There is no known way to predict which patients will fail to respond or will cease to respond to the treatment of pernicious anemia with orally ingested preparations.

(3) The substitution of a possibly inadequate treatment, such as the ingestion of oral preparations of vitamin B_{12} with intrinsic factor concentrate, in place of parenteral vitamin B_{12} products for a disease condition as serious as pernicious

anemia cannot be regarded as safe in all cases.

(4) The development of the classical symptoms of pernicious anemia that would cause a person to seek medical attention may in some cases be delayed by oral ingestion of intrinsic factor. Pernicious anemia is a disease that is associated, among other things, with a higher than normal incidence of cancer of the stomach and that for the safety of the patient, requires continuous expert medical supervision.

(5) With inadequate treatment there may be markedly deleterious effects on the nervous system. It is well established that whereas the development of anemia is completely reversible with adequate treatment, the involvement of the nervous system may not be completely reversible and thus may result in permanent damage.

(6) Some hematologists prescribe oral preparations of vitamin B_{12} in the treatment of pernicious-anemia patients.

(7) Intrinsic factor and intrinsic factor concentrate serve no known useful therapeutic or nutritive purpose except to the extent that they do increase the gastrointestinal absorption of vitamin B_{12} in patients with a deficiency or absence of intrinsic factor, which may eventually lead to pernicious anemia. This conclusion does not apply to diagnostic procedures using radioactive cyanocobalamin.

(8) Medical expertise is required for the diagnosis as well as the management of pernicious anemia.

(c) The Eleventh Edition of The National Formulary and its first Interim Revision include monographs for oral preparations of vitamin B_{12} with intrinsic factor concentrate, establish a unit of vitamin B_{12} with intrinsic factor concentrate, and provide for a National Formulary Anti-anemia Preparations Advisory Board to assign the potency of such preparations. This provides for the availability of such oral preparations, standardized within the meaning of the broad limits characteristic of the evaluation of such preparations.

(d) Any drug that is offered for or purports to contain intrinsic factor or intrinsic factor concentrate will be regarded as misbranded within the meaning of section 503(b) of the Federal Food, Drug, and Cosmetic Act unless it is labeled with the legend "Caution—Federal law prohibits dispensing without prescription."

(e) Any drug for oral ingestion intended, represented, or advertised for the prevention or treatment of pernicious anemia or which purports to contain any substance or mixture of substances described in paragraph (d) of this section (other than diagnostic drugs containing radioactive cyanocobalamin) will be regarded as misbranded under sections 502 (f)(2) and (j) of the act unless its labeling bears a statement to the effect that some patients afflicted with pernicious anemia may not respond to the orally ingested product and that there is no known way to predict which patients will respond or which patients may cease to respond to the orally ingested products. The labeling shall also bear a statement that periodic examinations and laboratory studies of pernicious-anemia patients are essential and recommended.

(f) Under section 409 of the Federal Food, Drug, and Cosmetic Act, intrinsic factor and intrinsic factor concentrate are regarded as food additives. No food additive regulation nor existing extension of the effective date of section 409 of the act authorizes these additives in foods, including foods for special dietary uses. Any food containing added intrinsic factor or intrinsic factor concentrate will be regarded as adulterated within the meaning of section 402(a)(2)(C) of the act.

(g) Regulatory action may be initiated with respect to any article shipped within the jurisdiction of the act contrary to the provisions of this policy statement after the 180th day following publication of this statement in the FEDERAL REGISTER.

(Secs. 402, 502, 503, 52 Stat. 1051, 1052 as amended; 65 Stat. 648, 72 Stat. 1784; 21 U.S.C. 342, 352, 353)

§ 250.203 Status of fluoridated water and foods prepared with fluoridated water.

(a) The program for fluoridation of public water supplies recommended by the Department of Health, Education, and Welfare, through the Public Health Service, contemplates the controlled addition of fluorine at a level optimum for the prevention of dental caries.

(b) Public water supplies do not ordinarily come under the provisions of the Federal Food, Drug, and Cosmetic Act. Nevertheless, a substantial number of inquiries have been received concerning the status of such water under the provisions of the act and the status, in interstate commerce, of commercially prepared foods in which fluoridated water has been used.

(c) The Department of Health, Education, and Welfare will regard water supplies containing fluorine, within the limitations recommended by the Public Health Service, as not actionable under the Federal Food, Drug, and Cosmetic Act. Similarly, commercially prepared foods within the jurisdiction of the act, in which a fluoridated water supply has been used in the processing operation, will not be regarded as actionable under the Federal law because of the flourine content of the water so used, unless the process involves a significant concentration of fluorine from the water. In the latter instance the facts with respect to the particular case will be controlling.

Subpart D—Requirements for Drugs and Cosmetics

§ 250.250 Hexachlorophene, as a component of drug and cosmetic products.

(a) *Antibacterial component.* The use of hexachlorophene as an antibacterial component in drug and cosmetic products has expanded widely in recent years. It is used in such products because of its bacteriostatic action against gram-positive organisms, especially against strains of staphylococcus; however, hexachlorophene offers no protection against gram-negative infections. In addition the antibacterial activity depends largely on repeated use. A notice published in the FEDERAL REGISTER of April 4, 1972 (37 FR 6775), invited data on OTC antimicrobial ingredients, including hexachlorophene, for review by an OTC Drug Advisory Review Panel to be convened under the procedures set forth in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464). This statement of policy will remain in effect unless and until replaced by a monograph resulting from the OTC Drug Advisory Review Panel.

(b) *Adverse effects.* Though considered safe for many years, recent information has become available associating hexachlorophene with toxic effects, including deaths. Studies have shown that toxic amounts of hexachlorophene can be absorbed through the skin of humans, especially the skin of premature babies or damaged skin. Human toxicity reports include data on symptomatology, blood

and tissue levels of hexachlorophene, and descriptions of neuropathologic lesions. Recent infant deaths due to use of baby powder accidentally contaminated with 6 percent hexachlorophene have occurred. The accumulated evidence of toxicity is sufficient to require that continued marketing of hexachlorophene containing products be carefully defined in order to protect consumers.

(c) *Prescription drugs.* (1) Because of their potential for harmful effect, drugs containing hexachlorophene, other than as a preservative as described below, are not considered to have been shown to be safe and effective, are regarded as new drugs requiring approved new drug applications, and would be misbranded for over-the-counter distribution. In the interest of public health protection, hexachlorophene containing drugs will be regarded as misbranded and subject to regulatory proceedings unless the label bears the legend "Caution: Federal law prohibits dispensing without a prescription," and the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by practitioners, in accord with § 201.100(c) of this chapter.

(2) The Food and Drug Administration recognizes that hexachlorophene is useful as a bacteriostatic skin cleanser. It further concludes that the margin of safety is such that products containing hexachlorophene may appropriately be used within clearly delineated conditions of use.

(3) In order for such drugs to bear adequate information for safe and effective use the following statements are representative of the type of labeling for products shown to be effective bacteriostatic skin cleansers. Labeling for products other than bacteriostatic skin cleansers will be determined through the new drug procedures based on the available data.

(i) In the labeling other than on the immediate container label.

INDICATIONS

1. Bacteriostatic skin cleanser for surgical scrubbing or handwashing as part of patient care.

2. For topical application to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

CONTRAINDICATIONS

1. Not for use on burned or denuded skin or on mucous membranes.

2. Not for routine prophylactic total body bathing.

WARNINGS

Rinse thoroughly after use. Patients should be closely monitored and use should be immediately discontinued at the first sign of any of the symptoms described below.

Hexachlorophene is rapidly absorbed and may produce toxic blood levels when applied to skin lesions such as ichthyosis congenita or the dermatitis of Letterer-Siwe's syndrome or other generalized dermatologic conditions. Application to burns has also produced neurotoxicity and death.

Infants have developed dermatitis, irritability, generalized clonic muscular contractions and decerebrate rigidity following application of a 6 percent hexachlorophene powder. Examination of brainstems of those infants revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3 percent hexachlorophene. Moreover, a study of histologic sections of premature infants who died of unrelated causes has shown a positive correlation between hexachlorophene baths and lesions in white matter of brains.

(ii) On the immediate container label prominently displayed and in bold print:

"Special Warning: This compound may be toxic if used other than as directed. Rinse thoroughly after use. Monitor patients closely for toxicity symptoms."

(4) Marketing of products for the indications listed in paragraph (c)(3) of this section may be continued if all the following conditions are met after the effectve date of this section (9–27–72):

(i) The product is labeled with the prescription legend and adequate information for safe and effective use as set forth in paragraph (c)(3) of this section.

(ii) Within 30 days, or by (10–27–72) the holder of an approved new drug application submits a supplement to provide for the revised label and full disclosure labeling. As the label and labeling will have been put into use, the supplement should be submitted under the provision of § 314.8(d) of this chapter.

(iii) Within 30 days, or by (10–27–72) the holder of an approved new drug application submits a supplement to provide for a revised formulation where appropriate to comply with this order.

(iv) Within 90 days, or by (12–26–72) the holder of an approved new drug application submits a supplement containing blood level data obtained from use of the drug as recommended, unless such information is a part of the new drug application file.

(v) Within 90 days, or by (12–26–72), the manufacturer or distributor of such a drug for which a new drug approval is not in effect submits a new drug application in accord with § 314.1 of the new drug regulations (21 CFR 314.1), including blood level data obtained from use of the drug as recommended.

(5) Prescription drug products may contain hexachlorophene as part of an effective preservative system only under the conditions and limitations provided for under paragraph (d) of this section.

(d) *Over-the-counter (OTC) drugs.* Over-the-counter drug products, other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, may contain hexachlorophene only as part of an effective preservative system, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. This use of hexachlorophene will not, by itself, require an approved new drug application. Use of hexachlorophene as a preservative at a level higher than 0.1 percent is regarded as a new drug use requiring an approved new drug application, which must be submitted within the time set out in paragraph (c)(4) of this section.

(e) *Cosmetics.* Hexachlorophene may be used as a preservative in cosmetic products other than those which in normal use may be applied to mucous membranes or which are intended to be used on mucous membranes, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. The component of a preservative system, whether hexachlorophene or other antimicrobial agent, should be selected on the basis of the effect on the total microbial ecology of the product, not merely on gram-positive bacteria.

(1) Adequate safety data do not presently exist to justify wider use of hexachlorophene in cosmetics.

(2) Antibacterial ingredients used as substitutes for hexachlorophene in cosmetic products, and finished cosmetic products containing such ingredients, shall be adequately tested for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing may be adulterated and will in any event be deemed misbranded unless it contains a conspicuous front panel statement that the product has not been adequately tested for safety and may be hazardous.

(f) *Content statement.* All reference to hexachlorophene limit in this order is on a weight-in-weight (w/w) basis. Quantitative declaration of hexachlorophene content on the labeling of the products, where required, shall be on a w/w basis.

(g) *Shipments of products.* Shipments of products falling within the scope of paragraph (c), (d), or (e) of this section which are not in compliance with the guidelines stated herein shall be the subject of regulatory proceedings after the effective date of the final order.

(h) *Prior notices.* This order preempts any conditions for marketing products set forth in the following prior notices.

1. DESI No. 4749 (34 FR 15389, October 2, 1969), "Certain OTC Drugs for Topical Use."

2. DESI No. 2855 (35 FR 12423, August 4, 1970), "Certain Mouthwash and Gargle Preparations."

3. DESI No. 8940 (36 FR 14510, August 6, 1971), "Topical Cream Containing Pyrilamine Maleate, Benzocaine, Hexachlorophene, and Cetrimonium Bromide."

