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MIL-STD-964 (DM)
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MILITARY STANDARD

MANUFACTURE AND PACKAGING OF DRUGS, PHARMACEUTICALS AND BIOLOGICAL PRODUCTS

FSC 6505

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DEPARTMENT OF DEFENSE
WASHINGTON, D. C. 20301

MILITARY STANDARD FOR THE MANUFACTURE AND PACKAGING OF DRUGS, PHARMACEUTICALS AND BIOLOGICAL PRODUCTS

MIL-STD-964(DM)

1. This Military Standard is mandatory for use by all Departments and Agencies of the Department of Defense in the procurement of Drugs, Pharmaceuticals and Biologicals, as a basis for qualifying drug manufacturers and packagers, in accordance with the requirements of the Armed Services Procurement Regulation.

2. Recommended corrections, additions or deletions should be addressed to Commanding Officer, Directorate of Medical Material, ATTN: DPSC-AT, Defense Personnel Support Center, 2800 South 20th Street, Philadelphia, Pa. 19101.

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FOREWORD

The Defense Personnel Support Center Standard for the manufacture and Packaging of Drugs, Pharmaceuticals and Biological Products dated 1 September 1968 was adopted on 20 May 1974 as a Military Standard and is approved for issue and use by all Activities of the Department of Defense. This Standard represents the minimum acceptable level for the technical qualification of drug manufacturers and packagers. Accordingly, to qualify, an interested company must comply with this Standard to the extent applicable, or operate under conditions comparable to this Standard as determined by the procuring Activity.

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1. SCOPE

1.1 PURPOSE

The purpose of these standards is to establish minimum acceptable standards for manufacturers, packagers, and holders of drug products.

1.2 APPLICATION

These standards serve as a basis for evaluating the acceptability of plants and facilities where drugs are manufactured, packaged, or held. Compliance with these standards shall not relieve a manufacturer, packager, or holder of drug products of the necessity of compliance with all applicable federal and state laws and regulations.

2. ORGANIZATIONAL STRUCTURE

The organizational structure of the company shall be such that Production shall be headed by a Production Director, and Quality Control shall be headed by a Quality Control Director. Production and Quality Control Directors shall be different persons, neither of whom shall be responsible to the other; both shall report to a higher level of management.

Production shall not have the responsibility or authority to approve the final product for release. Quality Control shall have the responsibility and authority to approve satisfactory products, and to reject raw materials, in-process materials, and final products which fail to comply with the applicable standards or are not manufactured in accordance with predetermined methods, procedures, and conditions.

The procedures applicable to each unit or group dealing with production, quality control, laboratory, warehousing, maintenance, and sanitation shall be in writing. Each unit or group shall maintain a copy of the procedures covering its operations.

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3. PERSONNEL REQUIREMENTS, QUALIFICATIONS, AND RESPONSIBILITIES

3.1 GENERAL PERSONNEL REQUIREMENTS

Personnel in the manufacturing, quality control, laboratory, warehousing, maintenance, and sanitation areas shall be well trained, dependable, conscientious, and quality minded.

Personnel shall have:

(a) Capabilities commensurate with their assigned functions;

(b) A thorough understanding of their position descriptions which are written descriptions of their duties and responsibilities;

(c) A thorough understanding of the operations which they perform; and

(d) The necessary training and experience related to the individual operations and products.

3.2 STAFFING

3.2.1 The number of personnel employed and working shall be adequate to perform and supervise the operations.

3.2.2 Staffing of personnel shall include:

(a) Production Director (see 3.3.2).

(b) Quality Control Director (see 3.3.3 and Dual Responsibilities 3.2.3).

(c) Laboratory Head (see 3.3.4 and Dual Responsibilities 3.2.3).

(d) Additional Qualified Professional Personnel (see 3.3.1) - sufficient number to perform or supervise the critical operations.

(e) Technicians (see 3.3.5) - sufficient number to perform or supervise assigned functions.

(f) Maintenance - sufficient number to maintain the facilities and plant in clean, orderly, and sanitary condition. Maintenance personnel are supervised by a Qualified Professional Person or Technician.

3.2.3 Dual responsibilities

The Quality Control Director may also be the Laboratory Head in exceptional circumstances when:

(a) The operation is small enough for one man to supervise effectively the quality control and laboratory activities.

(b) Quality Control and Laboratory are adequately staffed to operate effectively with reduced supervision.

(c) The Quality Control Director meets the qualifications for Laboratory Head.

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3. PERSONNEL REQUIREMENTS, QUALIFICATIONS, AND RESPONSIBILITIES (Cont'd)

3.3 PERSONNEL QUALIFICATIONS AND RESPONSIBILITIES

Qualifications and responsibilities of personnel shall be as stated herein.

3.3.1 Qualified professional personnel

A Qualified Professional Person shall be one who meets the following qualifications:

A. Graduate from an accredited college or university with a degree in pharmacy or a 4-year Bachelor degree or higher degree with a major in one of the biological, chemical, pharmaceutical, engineering, or physical sciences.

B. Possess the experience, knowledge, and ability to perform the assigned functions.

3.3.2 Production director

A. The Production Director shall be a Qualified Professional Person who has responsible experience in the manufacture of the drugs being produced, and a comprehensive understanding of the scientific principles and techniques involved in their manufacture. His responsibilities shall be well-defined and shall include:

(1) All matters relating to the manufacture of products

(2) Assignment of personnel engaged in the manufacture of products and the execution of the assigned functions

(3) The efficient, effective, and accurate manufacture of products

B. The Production Director shall be a full-time employee in that position.

C. In the temporary absence of the Production Director, a designated Assistant qualifying as a Qualified Professional Person and employed in the production operations, shall assume the duties and responsibilities for the operations.

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3. PERSONNEL REQUIREMENTS, QUALIFICATIONS, AND RESPONSIBILITIES (Cont'd)

3.3.3 Quality control director

A. The Quality Control Director shall be a Qualified Professional Person who has responsible experience in quality control of drug manufacture, and an intimate knowledge of the scientific principles and techniques in testing and quality control. He shall have the authority, independent of production authority, to approve satisfactory products and reject raw materials, in-process materials, and final products which fail to comply with the applicable standards or are not manufactured in accordance with predetermined methods, procedures, and conditions. His responsibilities shall be well-defined and shall include:

(1) Authority and organizational freedom to establish, identify, and evaluate quality programs, and to initiate, recommend, and provide solutions

(2) The laboratory and its operations

B. The Quality Control Director shall be a full-time employee in that position.

C. In the temporary absence of the Quality Control Director, a designated Assistant, qualifying as a Qualified Professional Person and employed in the quality control operations, shall assume the duties and responsibilities for the Quality Control Director.

3.3.4 Laboratory head

A. The Laboratory Head shall be a Qualified Professional Person having responsible laboratory testing experience. His responsibilities shall be well-defined and shall include:

(1) Supervision of or performance of chemical, biological, or other examinations or analyses.

(2) Performance of tests, explanation of reactions or effects, and interpretation of results. For purposes of this Standard, one who can only follow assay or other instructions in performing tests and is not knowledgeable in the theory or interpretation of the test, cannot be qualified as Laboratory Head. The Laboratory Head shall also apprise the Quality Control Director of difficulties encountered in analyses, modifications, or changes in specified test procedures and of noncomplying results, even though results may comply on retest.

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3. PERSONNEL REQUIREMENTS, QUALIFICATIONS, AND RESPONSIBILITIES (Cont'd)

3.3.4 Laboratory Head (Cont'd)

B. The Laboratory Head shall be a full-time employee in that position.

C. In the temporary absence of the Laboratory Head, a designated individual, qualifying as a Qualified Professional Person and employed in the quality control or laboratory operations, shall assume the duties and responsibility for the Laboratory Head.

D. Laboratory Head shall report to the Quality Control Director. (See 3.2.3 Dual Responsibilities)

3.3.5 Technicians

Technicians shall have the knowledge and ability to perform designated assignments required for the production or control of drug products by virtue of education and/or training and experience.

3.4 PERSONNEL TRAINING

All personnel shall be indoctrinated in the details, functions, and importance of their positions. There shall be formalized training emphasizing the importance of each job in the over-all quality of the final product. The personnel of each operational unit or group shall understand and apply the production, quality control, laboratory, warehousing, maintenance, and sanitation procedures applicable to the unit or group. Time devoted to training shall be commensurate with the complexity of duties assigned, with the result that each employee will be intimately familiar with his duties and responsibilities.

