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Subpart G—Product Quality Assurance

SOURCE: 51 FR 7390, Mar. 3, 1986, unless otherwise noted.

§ 225.142 Components.

Adequate procedures shall be established and maintained for the identification, storage, and inventory control (receipt and use) of all Type A medicated articles and Type B medicated feeds intended for use in the manufacture of medicated feeds to aid in assuring the identity, strength, quality, and purity of these drug sources. Packaged Type A medicated articles and Type B medicated feeds shall be stored in designated areas in their original closed containers. Bulk Type A medicated articles and bulk Type B medicated feeds shall be identified and stored in a manner such that their identity, strength, quality, and purity will be maintained. All Type A medicated articles and Type B medicated feeds shall be used in accordance with their labeled mixing directions.

§ 225.158 Laboratory assays.

Where the results of laboratory assays of drug components, including assays by State feed control officials, indicate that the medicated feed is not in accord with the permissible limits specified in this chapter, investigation and corrective action shall be implemented immediately by the firm and such records shall be maintained on the premises for a period of 1 year.

§ 225.165 Equipment cleanout procedures.

Adequate procedures shall be established and used for all equipment used in the production and distribution of medicated feeds to avoid unsafe contamination of medicated and nonmedicated feeds.

Subpart H—Labeling

§ 225.180 Labeling.

Labels shall be received, handled, and stored in a manner that prevents label mixups and assures that the correct labels are used for the medicated feed. All deliveries of medicated feeds, whether bagged or in bulk, shall be adequately labeled to assure that the feed can be properly used.

[51 FR 7390, Mar. 3, 1986]

Subpart I—Records

§ 225.202 Formula, production, and distribution records.

Records shall be maintained identifying the formulation, date of mixing, and if not for own use, date of shipment. The records shall be adequate to facilitate the recall of specific batches of medicated feed that have been distributed. Such records shall be retained on the premises for 1 year following the date of last distribution.

(Approved by the Office of Management and Budget under control number 0910–0152)

[51 FR 7390, Mar. 3, 1986]

PART 226—CURRENT GOOD MANUFACTURING PRACTICE FOR TYPE A MEDICATED ARTICLES

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226.80 Packaging and labeling.

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226.102 Master-formula and batch-production records.
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226.115 Complaint files.

AUTHORITY: Secs. 501, 502, 512, 701, 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 352, 360b, 371, 374).

SOURCE: 40 FR 14031, Mar. 27, 1975, unless otherwise noted.

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 Type A medicated article(s) conform to or are operated or administered in conformity with current good manufacturing practice to assure that a Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s) shall have a background of appropriate education or appropriate experience or combination thereof for assuming responsibility to assure that the Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s), their components, packaging, or labeling:

(1) The receipt, sampling, control, and storage of components.

(2) Manufacturing and processing operations performed on the Type A medicated article(s).

(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 Type A medicated article(s), and to avoid other conditions unfavorable to the safety, identity, strength, quality, and purity of the raw materials and Type A medicated article(s) before, during, and after production.

(c) Provide for adequate washing, cleaning, toilet, and locker facilities.

Work areas and equipment used for the production of Type A medicated article(s) or for the storage of the components of Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s).

(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 Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s) shall be received, adequately identified, and properly stored and handled in a manner 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 Type A medicated article(s) and to insure the integrity of the finished product.

(d) Competent and responsible personnel shall check actual against theoretical yield of a batch of Type A medicated article(s), and, in the event of any significant discrepancies, key personnel shall prevent distribution of the batch in question and other associated batches of Type A medicated article(s) 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 Type A medicated article(s) shall be used to avoid contamination of Type A medicated article(s).

(f) If there is sequential production of batches of a Type A medicated article(s) 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 Type A medicated article(s).

(g) Production and control procedures shall include provision for discontinuing distribution of any Type A medicated article(s) found by the assay procedures, or other controls performed to fail to conform to appropriate specifications. Distribution of subsequent production of such Type A medicated article(s) 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 Type A medicated article(s), 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 Type A medicated article(s) 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 Type A medicated article(s). This may consist of the manufacturer's or supplier's statement of specifications and methods of analyses.

(b) The establishment of specifications for Type A medicated article(s) and a description of necessary laboratory test procedures to check such specifications.

(c) Assays which shall be made of representative samples of finished Type A medicated article(s) in accordance with the following schedule:

(1) Each batch of a Type A medicated article(s) manufactured from an undiluted drug shall be assayed for its drug component(s).

(2) In the case of Type A medicated article(s) which are manufactured by dilution of Type A medicated article(s) 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 Type A medicated article(s) under ordinary conditions of shipment, storage, and use. This may consist of a determination on a Type A medicated article(s) of substantially the same formula and characteristics. Suitable expiration dates shall appear on the labels of the Type A medicated article(s) 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 Type A medicated article(s) has been completed.

[40 FR 14031, Mar. 27, 1975, as amended at 55 FR 11577, Mar. 29, 1990; 55 FR 23703, June 12, 1990]

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 Type A medicated article(s) that have met the specifications established in the master-formula records shall be distributed.

(2) To prevent mixups during the packaging and labeling operations.

[1] Copies may be obtained from: Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201–3301.

(3) To assure that correct labeling is employed for each Type A medicated article(s).

(4) To identify Type A medicated article(s) with lot or control numbers that permit determination of the history of the manufacture and control of the batch of Type A medicated article(s).

(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 Type A medicated article(s).

(c) Type A medicated article(s) 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 Type A medicated article(s) 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 and responsible individual. The record shall include:

(1) The name of the Type A medicated article(s) 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 Type A medicated article(s).

(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 Type A medicated article(s), 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 Type A medicated article(s) produced on a batch or continuous operation basis, including mixing steps and mixing times that have been determined to yield an adequately mixed Type A medicated article(s); and in the case of Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s) 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 Type A medicated article(s).

§ 226.110 Distribution records.

Complete records shall be maintained for each shipment of Type A medicated article(s) in a manner that will facilitate the recall, diversion, or destruction of the Type A medicated article(s), 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 Type A medicated article(s) 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 Type A medicated article(s). 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 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 [Reserved]
250.105 Gelsemium-containing preparations regarded as prescription drugs.
250.106 Cobalt preparations intended for use by man.
250.107 [Reserved]
250.108 Potassium permanganate preparations as prescription drugs.

Subpart C—Requirements for Drugs and Foods

250.201 Preparations for the treatment of pernicious anemia.

Subpart D—Requirements for Drugs and Cosmetics

250.250 Hexachlorophene, as a component of drug and cosmetic products.

AUTHORITY: Secs. 201, 306, 402, 502, 503, 505, 601(a), 602 (a) and (c), 701, 705(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 336, 342, 352, 353, 355, 361(a), 362 (a) and (c), 371, 375(b)).

SOURCE: 40 FR 14033, Mar. 27, 1975, 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 ''Investigational New Drug Application,'' set forth in part 312 of this chapter, must be submitted to cover clinical investigations designed to obtain evidence that such preparations are effective for such use.

(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.

[40 FR 14033, Mar. 27, 1975, as amended at 55 FR 11577, Mar. 29, 1990]