4. DESI No. 6615 (36 FR 18022, September 8, 1971), "Deodorant/Antiperspirant."

5. DESI No. 6270 (36 FR 23330, December 8, 1971), "Certain Preparations Containing Hexachlorophene".

(Secs. 201(n), 502 (a), (f), (j), 503(b), 505, 601(a), 602 (a), (c), 701(a), 52 Stat. 1041, 1050–55 as amended; 21 U.S.C. 321(n), 352 (a), (f), (j), 353(b), 355, 361(a), 362 (a), (c), 371(a))

Subpart E—Special Packaging Requirements

§ 250.300 Nitroglycerin for human use; packaging and warnings.

(a) Nitroglycerin preparations have long been used under medical supervision for the management of angina pectoris. The volatility of nitroglycerin has been recognized for many years, and consequently packaging requirements for preparations containing this drug provide for storage in tight containers. When glass containers were used almost exclusively this limited packaging requirement was probably adequate, even though no provisions were made to inform the user that his filled prescription should be kept in a tight container. The recent trend toward packaging containers made of materials other than glass presents new problems, because of the different properties of such materials. Recent information, including laboratory data, available to the Food and Drug Administration indicates that improper packaging of the drug either before or after dispensing to the patient will likely result in a substantial loss of nitroglycerin. The Food and Drug Administration's studies indicate that commonly used plastic containers and certain kinds of strip packaging allow appreciable evaporation of nitroglycerin from nitroglycerin tablets.

(b) The Commissioner views these findings as raising serious questions concerning the packaging practices for nitroglycerin preparations and their relationship to the potency characteristics of the drug at the time of dispensing and use by the patient. Stability studies with containers other than glass are needed before reasonable assurance can be made that packaging and storage in these containers does not contribute to the loss of nitroglycerin in any dosage form.

(c) The following packaging and labeling is required for preparations containing nitroglycerin:

(1) Preparations containing nitroglycerin shall be packaged in tight (as defined in the United States Pharmacopeia) glass containers with tightly fitting metal screw caps or in containers of materials approved by the Food and Drug Administration. No more than 100 dosage units shall be packaged in any such container.

(2) In addition to other required labeling information, the following shall be displayed on the container in a prominent and conspicious manner:

(i) A statement directed to the pharmacist that the drug should be stored at controlled room temperature (as defined in the United States Pharmacopeia) and dispensed only in the original, unopened container.

(ii) A warning statement to the patient as follows: "Warning. To prevent loss of potency, keep these tablets in the original container. Close tightly immediately after each use."

(d) The holder of an approved new drug application for a nitroglycerin preparation should either submit a supplement to his new-drug application under the provisions of § 314.8(d) of this chapter to provide for use of glass containers and labeling as described in this section or submit data or reference to data adequate to show that such changes are not necessary. The labeling and packaging requirements of this section must be met unless an approved supplement to a new-drug application provides for alternate packaging methods.

(e) For containers other than glass, approval must be obtained from the Food and Drug Administration on the basis of data submitted by interested persons establishing its suitability for packaging of nitroglycerin. Upon review and approval of alternate packaging this section will be amended to provide for such packaging. The data should be submitted to the Division of Cardiopulmonary Renal Drug Products (BD–110), Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852. Such data should be accompanied with a request that an exemption be made as provided for in this paragraph. Until approval for containers other than glass is given by the Food and Drug Administration, such alternate containers are not considered suitable for the packaging of nitroglycerin preparations.

(f) Any nitroglycerin drug preparation which is shipped or dispensed within the jurisdiction of the act and contrary to the provisions of this section after its effective date will be the subject of regulatory proceedings.

(Secs. 501, 502, 505, 52 Stat. 1049–53 as amended, 1056 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 351, 352, 355)

PART 290—CONTROLLED DRUGS

Subpart A—General Provisions

Sec.

Subpart B [Reserved]

Subpart C—Requirements for Specific Controlled Drugs

AUTHORITY: Sec. 701, 52 Stat. 1055–1056 as amended; 21 U.S.C. 371, unless otherwise noted.

Subpart A—General Provisions

§ 290.5 Drugs; statement of required warning.

The label of any drug listed as a "controlled substance" in schedule II, III, or IV of the Federal Controlled Substances Act shall, when dispensed to or for a patient, contain the following warning: "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed." This statement is not required to appear on the label of a controlled substance dispensed for use in clinical investigations which are "blind."

§ 290.6 Spanish-language version of required warning.

By direction of section 305(c) of the Federal Controlled Substances Act, § 290.5, promulgated under section 503(b) of the Federal Food, Drug, and Cosmetic Act, requires the following warning on the label of certain drugs when dispensed to or for a patient: "Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed." The Spanish version of this is: "Precaucion: La ley Federal prohibe el transferir de esta droga a otra persona que no sea el paciente para quien fue recetada."

(Secs. 502, 503; 68 Stat. 854, 65 Stat. 648; 21 U.S.C. 352, 353)

§ 290.10 Definition of emergency situation.

For the purposes of authorizing an oral prescription of a controlled substance listed in schedule II of the Federal Controlled Substances Act, the term "emergency situation" means those situations in which the prescribing practitioner determines:

(a) That immediate administration of the controlled substance is necessary, for proper treatment of the intended ultimate user; and

(b) That no appropriate alternative treatment is available, including administration of a drug which is not a controlled substance under schedule II of the Act, and

(c) That it is not reasonably possible for the prescribing practitioner to provide a written prescription to be presented to the person dispensing the substance, prior to the dispensing.

Subpart B—[Reserved]

Subpart C—Requirements for Specific Controlled Drugs

§ 290.35 Methadone in the maintenance treatment of narcotic addicts.

(a) The Food and Drug Administration and the Drug Enforcement Administration recognize that the investigational use of methadone requiring the prolonged maintenance of narcotic dependence as part of a total treatment effort has shown promise in the management and rehabilitation of selected narcotic addicts. It is also recognized that a number of dangers and possible abuses may arise from such efforts if professional services and controls are inadequately applied. It is further felt that additional research is urgently needed so that data may be accumulated which will permit sound determinations of safety, efficacy, and necessary procedural safeguards.

(b) Therefore, the Commissioner of Food and Drugs and the Director of the Drug Enforcement Administration, Department of Justice agree that interested professionals, municipalities, and organizations should be allowed to conduct further research in this area within a framework of adequate controls designed to protect the individual patients and the community. To facilitate this purpose, the Food and Drug Administration and the Drug Enforcement Administration, Department of Justice have jointly agreed upon acceptable criteria and guidelines which are set forth in pro-

posed 21 CFR 1319.505. In addition such other provisions of the Federal narcotic laws and regulations as are applicable must also be observed.

(Sec. 505, 52 Stat. 1052–53, as amended; 21 U.S.C. 355)

PART 299—DRUGS; OFFICIAL NAMES AND ESTABLISHED NAMES

Subpart A—General Provisions

Sec.
299.3 Definitions and interpretations.
299.4 Established names for drugs.
299.5 Drugs; compendial name.

Subpart B—Designated Names

299.20 Drugs; official names.

AUTHORITY: Secs. 508, 701(a), 52 Stat. 1055, 76 Stat. 1789; 21 U.S.C. 358, 371(a), unless otherwise noted.

Subpart A—General Provisions

§ 299.3 Definitions and interpretations.

(a) As used in this Part 299, "act" means the Federal Food, Drug, and Cosmetic Act, sections 201–902, 52 Stat. 1040 (21 U.S.C. 321–392), with all amendments thereto.

(b) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this Part 299.

(c) The term "official name" means, with respect to a drug or ingredient thereof, the name designated in this Part 299 under section 508 of the act as the official name.

§ 299.4 Established names for drugs.

(a) Section 508 of the Federal Food, Drug, and Cosmetic Act (added by the Kefauver-Harris Drug Amendments of 1962; Public Law 87–781) authorizes the Commissioner of Food and Drugs to designate an official name for any drug if he determines that such action is necessary or desirable in the interest of usefulness and simplicity. Section 502(e) of the act (as amended by said Drug Amendments) prescribes that the labeling of a drug must bear its established name, if there is one, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula) and, if the drug is fabricated from two or more ingredients, the established name of each active ingredient.

(b) The term "established name" is defined in section 502(e)(2) of the act as (1) an official name designated pursuant to section 508 of the act; (2) if no such official name has been designated for the drug and the drug is an article recognized in an official compendium, then the official title theretof in such compendium; and (3) if neither paragraph (b) (1) nor (2) of this section applies, then the common or usual name of the drug.

(c) The Food and Drug Administration recognizes the skill and experience of the U.S. Adopted Names Council (USAN) in deriving names for drugs. The U.S. Adopted Names Council is a private organization sponsored by the American Medical Association, the United States Pharmacopeia, and the American Pharmaceutical Association, and has been engaged in the assignment of names to drugs since January 1964. The Council negotiates with manufacturing firms in the selection of nonproprietary names for drugs.

(d) The Food and Drug Administration cooperates with and is represented on the USAN Council. In addition, the Food and Drug Administration is in agreement with the "Guiding Principles for Coining U.S. Adopted Names for Drugs," published in New Drugs Evaluated by A.M.A. Council on Drugs, 1967 edition, pages 556–561, and in U.S. Adopted Names (USAN), Cumulative List, number 5, 1961–1966, pages 100–105.[2] All applicants for new-drug applications and sponsors for "Notice of Claimed Investigational Exemption for a New Drug" (IND's) are encouraged to contact the USAN Council for assistance in selection of a simple and useful name for a new chemical entity. Approval of a new-drug application providing for the use of a new drug substance or a new antibiotic drug may be delayed if a simple and useful nonproprietary name does not exist for the substance and if one is not proposed in the application that meets the above-cited guidelines. Prior use of a name in the medical literature or otherwise will not commit the Food and Drug Administration to adopting such terminology as official.

(Secs. 502(e), 508, 52 Stat. 1050, as amended, 76 Stat. 789, 790, 21 U.S.C. 352(e), 358)

§ 299.5 Drugs; compendial name.

(a) The name by which a drug is designated shall be clearly distinguishing and differentiating from any name recognized in an official compendium unless such drug complies in identity with the identity prescribed in an official compendium under such recognized name.

(b) The term "drug defined in an official compendium" means a drug having the identity prescribed for a drug in an official compendium.

(c) A statement that a drug defined in an official compendium differs in strength, quality, or purity from the standard of strength, quality, or purity set forth for such drug in an official compendium shall show all the respects in which such drug so differs, and the extent of each such difference.

(Sec. 501, 52 Stat. 1050, as amended; 21 U.S.C. 351)

Subpart B—Designated Names

§ 299.20 Drugs; official names.