3.5 CONSULTANTS

When the company claims the use of a consultant to augment the personnel staffing, records shall be maintained stating the name, address, qualifications of consultant, subject and type of consultation, and time devoted to the consultation.

3.6 STANDARDS OF HEALTH REQUIREMENTS

A. Precautions shall be taken to assure that personnel engaged in drug manufacture (weighing, mixing, compounding, tableting, ampuling, packaging, etc.) are not afflicted with a communicable disease. The following practices shall be employed for personnel engaged in drug manufacture:

(1) Pre-employment medical examination is required which includes chest X-ray and serology, such as Wassermann Test. A statement shall be issued by appropriate medical authority stating that the person is not afflicted with an active communicable disease such as may be detected by such examinations.

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3. PERSONNEL REQUIREMENTS, QUALIFICATIONS, AND RESPONSIBILITIES (Cont'd)

3.6 STANDARDS OF HEALTH REQUIREMENTS (Cont'd)

(2) Re-examination for communicable disease (chest X-ray and Wassermann) is conducted approximately every 2 years while the person is engaged in drug manufacturing operations. Appropriate additional examination is required when there is a history of intestinal infections.

(3) Records of sick leave are maintained.

(4) Physicians' fit-for-duty statements are required for sick leave in excess of one week. Test for staphylococcus infection is performed when indicated.

B. Daily observations for visible signs of upper respiratory infections, infected cuts, open sores, and other lesions on the exposed surface of the body shall be made by supervisors of personnel engaged in drug manufacture. Personnel showing such symptoms shall not be permitted in areas where components, intermediates, or finished products may be exposed to contamination, unless medical authority has judged the condition to be noninfectious.

3.7 PERSONNEL CLEANLINESS

A. Personnel shall be suitably dressed for the duties performed. Clean working garments and head coverings shall be worn over, or in place of, street clothing for work in production and packaging areas where components, intermediates, or finished drug products are exposed. They shall practice good sanitation and health habits and shall not smoke, chew tobacco, or expectorate in the production and packaging areas.

B. Personnel engaged in critical stages of sterile operations (product contact areas) shall wear low-linting type, freshly laundered or sterilized uniforms (long sleeve); gowns; caps; and shoe covers; and sterilized gloves and masks. Such personnel shall also wash and rinse their hands with a suitable and harmless disinfectant prior to dressing and entering such areas. After leaving the area, a complete change of attire is required prior to returning.

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4. PLANT PREMISES, ARRANGEMENT, FACILITIES, AND EQUIPMENT

4.1 PLANT PREMISES

Plant Premises shall be of suitable size for the operations performed. They shall be of sound construction and in good state of repair. The surroundings of the premises shall be well drained and free of unsanitary environmental conditions (such as conditions leading to or actual presence of insects, rats, pests, objectionable odors, and other polluting substances) and materials that are a sanitation hazard.

4.2 ARRANGEMENT

The plant arrangement shall be such as to eliminate disorder, crowding, and the potential of cross-contamination and mixups between different drugs, components, packaging, and labeling materials. Operations shall be performed within designated and defined areas of adequate size (except where closed systems are employed). Walls, partitions, air curtains, or other suitable means shall be employed for separation of areas to prevent contamination or error. The operations and defined areas requiring such separation are:

A. Receiving

B. Quarantine

C. Raw materials (component) storage

D. Weighing/Measuring

E. Mixing

F. Granulating (comminuting)

G. Compounding and processing (tablets, capsules, parenterals, liquids, powders, ointments, etc.)

H. Storage of bulk tablets, capsules, pills, etc., awaiting packaging

I. Filling and packaging

J. Storage of dosage material awaiting quality control release

K. Inspection of dosage form and packaged product

L. Storage of finished products

M. Shipping

N. Laboratory

O. Animal Room (must be either in separate building or a separate, enclosed room)

P. Equipment washing

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4. PLANT PREMISES, ARRANGEMENT, FACILITIES, AND EQUIPMENT (Cont'd)

4.2.1 The plant shall be so arranged that the movement of traffic shall be minimal:

A. Within the manufacturing areas, and

B. Between the manufacturing areas and other parts of the plant.

4.2.2 There shall be no manufacture of non-drug items in drug production areas.

4.2.3 Plant shall be adequately lighted and ventilated.

4.2.4 Adequate protection shall be maintained to prevent contamination of products and to prevent the dissemination of micro-organisms from one area to another.

4.3 FACILITIES AND EQUIPMENT

Facilities and equipment shall be adequate for the operations performed, and shall be located, constructed, installed, and cleaned in such a manner to prevent contamination of material or equipment; arranged to prevent contamination when multiple operations are concurrently in progress; and designed and constructed to permit ready accessibility for cleaning and proper maintenance.

4.3.1 General requirements

A. Equipment and utensils used in drug manufacture shall be designed, constructed, and cleaned so that surfaces coming into contact with raw materials, intermediates, or finished drugs are of a suitable character to preserve the identity, quality, purity, and strength of the drug, and to avoid contamination. The equipment shall be constructed and operated so that any substances required for the operation or maintenance of the equipment, such as lubricants or coolants, cannot come into contact with or become additive to the drug products.

B. The equipment shall be of such design, construction, type, size, and durability to insure uniformity and accuracy of production (measuring, mixing, weighing, tableting, ampuling, filling, etc.). Ready means shall be available and utilized for adjustment, cleaning, and maintenance.

C. Light fixtures; pipes, fans, or other accessories shall not be located directly over a manufacturing operation where there is a potential that dust or dirt can fall into the material being manufactured.

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4. PLANT PREMISES, ARRANGEMENT, FACILITIES, AND EQUIPMENT (Cont'd)

4.3.1 General requirements (Cont'd)

D. The design of the facilities shall be such that temperature and humidity are controlled where conditions are necessary to protect the quality or uniformity of the product.

E. The major machines or equipment (tableting, encapsulating, mixing, filling, etc.) shall be permanently marked for identification and record purposes. The machines shall also be equipped to provide identification of product under production.

4.3.2 Special requirements

4.3.2.1 MANUFACTURE OF STERILE PRODUCTS

A. Rooms required in manufacture of sterile products:

(1) Clean-up Room for containers and equipment

(2) Preparation Room for compounding

(3) Filling and Sealing Room for immediate containers

(4) Anteroom for connecting Gowning Room and Filling and Sealing Room

(5) Gowning Room for dressing into gowns

B. General requirements for rooms used in manufacture of sterile products.

(1) The design, construction, and arrangement of the rooms shall:

(a) Prevent the potential for contamination from within the room, from one room to another, and from the surrounding areas.

(b) Include tight-fitting doors.

(c) Be of sufficient size and lighting so that any undesirable conditions can be readily detected.

(2) The material and surfaces of the floors, walls, and ceilings shall:

(a) Be impervious to water.

(b) Withstand hot water and detergent.

(c) Be cleanable and clean.

(d) Be of smooth construction with hard surfaces, free of holes and crevices.

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4.3.2.1 MANUFACTURE OF STERILE PRODUCTS (Cont'd)

(3) The rooms shall:

(a) Be temperature and humidity controlled within predetermined ranges for uniformity and consistency of atmospheric conditions when necessary for product quality.

(b) Have positive pressure or laminar flow system maintained with a suitable supply of "sterile" air.

"Sterile" air shall be obtained by use of filters, washers, electrostatic precipitators, or combinations of these. Banks of ultraviolet lights may be used in combination with the foregoing. The treatment of the air shall be designed to remove particles and micro-organisms greater than 0.5 microns. The effectiveness of the system shall be determined periodically, and filters, washers, lamps, and other devices replaced when necessary, in order to assure the continued source of "sterile" air.

(c) Be clean and orderly without accumulation of containers, cartons, rags, dust, debris, etc.

C. Additional requirements

(1) Clean-up Room.

Clean-up Room shall be designed to provide adequate exhaust to prevent extremes of temperature and humidity.

(2) Preparation Room.

(a) Sinks, cabinets, and counters shall be of stainless steel or equally nonreactive material which is easy to brush and clean with soap or detergent.

(b) Sinks, cabinets, and counters shall fit snugly so that there is no catch space for accumulation of dirt or other undesirable debris.

(3) Filling and Sealing Room for immediate containers.

