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New Jersey (State)
Department of Health
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GOOD DRUG MANUFACTURING PRACTICES

N.J.A.C. 8:64-2

The State Department of Health, pursuant to authority vested in it under the provisions of Chapter 2, Title 24 of the Revised Statutes, hereby promulgates the following regulations concerning "Good Drug Manufacturing Practices."

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State Commissioner of Health

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DRUGS; CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURE, PROCESSING, PACKING, OR HOLDING.

DEFINITIONS

1. Definitions

- (a) "Act" means N.J.S.A. 24:1 et seq. the Food, Drug and Cosmetic Law of New Jersey, and all amendments thereto.
- (b) The definitions and interpretations contained in the Food, Drug and Cosmetic Act shall be applicable to such terms when used in this regulation.
- (c) As used in Section 2 through 15 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:
 - a. The concentration of the drug substance (for example, w/w, w/v, or unit dose/volume basis) and/or
 - b. 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).

FINISHED PHARMACEUTICALS; MANUFACTURING PRACTICE

2. Current good manufacturing practice

- (a) The criteria in 3-15, 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 N.J.S.A. 24:6-1 et seq.
- (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.

3. 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

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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 ingredient 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 Section 13.
- (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 (PHS standards in 42 CFR Part 72) 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.

4. 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.

5. 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.

6. 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.

7. 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 number 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 Section 8(h).

8. 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.

9. 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. 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.

10. 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 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 133.8(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.

11. 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 Section 6(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 non-penicillin 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.

12. 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 N.J.S.A. 24:21-13 relating to records of registrants subject to the New Jersey Controlled Dangerous Substances Act.

13. 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.

14. 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 Section 13.
- (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.

15. 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 Section 8(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.

**It is recognized that some modification of these regulations may be indicated in connection with their application to the manufacture of chemicals and other raw materials used as components of finished drugs. Similarly these regulations relate to the manufacture of drugs in final dosage form and are inapplicable to the manufacture of medicated feeds and medicated premixes.*