The following are designated official under section 508 of the act and are "established" names within the meaning of section 502(e) of the act:

[2] Copies may be obtained from: U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

Official name	Chemical name or description	Molecular formula
Aceclidine	3-Quinuclidinol acetate (ester); 3-acetoxyquinuclidine	$C_9H_{15}NO_2$
Acedapsone	4',4'''-Sulfonylbis[acetanilide]	$C_{16}H_{16}N_2O_4S$
Acetylcysteine	*N*-Acetyl-L-cysteine	$C_5H_9NO_3S$
Acrisorcin	9-Aminoacridine, salt with 4-hexylresorcinol	$C_{13}H_{10}N_2C_{12}H_{18}O$
Acronine	3,12-Dihydro-6-methoxy-3,3,12-trimethyl-7 *H*-pyrano[2,3-*c*]acridin-7-one.	$C_{20}H_{19}NO_3$
Adenosine	6-Amino-9-β-D-ribofuranosyl-9*H*-purine	$C_{10}H_{13}N_5O_4$
Adiphenine	2-(Diethylamino)ethyl diphenylacetate	$C_{20}H_{25}NO_2$ or $C_{20}H_{26}N_2O_2$
Aklomide	2-Chloro-4-nitrobenzamide	$C_7H_5ClN_2O_3$
Alamecin	An antibiotic substance derived from *Trichoderma viride Pers. ex fries.*	
Alcuronium	*N,N'*-Diallylnortoxiferinium; diallylbisnortoxiferin	$C_{44}H_{48}N_4O_2$
Alexidine	1,1'-Hexamethylenebis[5-(2-ethylhexyl)biguanide]	$C_{28}H_{62}N_{12}$
Algestone	16α,17-Dihydroxypregn-4-ene-3,20-dione	$C_{21}H_{30}O_4$
Allobarbital	5,5-Diallylbarbituric acid	$C_{12}H_{14}N_2O_3$
Allopurinol	1*H*-Pyrazolo[3,4-*d*]pyrimidin-4-ol; 4-hydroxypyrazolo (3,4-*d*)-pyrimidine.	$C_5H_4N_4O$
Alprenolol	1-(*o*-Allylphenoxy)-3-(isopropylamino)-2-propanol	$C_{15}H_{23}NO_2$
Ambuphylline	Theophylline, compound with 2-amino-2-methyl-1-propanol	$C_7H_8N_4O_2.C_4H_{11}NO$
Ambuside	N¹-Allyl-4-chloro-6-[(3-hydroxy-2-butenylidene)amino]-*m*-benzenedisulfonamide; 2-allylsulfamyl-5-chloro-4-sulfamyl-*N*-(3-hydroxy-2-buteneylidene) aniline.	$C_{13}H_{13}ClN_4O_5S_3$
Amiloride	*N*-Amidino-3,5-diamino-6-chloropyrazinecarboxamide	$C_6H_8ClN_7O$
Aminacrine	9-Aminoacridine	$C_{13}H_{10}N_2$
Amphomycin	A substance produced by *Streptomyces canus*.	
Ampicillin	6-(D-2-Amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid.	$C_{16}H_{19}N_3O_4S$
Amquinate	Methyl 7-(diethylamino)-4-hydroxy-6-propyl-3-quinolinecarboxylate.	$C_{18}H_{24}N_2O_3$
Anisotropine	Tropine 2-propylvalerate	$C_{18}H_{33}NO_2$
Apazone	5-(Dimethylamino)-9-methyl-2-propyl-1*H*-pyrazolo[1,2-*a*][1,2,4] benzotriazine-1,3(2*H*)-dione.	$C_{16}H_{20}N_4O_2$
Aprotinin	Arg-Pro-Asp (tentative)-Phe-HCys-Leu-Glu (tentative)-Pro-Pro-Tyr-Thr-Gly-Pro-HCys-Lys-Ala-Arg-Ileu-Ileu-Arg-Tyr-Phe-Tyr-AspN-Ala-Lys-Ala-Gly-Leu-HCys-GluN-Thr-Phe-Val-Tyr-Gly-Gly-HCys-Arg-Ala-Lys-Arg-AspN-AspN-Phe-Lys-Ser-Ala-Glu-AspN-HCys-Met-Arg-Thr-HCys-Gly-Gly-Ala.	
Aranotin	5,5a,13,13a-Tetrahydro-5,13-dihydroxy-8*H*,16*H*-7a,15a-epidithio-7*H*,15*H*-bisoxepino[3',4':4,5]pyrrolo[1,2-*a*:1',2'-*d*]pyrazine-7,15-dione-5-acetate.	$C_{28}H_{18}N_2O_7S_2$
Arginine	L(+)-Arginine	$C_6H_{14}N_4O_2$
Artegraft	Arterial graft composed of a section of bovine carotid artery that has been subjected to enzymatic digestion with ficin and tanned with dialdehyde starch.	
Atolide	2-Amino-4'-(diethylamino)-*o*-benzotoluidide	$C_{18}H_{23}N_3O$
Azaperone	4' Fluoro-4-[4-(2-pyridyl)-5-piperazinyl]butyrophenone; 1[3-(4-fluorobenzoyl)-propyl]-4-(2-pyridyl)piperzaine.	$C_{19}H_{22}FN_3O$
Azaribine	2-β-D-Ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione-2',3',5'-triacetate; (2',3',5'-triacetyl)-2-β-D-ribofuranosyl-*as*-triazine-(2*H*,4*H*)-dione.	$C_{14}H_{17}N_3O_9$
Azaserine	Serine diazoacetate (ester)	$C_5H_7N_3O_4$
Azathioprine	6-[1-Methyl-4-nitromidazol-5-yl)thio]purine	$C_9H_7N_7O_2S$
Bamethan	α-[(Butylamino)methyl]-*p*-hydroxybenzyl alcohol	$C_{12}H_{19}NO_2$
Benzolinе	2-[(2-Methylbenzo[*b*]thien-3-yl)methyl]-2-imidazoline; 2-methyl-3-(Δ2-imidazolinylmethyl)benzo[*b*]thiophene.	$C_{13}H_{14}N_2S$
Bendazac	[(1-Benzyl-1*H*-indazol-3-yl)oxy]acetic acid	$C_{16}H_{14}N_2O_3$

Official name	Chemical name or description	Molecular formula
Bensalan	3,5-Dibromo-*N*-(*p*-bromobenzyl) salicylamide	$C_{14}H_{10}Br_3NO_2$
Benzetimide	2-(1-Benzyl-4-piperidyl)-2-phenylglutarimide	$C_{23}H_{26}N_2O_2$
Benzoctamine	*N*-Methyl-9,10-ethanoanthracene-9(10*H*)-methylamine	$C_{18}H_{19}N$
Benzoxiquine	8-Quinolinol benzoate (ester); 8-benzoyl-oxyquinoline	$C_{16}H_{11}NO_2$
Betahistine	2-[2-(Methylamino)ethyl]pyridine	$C_8H_{12}N_2$
Bialamicol	5,5'-Diallyl-α,α'-bis(diethylamino)-*m,m'*-bitolyl-4,4'-diol	$C_{28}H_{42}N_2O_2$
Bisobrin	1,1'-Tetramethylenebis[1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline].	$C_{28}H_{36}N_2O_4$
Bisoxatin	2,2-Bis(*p*-hydroxyphenyl)-2*H*-1,4-benzoxazin-3(4*H*)-one	$C_{20}H_{15}NO_4$
Boldenone	17β-Hydroxyandrosta-1,4-dien-3-one	$C_{19}H_{26}O_2$
Bolenol	19-Nor-17α-pregn-5-en-17-ol; 17-α-ethyl-5-estren-17-ol	$C_{20}H_{32}O$
Boxidine	1-[2-[[4'-(Trifluoromethyl)-4-biphenylyl]oxy]ethyl]pyrrolidine	$C_{19}H_{20}F_3NO$
Bromazepam	7-Bromo-1,3-dihydro-5-(2-pyridyl)-2*H*-1,4-benzodiazepin-2-one	$C_{14}H_{10}BrN_3O$
Bromelains	A concentrate of proteolytic enzymes derived from the pineapple plant.	
Bromhexine	2,5-Dibromo-*N*α-cyclohexyl-*N*α-methyltoluene-α, 2-diamine	$C_{14}H_{20}Br_2N_2$
Buclizine	1-(*p-tert*-Butylbenzyl)-4-(*p*-chloro-α-phenylbenzyl)-piperazine	$C_{32}H_{39}ClN_2$
Bucrylate	Isobutyl 2-cyanoacrylate	$C_8H_{11}NO_2$
Bunolol	(±)-5-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone.	$C_{17}H_{25}NO_3$
Butalbital	5-Allyl-5-isobutylbarbituric acid	$C_{11}H_{16}N_2O_3$
Butaperazine	1-[10-[3-(4-Methyl-1-piperazinyl)propyl]phenothiazin-2-yl]-1-butanone.	$C_{24}H_{31}N_3OS$
Buthiazide	6-Chloro-3,4-dihydro-3-isobutyl-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.	$C_{11}H_{16}ClN_3O_4S_2$
Calcitonin	Hormone from the thyroid gland, a polypeptide of molecular weight less than 10,000.	
Calcium carbaspirin	Calcium salicylate diacetate compound with urea	$C_{18}H_{14}CaO_8.CH_4N_2O$
Candicidin	An antibiotic substance derived from *Streptomyces griseus* Waksman and Henrici.	
Canrenone	17-Hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylic acid gamma-lactone; 17α-(2-carboxyethyl)-17β-hydroxy and rosta-4,6-dien-3-one lactone.	$C_{22}H_{28}O_3$
Capreomycin	An antibiotic substance derived from *Streptomyces capreolus*	
Captamine	2-(Dimethylamino)ethanethiol; N-(2-mercaptoethyl)dimethylamine	$C_4H_{11}NS$
Carbadox	Methyl-3-(2-quinoxalinylmethylene)carbazate-*N*^{1},N^4-dioxide	$C_{11}H_{10}N_4O_4$
Carbamazepine	5*H*-Dibenz[*b,f*]-azepine-5-carboxamide	$C_{15}H_{12}N_2O$
Carbenicillin	*N*-(2-Carboxy-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-6-yl)-2-phenylmalonamic acid; 6-(2-carboxy-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.	$C_{17}H_{18}N_2O_6S$
Carbocloral	Ethyl (2,2,2-trichloro-1-hydroxyethyl)carbamate	$C_5H_8Cl_3NO_3$
Carbomer	A polymer of acrylic acid crosslinked with allyl sucrose	
Carphenazine	1-[10-(3-[4-(2-Hydroxyethyl)-1-piperazinyl]propyl)phenothiazin-2-yl]-1-propanone.	$C_{30}H_{35}N_3O_2S$
Casanthranol	A purified mixture of the anthranol glycosides derived from *Cascara sagrada*.	
Cellaburate	Cellulose acetate butyrate	
Cellulase	A concentrate of cellulose-splitting enzymes derived from *Aspergillus niger* and other sources.	
Cephalexin	D-7-(2-Amino-2-phenylacetamido)-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid.	$C_{16}H_{17}N_3O_4S$
Cephalogiycin	7-(D-2-Amino-2-phenylacetamido)-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, acetate.	$C_{16}H_{18}N_3O_6S$
Cephaloridine	1-[[2-Carboxy-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo-[4.2.0]oct-2-en-3-yl]methyl]pyridinium hydroxide, inner salt.	$C_{19}H_{17}N_3O_4S_2$
Cephalothin	3-(Hydroxymethyl)-8-oxo-7-[2-(2-thienyl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, acetate.	$C_{16}H_{16}N_2O_6S_2$
Cetalkonium	Benzylhexadecyldimethylammonium ion	$C_{25}H_{46}N^+$
Cetophenicol	D-*threo*-*N*-[*p*-Acetyl-β-hydroxy-α-(hydroxymethyl)phenethyl]-2,2-dichloroacetamide.	$C_{19}H_{18}Cl_2NO_4$
Chlophedianol	2-Chloro-α-[2-(dimethylamino)ethyl]benzhydrol	$C_{20}H_{26}ClNO$
Chlordantoin	5-(1-Ethylpentyl)-3-[(trichloromethyl)thio]hydrantoin	$C_{11}H_{17}Cl_3N_2O_2S$
Chlorhexidine	1,1'-Hexamethylenebis[5-(*p*-chlorophenyl) biguanide]	$C_{22}H_{30}Cl_2N_{10}$
Chlorindanol	7-Chloro-4-indanol	C_9H_9ClO
Chlormadinone	6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione; 6-chloro-6-dehydro-17α-hydroxyprogesterone.	$C_{21}H_{27}ClO_3$
Chlorphenesin	3-(*p*-Chlorophenoxy)-1,2-propanediol	$C_9H_{11}ClO_3$
Chlorphentermine	4-Chloro-α,α-dimethylphenethylamine	$C_{10}H_{14}ClN$
Chlorprothixene	2-Chloro-*N*,*N*-dimethylthioxanthene $\Delta^9\gamma$-propylamine	$C_{18}H_{18}ClNS$
Chlorthalidone	2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide	$C_{14}H_{11}ClN_2O_4S$
Cingestol	19-Nor-17α-pregn-5-en-20-yn-17-ol; 17α-ethynyl-5-estren-17-ol	$C_{20}H_{28}O$
Cinnamedrine	α-[1-(Cinnamylmethylamino)-ethyl]benzyl alcohol; 2-(*N*-cinnamyl-methylamino)-1-phenylpropanol.	$C_{18}H_{21}NO$
Cinnarizine	1-Cinnamyl-4-diphenylmethylpiperazine	$C_{26}H_{28}N_2$
Cinoxate	2-Ethoxyethyl *p*-methoxycinnamate	$C_{14}H_{18}O_4$
Cinperene	2-(1-Cinnamyl-4-piperidyl)-2-phenylglutarimide; 1-cinnamyl-4-(2,6-dioxo-3-phenyl-3-piperidyl)piperidine.	$C_{24}H_{24}N_2O_2$