(a) Entrances (and exits) shall be protected by anterooms to avoid contamination.

(b) The room shall be disinfected between uses, preferably during the night when not being used.

(c) Ultraviolet lights or other suitable means may be employed to aid in maintaining appropriate conditions.

(d) Lighting fixtures, pipes, and accessories shall be recessed where possible.

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4.3.2.1 MANUFACTURE OF STERILE PRODUCTS (Cont'd)

(e) All equipment, fixtures, furnishings, and accessories shall be clean.

(f) A system for monitoring environmental conditions shall be established. The system shall include the routine use of suitable culture medium plates exposed for a sustained period in such locations as the sterile filling assemblies, laminar flow hoods, floors, tops of hoods, turntables, and capping hoods, and near the air registers. If air samplers are employed as an auxiliary indicator, the volume of air sampled per unit of time shall be determined. The monitoring system shall include plate counts and provisions for corrective action when the margin of safety is approached. Records shall be maintained of plate counts showing date, duration and location of culture plate exposures, and bacterial and mold counts.

(g) Gas cylinders and other apparatus and equipment shall be cleaned before being brought into the room.

(h) There shall be no window on an outside building wall.

(i) Products which are not terminally sterilized shall be aseptically filled under hoods with adequate shields or in suitable cubicles. The hoods or cubicles shall have a higher positive pressure than that maintained in the Filling and Sealing Room. A system for monitoring aseptic conditions within the hoods or cubicles shall include the use of suitable culture medium plates, evaluation of results, and a system for corrective action as required in (f) above.

(j) For products which are not terminally sterilized, the suitability of the aseptic filling system (representing a combination of equipment, utensils, sealing, atmosphere, and technique) shall be determined periodically. One method that may be used in evaluating the aseptic system is to process, under routine conditions, the equivalent of a representative lot of containers, filling them with a suitable sterile culture medium, incubating the entire lot, and examining for the presence of contamination. Records of evaluations and results are maintained.

(4) Anteroom

(a) Anteroom shall connect the Filling and Sealing Room and Gowning Room. The Anteroom shall act as an "airlock" between the two rooms.

(b) The room shall be disinfected regularly.

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4.3.2.1 MANUFACTURE OF STERILE PRODUCTS (Cont'd)

(c) Ultraviolet lights or other suitable means may be employed to aid in maintaining appropriate conditions.

(d) Light fixtures shall be recessed where possible.

(5) Gowning Room

(a) Gowning Room shall open into the Anteroom.

(b) The room shall be disinfected regularly.

(c) Ultraviolet lights or other suitable means may be employed to minimize contamination.

(d) The contents of the room shall be restricted to necessary furnishings.

4.3.2.2 MANUFACTURE OF TABLETS

A. Areas required in manufacture of tablets:

(1) Weighing

(2) Mixing

(3) Granulating

(4) Drying

(5) Tableting

(6) Coating and Polishing (when applicable)

(7) Filling and Packaging

(8) Inspection

(9) Packing

B. General requirements for areas used in manufacture of tablets:

(1) The design, construction, and arrangement of the areas shall:

(a) Avoid the potential for contamination from operations within the room, one room to another, and from the surrounding areas.

(b) Include tight-fitting doors, where necessary, and finished ceilings.

(c) Be of sufficient size and lighting to readily detect any undesirable conditions.

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4.3.2.2 MANUFACTURE OF TABLETS (Cont'd)

(2) The materials and surfaces of the floors, walls, and ceilings shall:

(a) Be cleanable and clean.

(b) Be impervious to water.

(c) Be of smooth construction with hard surfaces.

(3) Optimum environmental conditions of the areas shall be maintained by:

(a) An effective exhaust system where indicated.

(b) Temperature and humidity control within predetermined ranges for uniformity and consistency of atmospheric conditions.

(c) Clean and orderly arrangement without accumulation of containers, cartons, rags, debris, etc.

C. Additional Requirements

(1) Weighing Area

Weighing Area shall comply with the following:

(a) Adequate exhaust to remove dust and prevent the potential for contamination.

(b) Scales, weights, and measuring devices shall be of appropriate size and accuracy for the weighing and measuring performed. (See: Calibration of Instruments and Apparatus, Par. 7.7.)

(c) The weighing or measuring of quantities of raw materials beyond the capacity of the weighing area may be accomplished in other appropriate areas, provided the raw materials are adequately protected from the potential for contamination.

(2) Mixing Area

The Mixing Area shall comply with the following:

(a) Adequate exhaust to remove dust and avoid any potential for contamination within the area or from outside the area.

(b) Mixing and blending equipment shall be located near exhausts unless operating as closed systems.

(c) Mixers and blenders shall be adequately protected by partitions or other suitable means to avoid contamination when more than one product is mixed, blended, or exposed in the area.

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4.3.2.2 MANUFACTURE OF TABLETS (Cont'd)

(3) Granulating (comminuting) Area

Granulating (comminuting) Area shall comply with the following:

(a) Adequate exhaust to remove dust and avoid any potential for contamination within the area or from outside the area.

(b) Granulating and comminuting equipment shall be located near exhausts unless operating as closed systems.

(c) Granulating and comminuting equipment shall be adequately protected by partitions or other suitable means to avoid contamination when more than one product is mixed, blended, or exposed in the area.

(4) Drying Area

Drying Areas, consisting of ovens, dryers, and other specialized equipment for the purpose, shall comply with the following:

(a) Be maintained to avoid the potential for cross-contamination and to dry effectively under the designated conditions employed in its operations.

(b) Provide uniform temperature and humidity conditions.

(c) Filter effectively the air entering the dryer and air recirculating in the dryer. When the atmosphere contains perceptible noxious gases, the use of gas-absorbing filters shall also be required.

(d) Discharge the air out of the building, or filter the air prior to discharging inside the building.

(5) Tableting (compressing) Area

Tableting Area shall comply with the following:

(a) Tablet machines shall be in individual cubicles, or shall be separated by walls, solid partitions of suitable height, air curtains, or other suitable means to avoid the potential for contamination. The distance required between tablet machines shall depend upon the conditions of the tableting area, size and type of machines, the exhaust system, the height of partitions, the height of the ceiling, and other considerations. Generally a minimum distance of 8 feet between tablet machines is suitable providing the conditions and arrangement avoids the potential for contamination. There are no minimum distance limitations between tablet machines which are individually contained within cubicles.

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4.3.2.2 MANUFACTURE OF TABLETS (Cont'd)

(b) Tablet machines shall be equipped with effective and efficient vacuum attachments or shall have exhausts for rapid removal of dust and other airborne particles in order to prevent the potential for contamination.

(c) Containers of powder for tableting shall be kept within cubicles, partitions, or other defined areas in order to prevent the potential for mixup.

(d) Hoppers on tablet machines shall be suitably covered when machines are in operation or contain powder for tableting.

(e) Tablets shall be collected and stored in clean cartons or drums lined with unused paper bags or unused polyethylene or equivalent liners. (See Section Par. 9.3e.)

(6) Coating and Polishing (tablet) Area

(a) Coating pans and polishing pans shall be arranged in an orderly manner.

(b) Coating pans shall be equipped with hot-air and exhaust systems which shall be fitted with dampers for partial or total closing at the coating pans. Temperature and humidity of the hot-air shall be maintained within predetermined ranges as required for the particular material being processed.

(c) The hot-air supply shall be adequately filtered, and of sufficient volume and capacity for the number of pans serviced.

(d) The exhaust system shall be sufficiently effective to remove rapidly solvents used in the coating operation, and to remove powders and particles from the pans.

(7) Filling and Packaging Area

The Filling and Packaging Area shall comply with the following:

(a) Counting (or weighing) machines and filling and labeling equipment shall be arranged and clearly identified to prevent the potential for contamination of products, or mixups of products, containers, void space fillers, labels, labeling, and cartons.

(b) Adequate space shall separate multiple filling stations.

(c) Cartons and drums containing the bulk tablets shall be kept near the filling station or other defined areas, in order to avoid the potential for mixups.

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4.3.2.2 MANUFACTURE OF TABLETS (Cont'd)

(8) Inspection Area

Adequate space shall be allocated for inspection of tablets, containers, void space filler, labels, and labeling. Inspection shall be conducted under conditions favorable for ready detection of defective material. The area shall be sufficiently lighted for purposes of inspection, and shall be sufficiently ventilated in order to enhance employees' keenness and alertness for inspection details.