Official name	Chemical name or description	Molecular formula
Cintasone	2-Pentyl-6-phenyl-1*H*-pyrazolo[1,2*a*] cinnoline-1,3(2*H*)-dione	$C_{23}H_{28}N_2O_2$
Cirolemycin	An antibiotic substance derived from *Streptomyces bellus* var. *cirolerosis* var. nova.	
Cisclomiphene	2-[*p*-(2-Chloro-*cis*-1,2-diphenylvinyl)phenoxy]-triethylamine	$C_{26}H_{28}ClNO$
Citenamide	5*H*-Dibenzo[*a*,*d*]cycloheptene-5-carboxamide	$C_{16}H_{13}NO$
Clemastine	(+)-2-[2-[*p*-Chloro-α-methyl-α-phenylbenzyl)oxy]ethyl]-1-methyl-pyrrolidine.	$C_{21}H_{26}ClNO$
Clindamycin	Methyl 7(*S*)-chloro-6,7,8-trideoxy-6-*trans*-(1-methyl-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*-α-D-galacto-octopyranoside; 7(*S*)-chloro-7-deoxylincomycin.	$C_{18}H_{33}ClN_2O_5S$
Clioxanide	4'-Chloro-3,5-diiodosalicylanilide acetate; 2-acetoxy-4'-chloro-3,5-diiodobenzanilide.	$C_{15}H_{10}ClI_2NO_3$
Clodazon	5-Chloro-1-[3-(dimethylamino)propyl]-3-phenyl-2-benzimidazolinone	$C_{18}H_{20}ClN_3O$
Clofazimine	3-(*p*-Chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-(isopropylimino)phenazine.	$C_{27}H_{22}Cl_2N_4$
Clofibrate	Ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate	$C_{12}H_{15}ClO_3$
Clofucarban	4,4'-Dichloro-3-(trifluoromethyl)carbanilide	$C_{14}H_9Cl_2F_3N_2O$
Clogestone	6-Chloro-3β,17-dihydroxypregna-4,6-dien-20-one	$C_{21}H_{29}ClO_3$
Clomacran	2-Chloro-9-[3-(dimethylamino)-propyl] acridan	$C_{18}H_{21}ClN_2$
Clomegestone	6-Chloro-17-hydroxy-16α-methylpregna-4,6-diene-3,20-dione	$C_{22}H_{29}ClO_3$
Clomiphene	2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]-triethylamine	$C_{26}H_{28}ClNO$
Clonazepam	5-(o-Chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one	$C_{15}H_{10}ClN_3O_3$
Clonidine	2-(2, 6-Dichloroanilino)-2-imidazoline	$C_9H_9Cl_2N_3$
Clonixeril	2,3-Dihydroxypropyl 2-(3-chloro-o-toluidino)nicotinate	$C_{18}H_{17}ClN_2O_4$
Clonixin	2-(3-Chloro-o-toluidino)nicotinic acid	$C_{14}H_{11}ClN_2O_2$
Clopidol	3,5-Dichloro-2,6-dimethyl-4-pyridinol	$C_7H_7Cl_2NO$
Chlorazepic acid	7-Chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxylic acid.	$C_{15}H_{11}ClN_2O_4$
Clorexolone	6-Chloro-2-cyclohexyl-3-oxo-5-isoindoline-sulfonamide; 5-chloro-2-cyclohexyl-1-oxo-6-sulfamoylisoindoline.	$C_{14}H_{17}ClN_2O_3S$
Clortermine	o-Chloro-α,α-dimethylphenethylamine	$C_{10}H_{14}ClN$
Closiramine	8-Chloro-11-[2-(dimethylamino)ethyl]-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridine.	$C_{18}H_{21}ClN_2$
Cloxacillin	6-[3-(o-Chlorophenyl)-o-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.	$C_{19}H_{18}ClN_3O_5S$
Clozapine	8-Chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4] diazepine	$C_{18}H_{19}ClN_4$
Colestipol	Tetraethylenepentamine polymer with 1-chloro-2,3-epoxypropane	
Cosyntropin	H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Try-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-OH.	
Cromolyn	5,5'-[(2-Hydroxytrimethylene)dioxy]bis[4-oxo-4*H*-1-benzopyran-2-carboxylate]; 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxypropane.	$C_{23}H_{16}O_{11}$
Crufomate	4-*tert*-Butyl-2-chlorophenyl methyl methylphosphoramidate	$C_{12}H_{19}ClNO_3P$
Cyclacillin	6-(1-Aminocyclohexanecarboxamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.	$C_{16}H_{23}N_3O_4S$
Cycloguanil	4,6-Diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine	$C_{11}H_{14}ClN_5$
Cyclophenazine	10-[3-(4-Cyclopropyl-1-piperazinyl) propyl]-2-(trifluoromethyl) phenothiazine; 10-[3-(4-cyclopropylpiperazino)-propyl]-2-trifluoromethylphenothiazine.	$C_{23}H_{28}F_3N_3S$
Cyclopenthiazide	6-Chloro-3-(cyclopentylmethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.	$C_{13}H_{18}ClN_3O_4S_2$
Cyclothiazide	6-Chloro-3,4-dihydro-3-(5-norbornen-2-yl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.	$C_{14}H_{18}ClN_3O_4S_2$
Cyproquinate	Ethyl 6,7-bis(cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxylate.	$C_{20}H_{23}NO_5$
Cyproximide	1(*p*-Chlorophenyl)-1,2-cyclopropanedicarboximide	$C_{11}H_8ClNO_2$
Cytarabine	1-Arabinofuranosylcytosine	$C_9H_{13}N_3O_5$
Dactinomycin	Actinomycin D	$C_{62}H_{86}N_{12}O_{16}$
Danazol	17α-Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17-ol; 1-ethynyl-2,3,3a,3b,4,5,10, 10a, 10b, 11, 12, 12a-dodecahydro-10a, 12a-dimethyl-1 *H*-cyclopenta[7,8]-phenanthro[3,2-*d*]pyrazol-1-ol.	$C_{22}H_{27}NO_2$
Decoquinate	Ethyl 6-(decyloxy)-7-ethoxy-4-hydroxy-3-quinolinecarboxylate	$C_{24}H_{35}NO_5$
Deferoxamine	*N*-[5-[3-[(5-Aminopentyl)hydroxycarbamoyl]propionamido]pentyl]-3-[[5-*N*-hydroxyacetamido)pentyl]carbamoyl]propionohydroxamic acid.	$C_{25}H_{48}N_6O_8$
Desipramine	10,11-Dihydro-5-[3-(methylamino)propyl]-5*H*-dibenz[*b*,*f*]azepine	$C_{18}H_{22}N_2$
Dexivacaine	(+)-1-Methyl-2',6'-pipecoloxylidide; (+)-1-*N*-methylpipecolic acid 2,6-dimethylanilide.	$C_{15}H_{22}N_2O$
Dexpanthenol	D(+)-2,4-Dihydroxy-*N*-(3-hydroxypropyl)-3,3-dimethylbutyramide	$C_9H_{19}NO_4$
Dextran 40	A polysaccharide having a weight average molecular weight of 40,000; produced by the action of *Leuconostoc mesenteroides* on sucrose.	
Diamocaine	1-(2-Anilinoethyl)-4-[2-(diethylamino)ethoxy]-4-phenylpiperidine	$C_{31}H_{47}N_3O$
Diapamide	4-Chloro-*N*-methyl-3-(methylsulfamoyl) benzamide	$C_9H_{11}ClN_2O_3S$
Diatrizoic acid	3,5-Diacetamido-2,4,6-triiodobenzoic acid	$C_{11}H_9I_3N_2O_4$
Diazepam	7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one	$C_{16}H_{13}ClN_2O$