(9) Packing Area

Packing areas shall be suitable for the purpose and arranged in a manner to avoid mixups.

4.3.2.3 MANUFACTURE OF CAPSULE PRODUCTS

Requirements for the manufacture (filling) of capsules shall be in accordance with the requirements for the manufacture of tablets as stated in the following paragraphs:

A. 4.3.2.2A, (1), (2), (6), (7). (8), and (9). Filling of capsules shall be performed in an encapsulating area complying with the essential requirements of the tableting area.

B. 4.3.2.2B (all subparagraphs).

C. 4.3.2.2C, (1), (2), (5) which shall apply to encapsulating instead of tableting, (7), (8), and (9). Cleaning/polishing of the filled capsules shall be accomplished in an appropriate area and shall avoid the potential for contamination and mixup.

4.3.2.4 MANUFACTURE OF PILLS, TROCHES, AND OTHER SOLID DOSAGE FORMS

Requirements for areas used in manufacture of pills, troches, and other dosage forms shall be essentially the same as the requirements for the equivalent areas described in the requirements for manufacture of tablets.

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4.3.2.5 MANUFACTURE OF OPHTHALMIC OINTMENTS

Ophthalmic ointments shall be produced under appropriate conditions of cleanliness, and filled into tubes under aseptic environment or under a suitable hood to minimize the potential for bacterial or other contamination. The limit of particles in the ointment and bacterial contamination shall be as required by the procuring agency.

4.3.2.6 MANUFACTURE OF LIQUID PRODUCTS, TOPICAL OINTMENTS, SUPPOSITORIES, POWDERS, SPRAYS, OR OTHER LIQUID, POWDER, OR SEMI-SOLID DOSAGE FORMS

Requirements for areas used in the manufacture of liquid products, ointments, suppositories, powders, sprays, etc., shall comply with the applicable requirements above.

NOTE: 1. Areas exposed to operations causing dust shall contain effective exhaust facilities.

2. Finished ceilings and temperature and humidity controls are not required in areas where large mixing or storage vessels are located. Such vessels shall be covered and adequately protected from dust and cross-contamination.

3. Tanks and drums shall be properly identified and suitably located in order to avoid the potential for contamination or mixups.

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5. PRODUCT CONTROL STANDARDS

5.1 RAW MATERIALS (COMPONENTS)

Raw Materials are ingredients received or manufactured by the company intended for use in the manufacture of drug products.

5.1.1 Classification of raw materials

For purposes of this standard the classification of raw materials shall be as follows:

(a) Active Ingredient - Active ingredient is a drug intended to give the desired therapeutic effect. Examples: Aspirin, Phenobarbital, and Penicillin.

(b) Inactive Ingredient - Inactive ingredient is an excipient, diluent, preservative, buffer, solubilizer, vehicle, pharmaceutical solvent, or other material, irrespective of whether it appears in the finished product, used in preparing the active ingredient for dosage form. Examples: Starch, Magnesium Stearate, Alcohol, and Purified Water.

(c) Diluted Active Ingredient - Diluted active ingredient is an active ingredient to which its manufacturer has added an inactive ingredient. It is used in the manufacture of the finished product. Use of a diluted active ingredient is permitted when customary in the trade. Examples: Pentaerythritol with Mannitol or Lactose, Ascorbic Acid with Ethyl Cellulose, granulation of Aspirin and Starch.

(d) Bulk Ingredient - Bulk ingredient is a liquid, powder, crystalline drug, or chemical which is intended to be packaged for sale. Examples: Mineral Oil, Boric Acid, and Epsom Salt.

5.1.2 Specifications for raw materials

Written specifications shall be established for all raw materials. These specifications shall be used by the company in procurement of the raw materials. Specifications for raw materials shall comply with the following:

(a) For raw materials monographed in the USP or NF, reference shall be made to the latest revision of the USP plus any interim revisions or supplements, or the latest edition of the NF plus any interim revisions or supplements. Additional tests, standards, and physical characteristics shall also be included in the written specification.

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5.1.2 Specifications for raw materials (Cont'd)

(b) For raw materials not monographed in the USP or NF, specifications (tests, standards and physical characteristics) shall describe the identity and degree of purity. Such tests and examinations as assay, loss on drying, spectrography, melting range, boiling range, heavy metals, color, crystal size, etc., shall be included as applicable in the written specifications.

(c) For diluted active ingredients, specifications (tests, standards and physical characteristics) shall describe the identity and degree of purity of the diluted active ingredients and the components of the diluted active ingredients. Specifications shall include tests such as stated in Par. 5.1.2(b). Test protocols for each of the components entering into the diluted active ingredient shall be obtained and maintained. Such test protocols shall be in compliance with the specification requirements.

(d) For raw materials used in the manufacture of products approved by FDA under a new drug application, or certified under antibiotic act or insulin regulations, specifications shall include the tests, standards, and other characteristics described in the new drug application, or application for antibiotic or insulin certification, or in pertinent regulations.

5.1.3 Controls of raw materials

A. Raw materials shall be received in the Receiving Area; placed into quarantine after necessary records are prepared; sampled as required; held in quarantine until tested, approved and released for use; and moved into raw material storage. Raw materials requiring special environmental storage shall be maintained under such special conditions. Samples of raw materials shall be retained for reevaluation. (See Par. 5.1.3.9.)

B. Raw materials shall be stored and handled in a manner to avoid the potential for contamination with other substances or preparations.

5.1.3.1 RECEIVING AND RECORD MAINTENANCE

A. Raw materials shall be controlled in an orderly manner following receipt, and protected from conditions which may adversely affect the identity, purity, quality, or strength of the material. Each shipping container (cartons, drums, etc.) shall be visually examined for appropriate markings and for damage of containers, including security of seals and closures. Damaged containers or defective seals or closures shall be evaluated by Quality Control and a determination made as to their disposition. Receiving records of raw materials shall include:

(1) Name of item

(2) Vendor and/or manufacturer

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5.1.3.1 RECEIVING AND RECORD MAINTENANCE (Cont'd)

(3) Vendor's (manufacturer's) lot number or other identifying marking such as date of manufacture when the raw materials are not normally marketed with a lot number

(4) Total quantity (number of containers and amount per container) for each lot

(5) Invoice number

(6) Date received

(7) Receiver's assigned lot number for each lot of raw materials received

(8) Name of carrier

B. Receiving records of raw materials manufactured or produced by the company on the premises shall be established essentially as stated above.

5.1.3.2 QUARANTINE

A. All raw materials shall be impounded in a quarantine area which shall be under limited access such as would be provided by lock and key or other appropriate security system. Containers or special areas shall be prominently marked to show they are in a "hold" status. The containers shall not be released until Quality Control has determined the acceptability of the raw materials after laboratory testing and evaluation. When approved for use, each container in the lot shall be prominently marked to show approval. The approval markings shall also include date and identity of an adequately trained and knowledgeable person applying the marking. Such date and identity shall be included in the Quality Control records, along with the name of the laboratory personnel releasing the lot. Raw materials shall be released to the Raw Material Storage Area, or Manufacturing (weighing or measuring) Area when needed for use. There shall be no commingling of material in "hold" status and approved-for-use status.

B. Liquid raw materials received in tank car loads (or other equivalent deliveries) shall not be approved for use until the raw materials are tested for compliance with specifications. When adding the raw material to a storage tank, records shall be maintained of the residual quantity in storage tank, amount added to the storage tank, date, and lot number, or other identification. Release of material from the storage tank is described under Par. 5.1.3.7, Raw Material Storage.

NOTE: See Par. 5.1.3.4(c) for exception to 5.1.3.2 A and B regarding bulk ingredients.

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5.1.3.2 QUARANTINE (Cont'd)

C. Raw materials intended for special purposes such as research or investigation shall be stored and handled separately.

5.1.3.3 SAMPLING FOR LABORATORY TESTING

Raw materials shall be sampled by an experienced, knowledgeable person who is under the supervision of a Qualified Professional Person in Quality Control. The sampling procedures shall be in writing. One acceptable sampling plan is to sample a number of containers equal to the square root of the total number of containers, plus one. Experience with the raw materials and the particular bulk manufacturer/s product may have a bearing on the sampling plan employed. The sampling procedure, as a minimum, shall include:

(a) Selection of the appropriate number of containers from each lot.

(b) Cleaning by wiping or vacuuming the containers selected.

(c) Sampling of the selected containers shall be accomplished in a clean area suitable for exposure of drugs and where the potential for cross-contamination is avoided.

(d) Extracting a portion of the contents from the bottom, middle, and top of the containers. This shall be accomplished by a thief, pipet, or other suitable tool. The amount of samples extracted shall be predetermined.

(e) Resealing of containers from which samples were extracted.

(f) Identification of the resealed container for subsequent tracing to the sample extracted.

(g) Marking of specimen bottles with proper identification which can identify the container from which the the sample was extracted.

(h) Sample shall be submitted for analysis.

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5.1.3.4 TESTING OF RAW MATERIALS

Raw materials testing shall be performed by the company (manufacturer or packager of the end item) or by an independent qualified laboratory employed by the company. Each sampling of raw materials shall be tested for at least one identity test, organoleptically examined, and when indicated, microscopically examined for foreign matter. Drugs of animal origin and botanicals subject to contamination with salmonella or other pathogenic micro-organisms shall be subjected to bacteriological examination to rule out the presence of dangerous contamination. In addition, the testing required of a sample or composite sampling of a lot of raw material shall be as follows:

(a) Active Ingredients and Inactive Ingredients

Active ingredients and inactive ingredients shall be tested to determine compliance with requirements of Par. 5.1.2, Specifications for Raw Materials.

(b) Diluted Active Ingredient

Diluted active ingredients shall be tested to determine the identity of each constituent, the assay of the active ingredient, and whatever other tests may be appropriate to determine the purity, quality, and strength of the Diluted Active Ingredient. In addition, test protocols are required for each of the components entering into the Diluted Active Ingredient.

(c) Bulk Ingredient

Bulk ingredient intended only for repackaging shall be tested for identity plus any additional testing deemed necessary by the company. Compliance with this testing qualifies the bulk ingredient for release from quarantine, provided the containers are marked to indicate release for repackaging only. The final packaged products shall be fully tested to determine compliance with the designated specification. Upon determination that the final packaged product complies with the applicable specification, any unused bulk ingredient from the same lot shall be marked for approval and release from raw material storage.

5.1.3.5 RELEASE FOR USE

The raw materials shall be released from quarantine by Quality Control after laboratory tests reveal compliance with applicable specifications. Each container of approved lots shall be marked to show they are released, as stated in Par. 5.1.3.2. The material shall be released to Raw Material Storage Area or into Manufacturing (weighing or measuring) Area when needed for use. Identity of raw material shall be maintained until the raw material is consumed. Raw materials failing to comply with specifications shall be distinctively annotated and shall be retained in quarantine or embargo until disposed of or returned. Controls shall be established to prevent the inadvertent use of material failing to comply with specifications.

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5.1.3.6 RAW MATERIAL STORAGE

A. Raw materials, released by Quality Control and appropriately marked, shall be stored in Raw Material Storage Area until needed for use. Storage shall be maintained at temperatures and under conditions which will maintain the identity and integrity of the material, and avoid the potential for contamination.

B. Inventory records shall be maintained of distribution, use, and quantities.

5.1.3.7 TANK STORAGE

A. Raw materials tested and approved prior to or after adding to storage tank shall be considered released and available for use. Storage tanks containing raw materials not yet tested and approved shall be marked (on all outlets) with "Under Test" or other suitable designation, until the testing is completed, evaluated, and found to comply with the applicable specifications.

B. A Log shall be maintained of raw materials added to and withdrawn from each storage tank. Withdrawals shall be logged by quantity and date. The date of withdrawal may be used as the lot number for record purposes.

C. Storage tanks, pipes and outlets (hoses) shall bear the name of the contents or other adequate identification.

5.1.3.8 RETENTION OF RAW MATERIAL SAMPLES

Samples of each lot of active ingredients and diluted active ingredients shall be retained under appropriate storage conditions for at least 3 years or for 1 year past the expiration date when used in dated products, whichever is shorter. Samples of each lot of inactive ingredients shall be retained under appropriate storage conditions for at least 1 year. The quantity of raw materials retained shall be sufficient for at least 2 complete analyses in accordance with the applicable specifications.

5.1.3.9 REEVALUATION OF RAW MATERIAL IN STORAGE

Raw materials which have been in company storage for over 2 years shall be reevaluated prior to use. Raw materials subject to chemical or physical change during storage for shorter periods shall be retested at earlier intervals. For example, cottonseed oil is retested after 6 months; Vitamin A Acetate is retested after 60 days. Reevaluation of raw materials, when necessary, shall be accomplished by testing in accordance with the applicable specifications. Those tests which have no bearing on stability need not be performed. The containers shall state the date of reexamination and reapproval.

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5.1.3.10 EXAMINATION OF RAW MATERIAL LOTS RECEIVED ON SUBSEQUENT SHIPMENTS

The testing of raw materials bearing the same lot number as material previously received, tested, and accepted from the same supplier may be limited to identification and assay testing, providing the assay results of the material from the second shipment are within experimental error of the assay results found on the first shipment. This limited testing criterion shall apply when the second shipment of the same lot is received within one month of the first shipment, and the raw material is not inherently subject to deterioration or other adverse effects by wide temperature ranges, or adverse storage or shipping conditions. When shipment of the same lot is received later than one month from the first shipment, identity, assay, and further testing as appropriate shall be performed to determine compliance with the standard.

5.1.3.11 WATER FOR INJECTION

Water for Injection used in the manufacture of parenterals shall comply with A or B below.

A. Water for Injection shall be freshly distilled over a period of not more than 6 hours into a clean, non-reactive container (tank, bottle, etc.) and consumed within 4 hours after distillation. That quantity of Water for Injection shall be designated as a lot.

B. Water for Injection produced on a continuous distillation process shall not exceed that quantity which is distilled from the still(s) into one container during a 24-hour period. That quantity of Water for Injection shall be designated as a lot.

The storage conditions for the Water for Injection shall be in accordance with (1) or (2) below.

(1) Shall be sterilized in a clean, non-reactive container, protected from contamination.

(2) Shall be stored in a clean non-reactive container (tank, bottle, etc.), and maintained continuously at 80°C or above which shall be substantiated with temperature recording charts.

5.2 PACKAGING MATERIALS

Written specifications and test procedures shall be established for packaging materials, including immediate containers, closures, and other components in contact with the contents. These specifications shall be used by the company in procuring the material. Control of such materials shall be covered by receiving records, examination in accordance with company standards, and storage and handling in a manner to protect them from contamination and deterioration and to avoid mixups. Immediate containers, closures, and other components shall be examined visually for physical signs of defects and shall be tested in accordance with an established program for compliance with USP or NF standards, as applicable. Containers for products that are official in the USP or NF shall comply with USP or NF requirements.

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5.2 PACKAGING MATERIALS (Cont'd)

Immediate containers, closures, and other components in contact with the contents shall be suitable for their intended use. They shall not react with or be additive or absorptive to an extent that adversely affects the identity, strength, quality, or purity of the drug, and shall furnish adequate protection against deterioration and contamination.

5.3 MASTER-FORMULA AND BATCH-PRODUCTION RECORDS

5.3.1 Preparation and responsibility

Master-Formula and Batch-Production Records shall be employed in the manufacture of each drug product and each intermediate such as starch paste used in the manufacture of the final product. These documents shall be prepared jointly by Quality Control and Production, with both groups (or individuals from both groups) bearing the responsibility for completeness and correctness; or the records shall be prepared by a staff which is specifically responsible for this operation. The individual preparing, endorsing, and dating the Master-Formula shall be a Qualified Professional Person. A second Qualified Professional Person shall independently check, reconcile, endorse, and date the Master-Formula. When the Batch-Production Record is copied (by hand or retype) from the Master-Formula, the Batch-Production Record shall be examined, endorsed, and dated by one Qualified Professional Person and independently checked, verified, endorsed, and dated by a second Qualified Professional Person.