Official name	Chemical name or description	Molecular formula
Dibromsalan	4',5-Dibromosalicylanilide	$C_{13}H_7Br_2NO_2$
Dicloxacillin	6-[3-(2,6-Dichlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.	$C_{19}H_{17}Cl_2N_3O_5S$
Difuanine	1-(2-Anilinoethyl)-4-[4,4-bis(*p*-fluorophenyl)butyl]piperazine; 1-[4,4-di(4-fluorophenyl)butyl]-4-(2-anilinoethyl)piperazine.	$C_{28}H_{32}F_2N_2$
Difucortolone	6α,9-Difluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.	$C_{22}H_{28}F_2O_4$
Difumidone	3'-Benzoyl-1,1-difluoromethanesulfonanilide	$C_{14}H_{11}F_2NO_3S$
Difluprednate	6α,9-Difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate.	$C_{27}H_{34}F_2O_7$
Dimethindene	2-[1-[2-[2-(Dimethylamino)ethyl]inden-3-yl]ethyl]pyridine	$C_{20}H_{24}N_2$
Dimethisterone	17β-Hydroxy-6α-methyl-17-(1-propynyl)androst-4-en-3-one	$C_{23}H_{32}O_2$
Dioxybenzone	2,2'-Dihydroxy-4-methoxybenzophenone	$C_{14}H_{12}O_4$
Diphenidol	α,α-Diphenyl-1-piperidinebutanol	$C_{21}H_{27}NO$
Dipyridamole	2,2',2'',2'''-[4,8-Dipiperidinopyrimido[5,4-*d*]pyrimidine-2,6-diyl)dinitrilo]tetraethanol.	$C_{24}H_{40}N_8O_4$
Dipyrone	Sodium (antipyrinylmethylamino)methanesulfonate hydrate	$C_{13}H_{16}N_3NaO_4S \cdot H_2O$
Domiphen	Dodecyldimethyl(2-phenoxyethyl)ammonium	$C_{22}H_{40}NO$
Dopamine	4-(2-Aminoethyl)pyrocatechol	$C_8H_{11}NO_2$
Doxapram	1-Ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone	$C_{24}H_{30}N_2O_2$
Doxepin	*N,N*-Dimethyldibenz[*b,e*]oxepin-$\Delta^{\alpha(11),\gamma}$-propylamine	$C_{19}H_{21}NO$
Doxycycline	4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.	$C_{22}H_{24}N_2O_8$
Droperidol	1-[1-[3-(*p*-Fluorobenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone.	$C_{22}H_{22}FN_3O_2$
Dydrogesterone	9β,10α-Pregna-4,6-diene-3,20-dione	$C_{21}H_{28}O_2$
Epimestrol	3-Methoxyestra-1,3,5,(10)-triene-16α,17α-diol	$C_{19}H_{28}O_3$
Estrazinol	DL-*trans*-3-Methoxy-8-aza-19-nor-17α-pregna-1,3,5-trien-20-yn-17-ol	$C_{23}H_{33}NO_2$
Ethacrynic acid	[2,3-Dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid	$C_{13}H_{12}Cl_2O_4$
Ethambutol	(+)-2,2'-(Ethylenediimino)-di(1-butanol)	$C_{10}H_{24}N_2O_2$
Ethamivan	*N,N*-Diethylvanillamide	$C_{12}H_{17}NO_3$
Ethionamide	2-Ethylthioisonicotinamide	$C_8H_{10}N_2S$
Ethonam	Ethyl-1-(1,2,3,4-tetrahydro-1-naphthyl) imidazole-5-carboxylate; 1-(1,2,3,4-tetrahydro-1-naphthyl)-5-ethoxycarbonyl) imidazole.	$C_{16}H_{18}N_2O_2$
Ethosuximide	2-Ethyl-2-methylsuccinimide	$C_7H_{11}NO_2$
Ethoxazene	4-[(*p*-Ethoxyphenyl)azo]-*m*-phenylenediamine	$C_{14}H_{16}N_4O$
Ethynodiol	19-Nor-17α-pregn-4-en-20-yne-3β, 17-diol	$C_{20}H_{28}O_2$
Ethylestrenol	19-Nor-17α-pregn-4-en-17β-ol	$C_{20}H_{32}O$
Etidronic Acid	(1-Hydroxyethylidene)diphosphonic acid	$C_2H_8O_7P_2$
Etoxadrol	(+)-2-(2-Ethyl-2-phenyl-1,3-dioxolan-4-yl) piperidine	$C_{15}H_{21}NO_2$
Enprocin	*O*-6'-Isopentylhydrocupreine	$C_{24}H_{28}N_2O_2$
Famotine	1-[(*p*-Chlorophenoxy)methyl]-3,4-dihydroisoquinoline	$C_{16}H_{14}ClNO$
Fantridone	5-[3-(Dimethylamino)propyl]-6-(5*H*)-phenanthridone	$C_{18}H_{20}N_2O$
Fenalamide	Ethyl-*N*-[2-(diethylamino)]ethyl-2-ethyl-2-phenylmalonamate; phenylethylmalonic acid monethylester diethylaminoethylamide.	$C_{19}H_{32}N_2O_3$
Feuclonine	DL-3-(*p*-Chlorophenyl)alanine	$C_9H_{10}ClNO_2$
Fenestrel	5-Ethyl-6-methyl-4-phenyl-3-cyclohexene-1-carboxylic acid; 2-methyl-3-ethyl-4-phenyl-4-cyclohexenecarboxylic acid.	$C_{16}H_{20}O_2$
Fentanyl	*N*-(1-Phenethyl-4-piperidyl)propionanilide	$C_{22}H_{28}N_2O$
Fenticlor	2, 2'-Thiobis[4-chlorophenol]	$C_{12}H_8Cl_2O_2S$
Ferric fructose	Fructose iron complex, compound with potassium (2:1)	$(C_6H_{12}FeO_7)_nK_n$
Fetoxylate	2-Phenoxyethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate.	$C_{36}H_{36}N_2O_3$
Filipin	3,5,7,9,11,13,15,26,27-Nonahydroxy-2-(1-hydroxyhexyl)-16-methyl-15,18,20,22,24-octacosapentaenoic acid 1,27-lactone.	$C_{35}H_{58}O_{11}$
Flavoxate	2-Piperidinoethyl 3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxylate.	$C_{24}H_{25}NO_4$
Floxuridine	2'-Deoxy-5-fluorouridine	$C_9H_{11}FN_2O_5$
Fincrylate	2,2,2-Trifluoro-1-methylethyl 2-cyanoacrylate	$C_7H_6F_3NO_2$
Fincytosine	5-Fluorocytosine	$C_4H_4FN_3O$
Fludorex	β-Methoxy-*N*-methyl-*m*-(trifluoromethyl) phenethylamine	$C_{11}H_{14}F_3NO$
Flufenisal	4'-Fluoro-4-hydroxy-3-biphenylcarboxylic acid acetate	$C_{15}H_{11}FO_4$
Flumethasone	6α,9-Difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.	$C_{22}H_{28}F_2O_5$
Flunidazole	2-(*p*-Fluorophenyl)-5-nitroimidazole-1-ethanol	$C_{11}H_{10}FN_3O_3$
Fluocinolone	6α,9-Difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione; 6α,9α-difluoro-16α-hydroxyprednisolone.	$C_{24}H_{28}F_2O_6$
Fluocinonide	6α,9-Difluoro-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione, cyclic 16,17-acetal with acetone, 21-acetate.	$C_{26}H_{32}F_2O_7$
Fluprednisolone	6α-Fluoro-11β, 17α,21-trihydroxypregna-1,4-diene-3,20-dione; 6α-fluoroprednisolone.	$C_{21}H_{27}FO_5$
Flurazepam	7-Chloro-1-[2-(diethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.	$C_{21}H_{23}ClFN_3O$
Flurothyl	Bis(2,2,2-trifluoroethyl)ether	$C_4H_4F_6O$
Fluroxene	2,2,2-Trifluoroethyl vinyl ether	$C_4H_5F_3O$
Flutiazin	8-(Trifluoromethyl)phenothiazine-1-carboxylic acid	$C_{14}H_8F_3NO_2S$
Fonazine	10-[2-(Dimethylamino)propyl]-*N,N*-dimethylphenothiazine-2-sulfonamide.	$C_{19}H_{25}N_3O_2S_2$
Fospirate	Dimethyl 3,5,6-trichloro-2-pyridyl phosphate	$C_7H_7Cl_3NO_4P$
Furosemide	4-Chloro-*N*-furfury-5-sulfamoylanthranilic acid	$C_{12}H_{11}ClN_2O_5S$
Fursalan	3,5-Dibromo-*N*-(tetrahydrofurfuryl)salicylamide; 3,5-dibromosalicyl-*N*-tetrahydrofurfurylamide.	$C_{12}H_{13}Br_2NO_3$
Gentamicin	An antibiotic substance derived from *Micromonospora purpurea*, nonspecific.	----------