5.3.1.1 DETAILS OF A MASTER-FORMULA

The Master-Formula shall include:

(a) Name of product

(b) Description of product

(c) Weight or measure of each raw material per dosage unit or per unit of weight or measure of the finished product

(d) Statement of total weight or measure of the dosage unit

(e) Formulation for each batch size to be produced showing the following:

(1) The weight or measure of each raw material regardless of whether it appears in the finished product

(2) Quality standards for raw materials

(3) Theoretical weight or measure at various stages of processing

(4) Theoretical yield of product

(5) An appropriate statement regarding any calculated excess

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5.3.1.1 DETAILS OF A MASTER-FORMULA (Cont'd)

(f) Description of the containers, closures, packaging, and packing

(g) Details for each step in the manufacture of the product, including methods, instructions, procedures, specifications, special notations, and precautions to be followed

(h) Quality Control requirements, including in-process and end item testing and examinations against predetermined standards

(i) Copy of label and labeling

5.3.1.2 DETAILS OF BATCH-PRODUCTION RECORD (MANUFACTURING TICKET)

A Batch-Production Record shall consist of the essential information of the Master-Formula and shall include but not be limited to:

(1) Name and dosage strength of product

(2) Description of product including color, size, dimensions, and other physical characteristics as appropriate

(3) Date

(4) Lot, batch, or control number

(5) Formulation, listing all raw materials (active ingredients, inactive ingredients, coating, subcoatings, vehicles, and all other materials used in formulation, regardless of whether they appear in the finished product) by names sufficiently specific to indicate any special quality characteristics

(6) Lot number of each raw material used in the formulation

(7) Quantity of each raw material in the formulation, including annotation of calculated excesses

(8) Theoretical yield

(9) Details for each step in the manufacture of the product, including methods, instructions, procedures (such as sequence of adding new materials, conditions and duration of drying, mixing, heating; speed of operating equipment and machine, etc.), specifications, special notations, and precautions

(10) Quality Control requirements, including in-process and end item testing and examinations against predetermined standards

(11) Specimen or copy label and labeling

(12) Description of container, closure, packaging, and packing

(13) Endorsement and date of the operator(s) identifying the weighing or measuring of each raw material

(14) *Endorsement and date of the operator(s) verifying the correctness in the operation of Par. 13 above

(15) *Verification and endorsement of the addition of each ingredient to the batch

*Par. (14) and (15) shall be performed by a Qualified Professional Person or a specially trained and experienced Technician.

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5.3.1.2 DETAILS OF BATCH-PRODUCTION RECORD (MANUFACTURING TICKET) (Cont'd)

... (16) Records of each step in the manufacturing, processing, packaging, and labeling, including identification of production machines, storage tanks, and lines used

(17) Appropriate statement of weight or measure at various pertinent stages of processing

(18) Endorsements and dates of the individual actively performing and the individual actively supervising each manufacturing (compounding, mixing, tableting, coating, ampuling, sterilizing, filling, labeling, etc.), inspection, packaging, and packing operation

(19) In-process testing data such as weight checks, disintegration, hardness, clarity, viscosity, etc., and date, and initials of person performing test. In-process records shall include limits for each test as a ready reference

(20) In-process and laboratory control results, attached or referenced

(21) Final yield

(22) Signature and date of Quality Control approval for release

5.4 MANUFACTURING AND IN-PROCESS CONTROLS

5.4.1 Manufacturing controls and operations

5.4.1.1 GENERAL REQUIREMENTS FOR MANUFACTURING CONTROLS

All phases of manufacture, from the weighing or measuring of the raw materials through all operations to the final packaging and packing of the product, shall be performed in accordance with sound scientific methods and procedures which shall be delineated in the form of written instructions. The methods, procedures, conditions, and controls used in the manufacture, and as reflected in the Master-Formula and Batch-Production Record, shall be in accordance with good manufacturing techniques and practices, and shall yield accurate, uniform, and homogeneous products within each lot, and from lot to lot.

5.4.1.2 COMPLIANCE WITH EACH OF THE FOLLOWING SHALL BE REQUIRED:

(a) Raw materials shall be identified and weighed (or measured) by one person and verified by a Qualified Professional Person or a specially trained and experienced Technician. Identification shall consist of checking the name, lot number, grade, and quantity of the raw material against the Batch-Production Record, examining the physical appearance, and assuring that the material has been approved for release from storage.

(b) The Batch-Production Records shall be appropriately endorsed and shall include the lot number.

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5.4.1.2 COMPLIANCE WITH EACH OF THE FOLLOWING SHALL BE REQUIRED: (Cont'd)

(c) The addition of each raw material to the batch shall be performed by one person and verified by a Qualified Professional Person or a specially trained and experienced Technician. Batch-Production Record shall be endorsed by each.

(d) The manufacturing operations shall be performed in strict compliance with the Batch-Production Records.

(e) The Batch-Production Records shall be appropriately annotated for each step in the manufacture, processing, filling, packaging, labeling, and packing, including the identification of production machines, storage tanks, and lines used.

(f) Verification of weights or measures during manufacture is essential and results shall be recorded on the Batch-Production Records.

(g) The persons performing and supervising each manufacturing operation shall date and endorse the Batch-Production Records.

(h) Identity and correctness of labeling, packaging, and packing materials shall be verified for use.

(i) Final yield of the product shall be checked against theoretical yield. Records showing an unreasonable and unexplained difference between final yield and theoretical yield shall not be approved by Quality Control unless a satisfactory explanation is recorded and acceptable written criterion is delineated.

(j) Appropriate measures shall be taken to avoid the potential for contamination or cross-contamination. Effective means (such as exhaust or dust removal systems) shall be employed: to prevent the entry of contaminants into the work areas; to remove potential airborne contaminants or extraneous adulterants (dust or particles from one product to another) from the work areas by an effective air handling system that changes the air frequently; and to limit or prevent the generation of contaminants within the area. Particular attention shall be taken to assure that no contamination results when starting and stopping the exhaust system. The arrangement of the equipment shall be such that the exhaust current shall not move through other operations, causing a potential for contamination. The exhausted air shall be filtered or otherwise treated if there is a potential for re-entry.

(k) Production machines and equipment shall be operated in a manner appropriate with their mechanical capability to produce products in compliance with predetermined standards.

(l) Production machines and equipment used in the manufacturing process, regardless of the stage of manufacture, shall bear, by securely attached label or other suitable means, the name of the material being produced, stage of processing where applicable, and the lot number.

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5.4.1.2 COMPLIANCE WITH EACH OF THE FOLLOWING SHALL BE REQUIRED: (Cont'd)

(m) All containers of raw materials, intermediates, and finished products shall bear markings which clearly identify the contents by name of the material (or other identification), stage of processing where applicable, and the lot number.

(n) During all operations, materials shall be capable of positive identification by name of product, stage of processing where applicable, and lot number. For example, the pans of granulation material in or out of drying ovens; the material being processed in tableting machines, capsule machines, mixing vats, ampuling apparatus, filling machines, coating pans, etc., shall be marked with the name of product, stage of processing where applicable, and lot number.

(o) Records shall be maintained for each machine and equipment required to be numbered as per Par. 4.3.1.E. The records shall reveal the sequence of products manufactured with the machine or equipment, and the products manufactured concurrently in the same production area.

5.4.2 *Manufacture by automation or continuous process*

Control of manufacture by automatic mechanical or electronic equipment or continuous process shall be considered acceptable, providing that the system and procedures are scientifically sound and consistently produce material in compliance with predetermined in-process and end item specifications. The automatic and continuous process systems shall:

(a) Be capable of consistently reproducing its operations in a uniform and accurate manner.

(b) Be sufficiently durable for the designated period of continuous operation.

(c) Have adequate control instrumentation with accurate, sensitive, and automatic sensing and recording mechanisms reflecting all critical points of manufacture. Such built-in devices shall be capable of detecting departures from designated standards.

(d) Be capable of recording, by meters or other instrumentation, the quantities of raw materials or intermediates entering into the manufacture.

(e) Have control recording charts (automatic or manual) which are maintained as a permanent record and are annotated to reflect the lot number of the final product. The charts shall record such characteristics as: temperature, pressure, vacuum, relative humidity, pH, color, rate of reaction, final yield, etc.

(f) Be fully described in maintenance manual which, in addition to the operations and mechanism, shall include:

(1) Maximum period of continuous manufacture.

(2) Frequency of checking or replacing parts.

(g) Method for determining accuracy and sensitivity of instruments and mechanism, and frequency of such examinations.

See Par. 5.4.4.1.F for In-Process Controls.

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5.4.3 Preparation of containers for packaging (filling)

Prior to filling, containers shall be handled in accordance with specific method prescribed for each type of product. A system shall be established whereby the effectiveness of each method is periodically tested, and test results reviewed, evaluated, and maintained.