Official name	Chemical name or description	Molecular formula
Gloxazone	3-Ethoxy-2-oxobutyraldehyde-bis(thiosemicarbazone); α-ethloxyethylglyoxal dithiosemicarbazone.	$C_8H_{16}N_6OS_2$
Glucosamine	2-Amino-2-deoxy-β-D-glucopyranose	$C_6H_{13}NO_5$
Glyburide	1-[[p-[2-(5-chloro-o-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea; *N*-[4-(β-(2-methoxy-5-chlorobenzamido)-ethyl)benzosulfonyl]-*N'*-cyclohexylurea.	$C_{23}H_{28}ClN_3O_5S$
Glycopyrrolate	3-Hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate.	$C_{19}H_{28}BrNO_3$
Guanacline	[2-(3,6-Dihydro-4-methyl-1(2*H*)-pyridyl)ethyl]guanidine	$C_9H_{18}N_4$
Guanadrel	(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)guanidine	$C_{10}H_{19}N_3O_2$
Haloperidol	4-[4-(*p*-Chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone.	$C_{21}H_{23}ClFNO_2$
Halquinols	5,7-Dichloro-8-quinolinol, 5-chloro-8-quinolinol, and 7 chloro-8-quinolinol in proportions resulting naturally from chlorination of 8-quinolinol.	$C_9H_5Cl_2NO$ and C_9H_6ClNO
Hetacillin	6-(2,2-Dimeth-6-oxo-4-phenyl-1-imidazolidinyl)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.	$C_{18}H_{23}O_4S$
Hexafluorenium	Hexamethylenebis[9-fluorenyldimethylammonium] ion	$C_{40}H_{42}N_2^{++}$
Hoquizil	2-Hydroxy-2-bicinylpropyl 4-(6,7-dimethoxy-4-quinazolinyl)-1-piperazinecarboxylate.	$C_{32}H_{38}N_4O_8$
Hydroxocobalamin	Cobinamide hydroxide phosphate, 3'-ester with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole, inner salt.	$C_{62}H_{89}CoN_{13}O_{15}P$
Hydroxyurea	Hydroxyurea	$CH_4N_2O_2$
Ibuprofen	*p*-Isobutylhydratropic acid; 2(p-Isobutylphenyl)propionic acid	$C_{13}H_{18}O_2$
Ictasol	The sodium salt of a sulfonated derivative of bituminous slate	----------
Idoxuridine	2'-Deoxy-5-iodouridine	$C_9H_{11}IN_2O_5$
Indomethacin	1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid	$C_{19}H_{16}ClNO_4$
Indriline	*N,N*-Dimethyl-1-phenylindene-1-ethylamine	$C_{19}H_{21}N$
Inositol niacinate	*myo*-Inositol hexanicotinate	$C_{42}H_{30}N_6O_{12}$
Iocetamic acid	*N*-Acetyl-*N*-(3-amino-2,4,6-triiodophenyl)-2-methyl-β-alanine	$C_{12}H_{13}I_3N_2O_3$
Iodamide	α,5-Diacetamido-2,4,6-triiodo-*m*-toluic acid	$C_{12}H_{11}I_3N_2O_3$
Iomethin I 125	4-[[3-(Dimethylamino)propyl]amino]-7-iodo-^{125}I-quinoline	$C_{14}H_{18}IN_3$ (in which the iodine atom is ^{125}I).
Iomethin I 131	4-[[3-(Dimethylamino)propyl]amino]-7-iodo-^{131}I-quinoline	$C_{14}H_{18}IN_3$ (in which the iodine atom is ^{131}I).
Iopydol	1-(2,3Dihydroxypropyl-3,5-diiodo-4(1*H*)-pyridone	$C_8H_9I_2NO_3$
Iopydone	3,5-Diiodo-4(1*H*)-pyridone	$C_5H_3I_2NO$
Iothalamic acid	5-Acetamido-2,4,6-triiodo-*N*-methylisophthalamic acid	$C_{11}H_9I_3N_2O_5$
Ipronidazole	2-Isopropyl-1-methyl-5-nitroimidazole	$C_7H_{11}N_3O_2$
Iron sorbitex	A sterile, colloidal solution of a complex of trivalent iron, sorbitol, and citric acid, stabilized with dextrin and sorbitol.	
Isoetharine	3,4-Dihydroxy-α-[1-(isopropylamino)propyl]benzyl alcohol	$C_{13}H_{21}NO_3$
Isomylamine	2-(Diethylamino)ethyl 1-isopentylcyclohexanecarboxylate	$C_{18}H_{35}NO_2$
Kalafungin	An antibiotic substance derived from *Streptomyces tanashiensis* strain, *kala*.	
Ketamine	(±)-2-(o-Chlorophenyl)-2-(methylamino)cyclohexanone	$C_{13}H_{16}ClNO$
Kethoxal	3-Ethoxy-1,1-dihydroxy-2-butanone	$C_6H_{12}O_3$
Ketipramine	5-[3-(Dimethylamino)propyl]5,11-dihydro-10*H*-dibenz[*b*,*f*]-asepin-10-one.	$C_{20}H_{22}N_2O$
Kitasamycin	An antibiotic substance obtained from cultures of *Streptomyces kitasatoensis*.	$C_{35-36}H_{54-58}NO_{13-15}$
Levamfetamine	(−)-α-Methylphenethylamine	$C_9H_{13}N$
Levodopa	(-)-3-(3,4-Dihydroxyphenyl)-L-alanine	$C_9H_{11}NO_4$
Lincomycin	An antibiotic substance derived from *Streptomyces lincolnensis*; methyl 6-8-dideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidine-carboxamido)-1-thio-D-erythro-α-D-galacto-octopyranoside.	$C_{18}H_{34}N_2O_6S$
Liotrix	A mixture of: Sodium liothyronine (sodium L-3,3',5-triiodothyronine) and sodium levothyroxine (sodium L-3,3'5,5'-tetraiodo thyronine).	$C_{15}H_{11}I_3NNaO_4$ and $C_{15}H_{10}I_4NNaO-XH_2O$
Lithium carbonate	Lithium carbonate	Li_2CO_3
Lomofungin	An antibiotic substance derived from *Streptomyces lomondensis* var. *lomondensis*.	----------
Lorazepam	7-Chloro-5-(o-chlorophenyl)-1, 3-dihydro-3-hydroxy-2*H*-1, 4-benzodiazepin-2-one.	$C_{15}H_{10}Cl_2N_2O_2$
Lucanthone	1-[[2-(Diethylamino)ethyl]amino]-4-methylthioxanthen-9-one	$C_{20}H_{24}N_2OS$
Lydimycin	An antibiotic substance derived from *Streptomyces lydicus*	
Lypressin	8-Lysine vasopressin	$C_{46}H_{65}N_{13}O_{12}S_2$
Mafenide	α-Amino-*p*-toluenesulfonamide	$C_7H_{10}N_2O_2S$
Magaldrate	Tetrakis (hydroxymagnesium) decahydroxydialuminate dihydrate	$Al_2H_{14}MgO_{14}\cdot 2H_2O$
Mebutamate	2-sec-Butyl-2-methyl-1,3-propanediol dicarbamate; or 2-methyl-2-*sec*-butyl-1,3-propanediol dicarbamate.	$C_{12}H_{24}N_2O_4$
Mecrylate	Methyl 2-cyanoacrylate	$C_5H_5NO_2$
Medazepam	7-Chloro-2,2-dihydro-1-methyl-5-phenyl-1*H*-1, 4-benzo-diazepine	$C_{16}H_{15}ClN_2$
Medrysone	11β-Hydroxy-6α-methylpregn-4-ene-3,20-dione	$C_{22}H_{32}O_3$
Mefenamic acid	*N*-(2,3-Xylyl)anthranilic acid	$C_{15}H_{15}NO_2$
Mefenorex	*N*-(3-Chloropropyl)-α-methylphenethylamine	$C_{12}H_{18}ClN$
Mefexamide	*N*-[2-(Diethylamino)ethyl]-2-(*p*-methoxy-phenoxy)acetamide	$C_{15}H_{24}N_2O$
Melitracen	*N,N*,10,10-Tetramethyl-Δ^9(10*H*),γ-anthracenepropylamine; 9-(3-dimethylaminipropylidine)-10,10-dimethyl-9,10-dihydroanthracene.	$C_{21}H_{25}N$
Melphalan	L-3-[*p*[Bis(2-chloroethyl)aminophenyl] alanine	$C_{13}H_{18}Cl_2N_2O_2$

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Memotine	3,4-Dihydro-1-[(*p*-methoxyphenoxy)methyl]isoquinoline	$C_{17}H_{17}NO_2$
Menoctone	6-(8-Cyclohexyloctyl)-3-hydroxy-1,4-naphthoquinone	$C_{24}H_{32}O_3$
Mephenytoin	5-ethyl-3-methyl-5-phenylhydantoin	$C_{12}H_{14}N_2O_2$
Meprednisone	17,21-Dihydroxy-16*β*-methylpregna-1,4-diene-3,11,20-trione	$C_{22}H_{28}O_5$
Mequidox	3-Methyl-2-quinoxalinemethanol 1,4-dioxide	$C_{10}H_{10}N_2O_3$
Mesoridazine	10-[2(1-Methyl-2-piperidyl)ethyl]-2-(methylsulfinyl) prenothiazine	$C_{21}H_{26}N_2OS_2$
Mestranol	3-Methoxy-19-nor-17*α*-pregna-1,3, 5(10)-trien-20-yn-17-ol	$C_{21}H_{26}O_2$
Mesuprine	2′-Hydroxy-5′-[1-hydroxy-2-[(*p*-methoxyphenethyl)amino]propyl] methanesulfonanilide.	$C_{18}H_{24}N_2O_5S$
Metabromasalan	3,5-Dibromosalicylanilide	$C_{13}H_9Br_2NO_2$
Metalol	4′-[1-Hydroxy-2-(methylamino)propyl]methanesulfonanilide	$C_{11}H_{18}N_2O_3S$
Metaxalone	5-[3,5-Xylyoxy)methyl]-2-oxazolidinone	$C_{12}H_{15}NO_3$
Metformin	1,1-Dimethylbiguanide	$C_4H_{11}N_5$
Methacycline	4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methnylene-1,11-dioxo-2-naphthacenecarboxamide; 6-deoxy-6-demethyl-6-methylene 5-oxytetracycline.	$C_{22}H_{22}N_2O_8$
Methallibure	1-Methyl-6-(1-methylallyl)-2,5-dithiobiurea	$C_7H_{14}N_4S_2$
Methaqualone	2-Methyl-3-*o*-tolyl-4(3*H*)-quinazolinone	$C_{16}H_{14}N_2O$
Methixene	1-Methyl-3-(thioxanthen-9-ylmethyl)piperidine	$C_{20}H_{23}NS$
Methoxyflurane	2,2-Dichloro-1,1-difluoroethyl methyl ether	$C_3H_4Cl_2F_2O$
Methyldopa	*l*-3-(3,4-Dihydroxyphenyl)-2-methylalanine	$C_{10}H_{13}NO_4$
Metiapine	2-Methyl-11-(4-methyl-1-piperazinyl) dibenzo[*b,f*][1,4]thiazepine	$C_{19}H_{21}N_3S$
Metizoline	2-[(2-Methylbenzo[*b*]thien-3-yl)methyl]-2-imidazoline	$C_{13}H_{14}N_2S$
Metolazone	7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide.	$C_{16}H_{16}ClN_3O_3S$
Metoserpate	Methyl 11,17*α*,18*α*-trimethoxy-3*β*,20*α*-yohimban-16*β*-carboxylate	$C_{24}H_{32}N_2O_6$
Metronidazole	2-Methyl-5-nitroimidazole-1-ethanol	$C_6H_9N_3O_3$
Mianserin	1,2,3,4,10,14b-Hexahydro-2-methyldibenzo[*c,f*]pyrazino[1,2-*a*] azepine	$C_{18}H_{20}N_2$
Midaflur	4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline	$C_7H_4F_{12}N_2$
Milipertine	5,6-Dimethoxy-3-[2-[4-(*o*-methoxyphenyl)-1-piperazinyl] ethyl]-2-methylindole.	$C_{24}H_{31}N_3O_3$
Minocycline	4,7-Bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydro-1,11-dioxo-2-naphthacenecarboxamide.	$C_{23}H_{27}N_3O_7$
Mithramycin	From *Streptomyces argillaceus* n.sp. and *Streptomyces tanashiensis*	----------
Mitocromin	An antibiotic substance produced by *Streptomyces viridochromogenes*.	----------
Mitomalcin	An antibiotic substance produced by *Streptomyces malayensis*	----------
Mitotane	1,1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane	$C_{14}H_{10}Cl_4$
Molindone	3-Ethyl-6,7-dihydro-2-methyl-5-(morpholinomethyl)indol-4(5*H*)-one	$C_{15}H_{24}N_2O_2$
Monensin	2-[5-Ethyltetrahydro-5-[tetrahydro-3-methyl-5-[tetrahydro-6-hydroxy-6-(hydroxymethyl)-3,5-dimethylpyran-2-yl]-2-furyl]-2-furyl]-9-hydroxy-*β*-methoxy-*α*,γ 2,8-tetramethyl-1,6-dioxaspiro [4,5] decane-7-butyric acid.	$C_{36}H_{62}O_{11}$
Morantel	(*E*)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl) vinyl] pyrimidine.	$C_{12}H_{16}N_2S$
Nadide	3-Carbamoyl-1-*β*-D-ribofuranosylpyridinium hydroxide, 5′-ester with adenosine-5′-pyrophosphate, inner salt; codehydrogenase I.	$C_{21}H_{27}N_7O_{14}P_2$
Nafcillin	6-(2-Ethoxy-1-naphthamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid; 6-(2-ethoxy-1-naphthamido) penicillanic acid.	$C_{21}H_{22}N_2O_5S$
Nafronyl	2-(Diethylamino)ethyl tetrahydro-*α*-(1-naphthylmethyl)-2-furanpropionate.	$C_{28}H_{39}NO_3$
Nalbuphine	17-(Cyclobutylmethyl)-4,5*α*-epoxymorphinan-3,6*α*,14-triol	$C_{21}H_{27}NO_4$
Nalidixic acid	1-Ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid.	$C_{12}H_{12}N_2O_3$
Nalmexone	7,7a,8,9-Tetrahydro-3,7a-dihydroxy-12-(3-methyl-2-butenyl)-6*H*-8,9c-imino-ethanophenanthro[4,5-bcd]furan-5(4a*H*)-one; *N*-3,3′-dimethylallylnoroxymorphone.	$C_{24}H_{29}NO_4$
Naloxone	(−)-17-Allyl-4,5*α*-epoxy-3,14-dihydroxymorphinan-6-one	$C_{19}H_{21}NO_4$
Nandrolone	17*β*-Hydroxyester-4-en-3-one	$C_{18}H_{26}O_2$
Naranol	8,9,10,11,11a,12-Hexahydro-6,10-dimethyl-7a*H*-naphthbol[1′,2′:5,6] pyrano[3,2-c]pyridin-7a-ol.	$C_{13}H_{19}NO_2$
Nebramycin	An antibiotic substance derived from *Streptomyces tenebrarius*	----------
Nequinate	3-Acetoxy-6-butyl-7-benzyloxy-4-oxoquinoline	$C_{24}H_{25}NO_4$
Nifuraldezone	5-Nitro-2-furaldehyde semioxamazone	$C_7H_6N_4O_5$
Nifurimide	(±)-4-Methyl-1-(5-nitrofurfurylidene)amino]-2-imidazolidinone	$C_9H_{12}N_4O_4$
Nifursol	3,5-Dinitrosalicylic acid (5-nitrofurfurylidene)hydrazide	$C_{12}H_7N_5O_7$
Nimazone	3-(*p*-Chlorophenyl)-4-imino-2-oxo-1-imidazolidineacetonitrile	$C_{11}H_9ClN_4O$
Niridazole	1-(5-Nitro-2-thiazolyl)-2-imidazolidinone	$C_6H_6N_4O_3S$
Nisobamate	Isopropylcarbamic acid ester with 2-(hydroxymethyl)-2,3-dimethylpentyl carbamate.	$C_{12}H_{24}N_2O_4$
Nonoxynol 4	Nonylphenoxypolyethyleneoxyethanol	$C_{15}H_{24}O(C_2H_4O)_n$ (n=approximately 4)
Nonoxynol 9	------do	$C_{15}H_{24}O(C_2H_4O)_n$ (n=approximately 9)
Nonoxynol 15	------do	$C_{15}H_{24}O(C_2H_4O)_n$ (n=approximately 15)
Nonoxynol 30	------do	$C_{15}H_{24}O(C_2H_4O)_n$ (n=approximately 30)
Norethindrone	17-Hydroxy-19-nor-17*α*-pregn-4-en-20-yn-3-one	$C_{20}H_{26}O_2$
Norethynodrel	17-Hydroxy-19-nor-17*α*-pregn-5(10)-en-20-yn-3-one; 17*α*-ethynyl-17-hydroxy-5(10)-estren-3-one.	$C_{20}H_{26}O_2$