5.4.3.1 CONTAINERS FOR PARENTERALS

(a) Containers (ampuls, vials, bottles, tubes, etc.) shall be cleaned and treated by a method effective in destroying microorganisms and pyrogens. One acceptable method is the washing of containers, rinsing with pyrogen-free distilled or deionized water, and drying at 260°C with dry heat for 2 consecutive hours.

(b) Rubber closures shall be washed, thoroughly rinsed with distilled or deionized water, and autoclaved at 121°C for 15 to 20 minutes, and dried when moisture can adversely affect the product. Rubber closures shall be adequately protected against contamination until used.

(c) Sterilized ampuls, vials, bottles, tubes, etc., for parenterals shall be held in hermetically sealed sterile containers to maintain sterility until used for filling. If the containers are not hermetically sealed, they shall be stored under conditions equivalent to the filling room for parenterals. When stored in containers that are not hermetically sealed, ampuls, vials, bottles, and tubes, shall be used as soon as possible but not more than 48 hours later without resterilizing.

5.4.3.2 CONTAINERS FOR OPHTHALMIC LIQUIDS

Containers for ophthalmic liquids shall be adequately washed and rinsed with distilled or deionized water. Glass bottles shall be dried by heat; plastic bottles shall be dried by heat or drained. Containers and appendages used for ophthalmic liquids shall be sterile.

5.4.3.3 CONTAINERS FOR TABLETS, CAPSULES, PILLS, TROCHES, AND SIMILAR DOSAGE FORMS AND DRY POWDERS

Containers for tablets, capsules, pills, troches, etc., and dry powder shall be cleaned by blowing out with dry, filtered air or by suction. Powder jars having a particularly wide mouth may be inverted and tapped.

5.4.3.4 OINTMENT TUBES

Ointment tubes shall be cleaned by blowing out with dry, filtered air. Ointment tubes used for ophthalmic products shall be specially treated, such as by sterilization, supersonic treatment, or other suitable means, to assure adequately clean tubes.

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5.4.3.5 OINTMENT JARS

Ointment jars shall be cleaned by blowing out with dry, filtered air or wiped with a clean chamois.

5.4.3.6 CANS, DRUMS, CARTONS, AND CANISTERS

Cans, drums, cartons, and canisters shall be cleaned by blowing out with dry, filtered air or by suction, or shall be inverted and tapped.

5.4.4 *In-process controls*

In-process controls are a means of checking and maintaining quality during manufacture. It is required that all Quality Control checks during manufacture be accomplished precisely as delineated in written procedures and instructions. Such procedures and instructions for in-process controls shall be in accordance with sound scientific principles and good pharmaceutical manufacturing practices.

Records of in-process control testing shall be retained as an integral part of the manufacture of the product. In-process control testing may include simple, rapid tests performed manually or by instrumentation, visual examinations, measurements, etc., accomplished during the manufacturing processes.

5.4.4.1 GENERAL REQUIREMENTS FOR IN-PROCESS CONTROLS

General requirements for in-process controls shall include the following:

A. All raw materials and intermediates shall be maintained or stored at temperatures and under conditions which will maintain the identity and integrity of the product. Those raw materials and intermediates requiring special storage conditions, such as refrigeration, freezing, or warm room, shall be stored under those conditions. Suitable temperature recording devices shall be employed, or temperature readings shall be recorded on a regular routine basis.

B. Bulk material (tablets, capsules, etc.) awaiting packaging, and packaged material awaiting Quality Control approval or FDA certification certificate or NIH approval, shall be maintained in a "Hold" status until released. Containers shall be appropriately marked to identify the material and to prevent its premature release.

C. Material awaiting further processing shall be maintained in a "Hold" status. Containers shall be appropriately marked for identity of material and stage of processing.

D. In-process testing shall be performed on representative samples selected at predetermined intervals during the manufacturing and packaging operations. The frequency of in-process sampling control testing and examination shall be predicated upon the experience developed by the company in the manufacture of the particular product. Significant revisions in the conditions and procedures of manufacture shall result in more frequent in-process control sampling, testing, and examination until uniformity and reproducibility of the product is assured.

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5.4.4.1 GENERAL REQUIREMENTS FOR IN-PROCESS CONTROLS (Cont'd)

E. A downtime period shall be allocated after completion of each manufacturing operation, during which time all residues, debris, containers, labels, labelings, cartons, and all other materials remaining from the previous product shall be removed from the area. Machines and equipment, and nearby surroundings, shall be thoroughly and appropriately cleaned in order to avoid a potential for mixups and cross-contamination. The cleaning procedures shall be delineated and shall include the cleaning agents employed as applicable. Prior to using the machines or equipment for subsequent production, a Qualified Professional Person shall examine and approve the condition of the machines, equipment, and area. Records shall be maintained including the date and identification of the person giving approval.

F. During manufacture by automation or continuous process, sampling shall be accomplished at critical stages of production, and such samples shall be tested for compliance with applicable standards. Records, charts, gages, and instruments shall be examined by Qualified Professional Personnel on a predetermined basis to determine compliance with designated standards. Batch-Production records, appropriately modified to represent the automation or continuous system, shall be maintained. Such records shall be reviewed and approved by Quality Control.

G. Glassware and other equipment used in preparing and filling parenterals, and those parts of the filling machine coming in contact with the parenterals, shall be cleaned and treated by a method effective in destroying micro-organisms and pyrogens. One acceptable method is the washing of the glassware, parts and equipment; rinsing with pyrogen-free distilled or deionized water; and drying at 260°C with dry heat for 2 consecutive hours. The glassware and machine parts shall be protected from contamination while awaiting use.

H. Glassware and other equipment used in preparing and filling sterile ophthalmic liquids and other non-parenteral sterile products, and those parts of the machine coming in contact with the sterile product, shall be cleaned and sterilized. One acceptable method is the washing of the glassware, equipment and parts; rinsing with distilled or deionized water; and autoclaving at 121°C for 15 to 20 minutes. The glassware and machine parts shall be protected from contamination while awaiting use.

5.4.4.2 SPECIAL REQUIREMENTS FOR IN-PROCESS CONTROLS

In-process testing required herein shall apply to each lot of material produced on each machine (tableting, filling, encapsulating, etc.). All in-process test results shall be recorded and made part of the Batch-Production Records.

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5.4.4.2 SPECIAL REQUIREMENTS FOR IN-PROCESS CONTROLS (Cont'd)

In-process testing shall be performed on representative samples selected at predetermined intervals during the manufacturing and packaging operations. The samples shall be tested for those characteristics that are an index of purity, quality and strength; and accuracy, uniformity, and homogeneity. The extent of in-process control testing and examination shall be predicated upon the statistical records developed by the company in the manufacture of the particular product with the equipment employed. The frequency and size of sampling shall be such as to assure, to a 95 per cent confidence level, that material being produced is in compliance with specification requirements. Significant revisions in the conditions and procedures of manufacture shall result in more frequent in-process control testing and examination until compliance with above requirements is assured.

In-process testing and examination shall be performed for appropriate characteristics. Appendix I exemplifies the use of a chart for recording in-process test results during the manufacture of compressed tablets. It gives the operator and supervisor a rapid and accurate means of determining the progress and trends for the particular characteristics during production. This technique can be adapted for the recording of in-process test results during manufacture of most drug products.

A. In-process testing and examination of parenterals and other sterile products:

(1) Bulk solutions shall be checked for pH, color, clarity, completeness of solution, extraneous material, and other characteristics before filling.

(2) The volumes of liquid in final containers shall be checked.

(3) The weights of sterile powders for injection shall be checked.

(4) Products not subjected to terminal sterilization shall be sampled for sterility testing at predetermined intervals, in accordance with written procedures, so as to represent the total filling operation. Those samples, reflecting the aseptic filling of the final containers, shall be tested for sterility in accordance with the methods and procedures of the USP/NF, or NIH for products under NIH control.

(a) When more than one filling machine is used in the filling of one batch, samples shall be drawn from each filling machine and shall be marked to identify the filling machine.

(b) When one batch is filled in a continuous filling operation and there are no changes in equipment or procedure, sterility testing shall be performed on samples drawn from each filling device of the batch during each working shift. When filling period is disrupted, samples shall be taken for each uninterrupted portion.