Official name	Chemical name or description	Molecular formula
Norflurane	1,1,1,2-Tetrafluoroethane	$C_2H_2F_4$
Norgestrel	(±)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one	$C_{21}H_{28}O_2$
Nortriptyline	10,11-Dihydro-*N*-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene-Δ^{5},γ-propylamine.	$C_{19}H_{21}N$
Ocrylate	Octyl 6-cyanoacrylate	$C_{12}H_{19}NO_2$
Octicizer	2-Ethylhexyl diphenyl phosphate	$C_{20}H_{27}O_4P$
Octodrine	1,5-Dimethylhexylamine	$C_8H_{19}N$
Opipramol	4-[3-(5*H*-dibenz[*b*,*f*]azepin-5-yl)propyl]-5-piperazine ethanol	$C_{23}H_{29}N_3O$
Orgotein	A pure, water-soluble, highly compact protein of fairly low molecular weight (about 34,000) with a predominantly alpha-helical configuration; the molecule is chelated with from two (2) to four (4) atoms of divalent metals, for example, Mg, Zn, and Cu, and it is presently produced from bovine liver in a multistep process.	----------
Ormetoprim	2,4-Diamino-5-(6-methylveratryl)pyrimidine	$C_{14}H_{18}N_4O_2$
Oxandrolone	17β-Hydroxy-17-methyl-6-oxa-5α-androstan-3-one	$C_{19}H_{30}O_2$
Oxazepam	7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one	$C_{15}H_{11}ClN_2O_2$
Oxethazaine	2,2'-[(2-Hydroxyetbyl)imino]-bis[*N*-(α,α-dimethylphenetbyl)-*N*-metbylacetamide].	$C_{32}H_{41}N_3O_3$
Oxisuran	(Methylsulfinyl)methyl 6-pyridyl ketone	$C_8H_9NO_2S$
Oxogestone	20β-Hydroxy-19-norpregn-4-en-3-one;20β-hydroxy-19-nor-4-pregnen-3-one.	$C_{20}H_{30}O_3$
Oxprenolol	1-(o-(Allyloxy)phenoxy]-3-(isopropylamino)-2-propanol	$C_{15}H_{23}NO_3$
Oxybenzone	2-Hydroxy-4-methoxybenzophenone	$C_{14}H_{12}O_3$
Oxychlorosene	Tbe hypochlorous acid complex of a mixture of the phenyl sulfonate derivatives of aliphatic hydrocarbons.	
Oxycodone	Dihydrohydroxycodeinone	$C_{18}H_{21}NO_4$
Oxymetazoline	6-*tert*-Bntyl-3-(6-imidazolin-2-ylmethyl)-2,4-dimethylphenol	$C_{15}H_{24}N_2O$
Oxymetholone	17β-Hydroxy-2-(hydroxymethylene)-17α-methyl-5α-androstan-3-one	$C_{21}H_{32}O_3$
Oxypertine	5,6-Dimethoxy-2-methyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]-indole	$C_{23}H_{29}N_3O_2$
Pancrelipase	A concentrate of pancreatic enzymes standardized for lipase content	----------
Pancuronium	1,1'-(3α, 17β-Dihydroxy-5α-androstan-2β, 16β-ylene)bis[5-methylpiperidinium ion diacetate.	$C_{35}H_{60}N_2O_4^{++}$
Pantbenol	(±)2,4-Dihydroxy-*N*-(3-hydroxypropyl)-3,3-dimethylbutyramide; pantotbenyl alcohol.	$C_9H_{19}NO_4$
Paramethasone	6α-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.	$C_{22}H_{29}FO_5$
Parbendazole	Methyl 5-butyl-2-benzimidazolecarbamate	$C_{12}H_{17}N_3O_2$
Pargyline	*N*-Methyl-*N*-2-propynylbenzylamine	$C_{11}H_{13}N$
Pemoline	2-Amino-5-phenyl-5-oxazolin-4-one	$C_9H_8N_2O_2$
Penicillamine	p-3-Mercaptovaline	$C_5H_{11}NO_2S$
Pentagastrin	*N*-(α-Carbamoylphenethyl)-3-[2-[2-[3-(carboxyamino)propionamido]-3-indol-3-yl]propionamido]-4-(methylthio)butyramido]succinamic acid *N*-*tert*-butyl ester; *N*-*tert*-butyloxycarbonyl-β-alanyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide.	$C_{37}H_{49}N_7O_9S$
Pentazocine	(±)1,2,3,4,5,6-Hexahydro-*cis*-6,11-dimethyl-3-(3-metbyl-6-hutenyl)-2,6-methano-3-benzazocin-8-ol.	$C_{19}H_{27}NO$
Perhexilene	2-(2,2-Dicyclohexylethyl) piperidine	$C_{19}H_{35}N$
Perlapine	6-(4-Metbyl-1-piperazinyl)morphanthridine	$C_{18}H_{21}N_3$
Phentermine	α,α-Dimethylphenetbylamine	$C_{10}H_{15}N$
Phenyramidol	α-(2-Pyridylamino)methyl]benzyl alcohol	$C_{13}H_{14}N_2O$
Phthalofyne	Mono(1-ethyl-1 methyl-2-propynyl) phthalate	$C_{14}H_{14}O_4$
Pimozide	1-[1-[4,4-Bis-(*p*-fluorophenyl)butyl]-4-piperidyl]-1-henzimidazolinone; 1-[4,4-bis(*p*-fluorophenyl)hutyl]-4-(2-oxo-1-henzimidazolinyl)piperidine.	$C_{28}H_{29}F_2N_3O$
Pipazethate	2-(2-Piperidinoetboxy)ethyl 10*H*-pyrido[3,2-*b*][1,4]henzothiazine-10-carboxylate.	$C_{21}H_{25}N_3O_3S$
Piperacetazine	10-[3-[4-(2-Hydroxyethyl)piperidino]propyl]pbenothiazin-2-yl methyl ketone.	$C_{24}H_{30}N_2O_2S$
Piprozolin	Ethyl 3-etbyl-4-oxo-5-piperidino-Δ^{2}-e-thiazolidineacetate	$C_{14}H_{22}N_2O_3S$
Piquizil	Isohutyl 4-(6-7-dimetboxy-4-quinazolinyl)-5-piperazinecarboxylate	$C_{19}H_{28}N_4O_4$
Polacrilin	A synthetic ion-exchange resin prepared through tbe polymerization of methacrylic acid and divinylhenzene and supplied in the hydrogen or free-acid form.	----------
Polacrilin potassium	The potassium salt of a synthetic ion-exchange resin derived through the copolymerization of methacrylic acid and divinylbenzene.	----------
Poldine	2-(Hydroxymethyl)-1,1-dimethylpyrrolidinium benzilate	$C_{21}H_{26}NO_3$
Poligeenan	3,6-Anhydro-4-*O*-β-D-galactopyranosyl-α-D-galactopyranose 2,4'-bis-(potassium/sodium sulfate)(1→3')-polysaccharide.	$[C_{12}H_{18}M_2O_{18}S_3]_n$ where M=Na of K
Poloxalene	Liquid nonionic surfactant polymer of the polyoxypropylene polyoxyetbylene type, having an average molecular weight of 3000.	
Polyglycolic acid	Poly(oxycarbonylmetbylene)	$(C_2H_2O_2)_n$
Polymacon	Poly(2-hydroxyethyl metbacrylate)	$(C_6H_{10}O_3)_n$
Polytef	Poly(tetrafluoroethylene)	$(C_2F_4)_n$
Polythiazide	6-Chloro-3,4-dihydro-2-methyl-3-[[(2,2,2-trifluoroethyl)thio]-methyl]-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.	$C_{11}H_{11}ClF_3N_3O_4S_3$
Poncuronium	1,1'-(3α, 17β-Dihydroxy-5α-androstan-2β,16β-ylene)bis[1-methylpiperidinium]diacetate.	$C_{36}H_{60}N_2O_4$
Povidone	Polyvinylpyrrolidone	----------
Pralidoxime	2-Formyl-1-metbylpyridinium oxime	$C_7H_9N_2O$
Prednival	11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 17-valerate	$C_{26}H_{34}O_6$
Pregnenolone	3β-Hydroxypregn-5-en-20-one	$C_{21}H_{32}O_2$
Prilocaine	2-(Propylamino)-o-propionotoluidide	$C_{13}H_{20}N_2O$
Procarbazine	*N*-Isopropyl-α-(2-methylhydrazine)-*p*-toluamide	$C_{12}H_{19}N_3O$
Profadol	*m*-(1-Methyl-3-propyl-3-pyrrolidinyl)phenol	$C_{14}H_{21}NO$

Official name	Chemical name or description	Molecular formula
Propiolactone	2-Oxetanone; β-propiolactone	$C_3H_4O_2$
Propranolol	1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol	$C_{16}H_{21}NO_2$
Protriptyline	*N*-Methyl-5*H*-dibenzo[*a,d*]cycloheptene-5-propylamine	$C_{19}H_{21}N$
Pyrantel	(*E*)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine	$C_{11}H_{14}N_2S$
Pyrithione zinc	Bis[1-hydroxy-2(1*H*)-pyridinethionato]zinc	$C_{10}H_8N_2O_2S_2Zn$
Pyrrocaine	1-Pyrrolidineaceto-2′,6′-xylidide	$C_{14}H_{20}N_2O$
Pyrroinitrin	3-Chloro-4-(3-chloro-2-nitrophenyl)pyrrole	$C_{10}H_6Cl_2N_2O_2$
Quazodine	4-Ethyl-6,7-dimethoxyquinazoline; 6,7-dimethoxy-4-ethylquinazoline	$C_{12}H_{14}N_2O_2$
Quinaldine blue	1-Ethyl-2-[3-(1-ethyl-2(1*H*)quinolylidene)propenyl] quinolinium chloride.	$C_{23}H_{23}ClN_2$
Quingestanol	3-(Cyclopentyloxy)-19-nor-17α-pregna-3,5-dien-20-yn-17-ol	$C_{23}H_{32}O_2$
Quinternol	8-Hydroxy-α-[(isopropylamino)methyl]-5-quinolinemethanol	$C_{14}H_{18}N_2O_2$
Racephenicol	(±)-*threo*-2,2-Dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-*p*-(methylsulfonyl)phenethyl]-acteamide.	$C_{13}H_{16}Cl_2NO_6S$
Ranimycin	An antibiotic substance derived from *Streptomyces lincolnensis*	$C_{12}H_{16}O_2$
Ribaminol	Ribonucleic acid compound with 2-(diethylamino)ethanol; 2-hydroxytriethylammonium ribonucleate.	----------
Riboprine	*N*-(3-Methyl-2-butenyl)adenosine; 6-*N*-(3-methyl-2-butenylamino(9-β-D-ribofuranosyl-purine.	$C_{15}H_{21}N_5O_4$
Rifampin	5,6,9,17,19,21-Hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[*N*-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate; 3-(4-methylpiperazinyliminomethyl) rifamycin SV.	$C_{43}H_{58}N_4O_{12}$
Ritodrine	*Erythro*-*p*-hydroxy-α-[1-[(*p*-hydroxyphenethyl)amino]ethyl]benzyl alcohol.	$C_{17}H_{21}NO_3$
Ronidazole	(1-Methyl-5-nitroimidazol-2-yl)methylcarbamate	$C_6H_8N_4O_4$
Rotoxamine	*l*-2-[*p*-Chloro-α-[2-(dimethylamino)-ethoxy] benzyl]pyridine	$C_{16}H_{19}ClN_2O$
Roxarsone	4-Hydroxy-3-nitrobenzenearsonic acid	$C_6H_6AsNO_6$
Salethamide	*N*-[2-(Diethylamino)ethyl]salicylamide	$C_{13}H_{20}N_2O_2$
Seperidol	4-[4-(4-chloro-α,α,α-trifluoro-*m*-tolyl)-4-hydroxy-piperidinol]-4′-fluorobutyrophenone; 1-[3-(4-fluorobenzoyl)-propyl]-4-hydroxy-4-(3-trifluoromethyl-4-chlorophenyl)-piperidine.	$C_{28}H_{32}ClF_4NO_4$
Silandrone	17β-(Trimethylsiloxy) androst-4-en-3-one	$C_{22}H_{36}O_2Si$
Simethicone	A mixture of dimethyl polysiloxanes and silica gel.	----------
Sotalol	4′-[1-Hydroxy-2-(isopropylamino)-ethyl]-methanesulfonanilide	$C_{12}H_{20}N_2O_3S$
Soterenol	2′-Hydroxy-5′-[1-hydroxy-2-(isopropylamino)ethyl]methanesulfonanilide.	$C_{12}H_{20}N_2O_4S$
Stanozolol	17-Methyl-5α-androstano[3,2-c]pyrazol-17β-ol	$C_{21}H_{32}N_2O$
Steffimycin	An antibiotic substance derived from *Streptomyces steffisburgensis* var. *steffisburgensis* sp.n.	----------
Sulfadoxine	N^1-(5,6-Dimethoxy-4-pyrimidinyl)sulfanilamide	$C_{12}H_{14}N_4O_4S$
Sulfameter	N^1-(5-Methoxy-2-pyrimidinyl)sulfanilamide	$C_{11}H_{12}N_4O_3S$
Sulfamoxole	N^1-(4,5-Dimethyl-2-oxazolyl)sulfanilamide	$C_{11}H_{13}N_3O_3S$
Sulfanitran	4′[(*p*-Nitrophenyl)sulfamoyl]acetanilide	$C_{14}H_{13}N_3O_5S$
Sulfazamet	N^1-(3-Methyl-1-phenylpyrazol-5-yl)sulfanilamide	$C_{16}H_{16}N_4O_2S$
Sulisobenzone	5-Benzoyl-4-hydroxy-2-methoxybenzenesulfonic acid	$C_{14}H_{12}O_5S$
Sulpiride	*N*-[(1-Ethyl-2-pyrrolidinyl)methyl]-5-sulfamoyl-o-anisamide	$C_{15}H_{23}N_3O_4S$
Surgibone	Bone and cartilage obtained from bovine embryos and young calves.	
Temazepam	7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1, 4-benzodiazepin-2-one.	$C_{16}H_{13}ClN_2O_2$
Testolactone	13-Hydroxy-3-oxo-13,17-secoandrosta-1,4-dien-17oic acid δ-lactone	$C_{19}H_{24}O_4$
Tetrydamine	4,5,6,7-Tetrahydro-2-methyl-3-(methylamino)-2*H*-indazole; 2-methyl-3-methylamino-4,5,6,7-tetrahydroindazole.	$C_9H_{15}N_3$
Thiamphenicol	D-(+)-*threo*-2,2-Dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-*p*-(methylsulfonyl)-phenethyl]acetamide.	$C_{12}H_{15}Cl_2NO_6S$
Thioguanine	2-Aminopurine-6-thiol,hemihydrate	$C_5H_5N_5S \cdot \frac{1}{2}H_2O$
Thioridazine	10-[2-(1-Methyl-2-piperidyl)ethyl]-2-(methylthio)phenothiazine	$C_{21}H_{26}N_2S_2$
Thiosalan	3,4′,5-Tribromo-2-mercaptobenzanilide; 3,4′,5-tribromothiosalicylanilide.	$C_{13}H_7Br_3NOS$
Thiothixene	*N,N*-Dimethyl-9-[3-(4-methyl-1-piperazinyl)propylidene]thioxanthene-2-sulfonamide.	$C_{23}H_{29}N_3O_2S_2$
Thiphenamil	S[2-(Diethylamino)ethyl] diphenylthioacetate	$C_{20}H_{25}NOS$
Thiram	Bis(dimethylthiocarbamoyl) disulfide	$C_6H_{12}N_2S_4$
Thonzonium	Hexadecyl[2-[(*p*-methoxybenzyl)-2-pyrimidinylamino]ethyl]-dimethylammonium ion.	$C_{32}H_{54}N_4O^+$
Tibolone	17-Hydroxy-7α-methyl-19-nor-17α-pregn-5(10)-en-20-yn-3-one	$C_{21}H_{28}O_2$
Tibrofan	4,4′,5-Trihromo-2-thiophenecarboxanilide; 4,5-dihromothiophene-2-carboxyl-4-bromanilide.	$C_{11}H_4Br_3NOS$
Tigestol	19-Nor-17α-pregn-5(10)-en-20-yn-17-ol; 17α-ethynyl-5(10)-estren-17-ol.	$C_{20}H_{28}O$
Tiletamine	2-(Ethylamino)-2-(2-thienyl)cyclohexanone	$C_{12}H_{17}NOS$
Tilidine	Ethyl 2-(dimethylamino)-1-phenyl-3-cyclohexene-1-carboxylate	$C_{17}H_{23}NO_2$
Tinidazole	1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole	$C_8H_{13}N_3O_4S$
Tocamphyl	1-(*p*,α-Dimethylbenzyl) camphorate 1:1 salt with 2,2′-iminodiethanol.	$C_{16}H_{28}O_4 \cdot C_4H_{11}NO_2$ or $C_{28}H_{47}NO_6$
Tofenacin	*N*-Methyl-2-[(*o*-methyl-α-phenylbenzyl)-oxy]ethylamine	$C_{17}H_{21}NO$
Tolazamide	1-(Hexahydro-1*H*-azepin-1-yl)-3-(*p*-tolylsulfonyl)urea	$C_{14}H_{21}N_3O_3S$
Tolnaftate	*O*-2-Naphthyl *m,N*-dimethylthiocarbanilate	$C_{19}H_{17}NOS$
Tramadol	(±)-*trans*-2-[(Dimethylamino)methyl]-1-(*m*-methoxyphenyl)cyclohexanol.	$C_{15}H_{23}NO_2$
Transclomiphene	2-[*p*-(2-Chloro-*trans*-1,2-diphenylvinyl)phenoxy]-triethylamine	$C_{26}H_{28}ClNO$
Triamterene	2,4,7-Triamino-6 phenylpteridine	$C_{12}H_{11}N_7$
Tribromsalan	3,4′5-Trihromosalicylanilide	$C_{13}H_7Br_3NO_2$
Triclocarban	3,4,4′-Trichlorocarbanilide	$C_{13}H_9Cl_3N_2O$

Official name	Chemical name or description	Molecular formula
Triciofos	2,2,2-Trichloroethyl dihydrogen phosphate	$C_2H_4Cl_3O_4P$
Triflocin	4-(α,α,α-Trifluoro-*m*-toluidino)nicotinic acid	$C_{13}H_9F_3N_2O_2$
Triflumidate	Ethyl *m*-benzoyl-*N*-[(trifluoromethyl)sulfonyl] carbanilate	$C_{17}H_{14}F_3NO_5S$
Trifluperidol	4'-Flouro-4-[4-hydroxy-4-(α,α,α-trifluoro-*m*-tolyl) piperidino] butyrophenone.	$C_{23}H_{23}F_4NO_2$
Trimipramine	5-[3-(Dimethylamino)-2-methylpropyl]-10,11-dihydro-5*H*-diben -[*b*,*f*]azepine.	$C_{20}H_{26}N_2$
Trioxsalen	6-Hydroxy-*Θ*,2,7,-trimethyl-5-benzofuranacrylic acid, *δ*-lactone	$C_{14}H_{12}O_3$
Tromethamine	2-Amino-2-(hydroxymethyl)-1,3-propanediol	$C_4H_{11}NO_3$
Tropicamide	*N*-Ethyl-2-phenyl-*N*-(4-pyridylmethyl)-hydracrylamide	$C_{17}H_{20}N_2O_2$
Tybamate	2-Methyl-2-propyltrimethylene butylcarbamate carbamate; or 2-(hydroxymethyl)-2-methylpentyl butylcarbamate carbamate.	$C_{12}H_{24}N_2O_4$
Tyloxapol	*p*-(1,1,3,3-Tetramethylbutyl)phenol polymer with formaldehyde, ether with polyethylene glycol.	
Verapamil	5-[(3,4-Dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile.	$C_{27}H_{38}N_2O_4$
Vinblastine	An alkaloid (vincaleukoblastine) extracted from *Vinca rosea*	$C_{46}H_{58}N_4O_9$
Vincristine	Alkaloid from *Vinca rosea*, Linn.	$C_{46}H_{56}N_4O_{10}$
Volazocine	3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocine.	$C_{19}H_{25}N$
Zolamine	2-[(2-Dimethylamino)ethyl](*p*-methoxybenzyl)amino]thiazole	$C_{14}H_{21}N_3OS$

NOTE.—Incorporation by reference materials approved by the Director, Office of the FEDERAL REGISTER March 20, 1973 and March 25, 1975.

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an invaluable reference tool

1974–75 Edition

This official guidebook provides useful information about U.S. Government agencies, including:

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