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5.4.4.2 SPECIAL REQUIREMENTS FOR IN-PROCESS CONTROLS (Cont'd)

(5) Products subjected to terminal sterilization shall be sampled for sterility. Such samples shall be representative of all layers of the sterilizer load or sterilization apparatus. Sterility testing shall be in accordance with the methods and procedures of the USP/NF, or NIH for products under NIH control.

(6) Flame-sealed ampuls shall be effectively tested for leakage. If terminal sterilization is employed, the test for leakage shall be performed after the sterilization procedure. Acceptable methods for testing flame-sealed ampuls for leakage are contained in Appendix II.

(7) Parenterals shall be individually subjected to visual and physical (ocular or suitable mechanical device) examination for color, clarity, particulation, and container and closure defects. Parenterals subjected to terminal sterilization shall be inspected after the sterilization procedure. All parenterals failing to meet the requirements for color, clarity, absence of particulation, and suitability of container and closure shall be rejected.

(8) Sterilization indicators shall be placed in each tray or shelf of each sterilizer load. These indicators shall be identified and examined after the sterilization process to establish that the necessary indicator change occured.

(9) In intermittent sterilization procedures, complete records shall be maintained of the sterilization conditions employed, such as temperatures, duration of exposure and intervals.

(10) In lyophilization procedures, temperature and vacuum controls shall be maintained at the freezing stage and at the drying stage. Filtered inert gas or "sterile" dry air shall be used when releasing the vacuum in the final stage of drying. The containers shall be handled and sealed in a manner to avoid the potential for contamination.

B. In-process testing and examination of tablets, capsules, and pills:

(1) Uncoated tablets, capsules, and pills from each lot shall be tested for compliance with applicable weight requirements by drawing samples from each machine at regular intervals. Samples shall be obtained from each platform of multiple stage machines. In addition, the weight test shall be performed promptly after machine adjustment.

(2) Prior to coating, the uncoated tablets and pills shall be tested to determine compliance with weight variation requirements.

(3) Tablets, capsules, and pills shall be tested for compliance with disintegration time, and dissolution time when included as a specification requirement.

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5.4.4.2 SPECIAL REQUIREMENTS FOR IN-PROCESS CONTROLS (Cont'd)

(4) Coated tablets, capsules, and pills from each coating pan shall be tested for disintegration time, and dissolution time when included as a specification requirement.

(5) Soluble tablets shall be tested for compliance with applicable solubility time.

(6) Compressed tablets shall be tested for hardness at regular intervals during tableting.

(7) Uncoated tablets and tablet cores, prior to coating, shall be visually examined for defects on a statistical sampling basis. Approval of the lot shall be predicated upon compliance with a predetermined acceptable quality level.

(8) Coated tablets, capsules, and pills shall be visually examined for defects by inspection on a moving belt, or other equally suitable means. Defective tablets, capsules, and pills shall be removed prior to packaging.

(9) Representative samples of containers of tablets, capsules, and pills shall be randomly selected during the filling operation. The finished containers shall be examined for tightness of closures. The contents shall be counted and visually examined for defects, including extraneous material, and the results compared against established limits to determine compliance with the requirements.

C. In process testing and examination of ointments and creams

(1) Ointments and creams shall be checked for color, consistency, uniformity, homogeneity, and extraneous material during manufacture.

(2) Particle size determinations shall be made when appropriate. Particle size in the ointment or cream shall be within predetermined standards.

(3) Finished jars and tubes shall be examined for tightness of closures or leakage.

(4) Finished jars and tubes shall be taken from the filling line at predetermined intervals and tested for net weight, or automatic rejection system (for weight) may be employed.

D. In-process testing and examination of suppositories

(1) Suppositories shall be checked for appearance, uniformity, homogeneity, and extraneous material during manufacture.

(2) Sizes and weights of suppositories shall be checked to assure compliance with specification requirements.

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5.4.4.2 SPECIAL REQUIREMENTS FOR IN-PROCESS CONTROLS (Cont'd)

E. In-process testing and examination of liquids:

(1) Liquid products (solutions, suspensions, emulsions, etc.) shall be checked for uniformity, homogeneity, clarity of solution (when applicable), and extraneous material during manufacture.

(2) Finished containers shall be taken from the filling line at predetermined intervals and tested for net volume/weight.

(3) Finished containers shall be examined for tightness of closures or leakage.

F. In-process testing and examination of powders

Finished containers shall be taken from the filling line at predetermined intervals and checked for appearance, uniformity, extraneous material, and net weight.

G. In-process testing and examination of lozenges, troches, and similar dosage forms

(1) Lozenges, troches, and similar dosage forms shall be tested for compliance with weight requirements, appearance, and uniformity at predetermined intervals during manufacture.

(2) The finished containers shall be examined for tightness of closures.

(3) Representative samples of containers of lozenges, troches, and similar dosage forms shall be randomly selected during the filling operation. The contents shall be counted and visually examined for defects on a statistical basis.

5.4.5 *Finished product inspection*

Visual, on-line, or other suitable inspection shall be made of the finished products to insure:

(a) The acceptability of the immediate containers and closures

(b) The identity and adherence of labels and presence of required inserts, cartons, and other labeling

(c) The absence of physical defects

5.5 *END PRODUCT TESTING, EXAMINATION, AND RELEASE*

5.5.1 Representative samples from each lot shall be tested and examined as required in the applicable specification. Specifications for official products shall comply with the official compendia and company standards. Specifications for non-official products shall include standards for quality, purity, and strength. In those instances when the testing is performed on drugs prior to filling into final containers, additional testing or examination shall be performed on finished product to safeguard against any error in the finishing operation.

Samples of each lot of the finished products shall be selected on a random basis and examined for defects, in accordance with a suitable inspection plan which delineates a classification of defects and an acceptable quality level.

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5. PRODUCT CONTROL STANDARDS (Cont'd)

5.5.2 No lot shall be released for marketing prior to examination of production records, data obtained from in-process and end item testing and examinations; and inspection for signs of visual defects. Release of the lot shall be made by authorized Qualified Professional Personnel in Quality Control.

5.5.3 Each lot of finished product (other than penicillin items) is tested for penicillin content if the company handles penicillin in the same plant. Material containing more than the allowable penicillin is rejected.

5.6 STORAGE OF FINISHED PRODUCTS

Finished products shall be stored or warehoused at temperature ranges and under conditions stated on the labels or required for the item.

Finished products awaiting Quality Control approval shall be marked to reflect this status, and shall not be commingled with approved material. Regular retesting shall be performed when material which is subject to deterioration is not shipped within a reasonable period.

Those products requiring special storage conditions, such as refrigeration, freezing, humidity control, or warm room, shall be stored under those conditions. Suitable temperature/humidity recording devices shall be employed, or temperature readings shall be recorded on a routine basis.

5.7 SHIPPING OF FINISHED PRODUCTS

Finished products shall be released from storage to the shipping area which shall be of suitable size for the volume and frequency of material shipped. Finished products shall not be commingled with receiving materials.

5.8 DISTRIBUTION OF PRODUCTS

Perpetual inventory records shall be maintained of the distribution of each lot of drugs, in a manner that will facilitate its recall if necessary. Such records shall be retained for at least 2 years after distribution has been completed or 1 year after expiration date, whichever is sooner.

5.9 RETENTION SAMPLES

Retention samples of at least two finished, labeled products shall be retained from each lot for at least 2 years after distribution or, for dated products, for 1 year after the expiration date. The retention samples shall include a quantity of representative material of each lot sufficient for at least two completed analyses, except for sterility testing. Retention samples shall be stored within the temperature range and under conditions stated on the labels or required for the item. If no special storage conditions are applicable, the material shall be stored between 50° and 80°F.

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6. QUALITY CONTROL TESTING LABORATORY

6.1 COMPANY LABORATORY

Company shall have a Quality Control Laboratory to perform the required testing or it shall employ a commercial laboratory to augment its testing capability or capacity. As a minimum a company laboratory shall be capable of performing in-process controls and examination for Classification of Defects.

The company laboratory shall be directed by the Laboratory Head (see Par. 3.3.4). The Laboratory shall be independent of production management. It shall comply with each of the following requirements.

6.1.1 Facilities and arrangement

The Laboratory shall be of suitable size and construction for the operations performed. It shall be in good state of repair and walled-off from the manufacturing areas. The arrangement of the Laboratory shall eliminate confusion and crowding. The Laboratory shall have adequate lighting and ventilation, and be clean and orderly.

The facilities shall include laboratory workbench, hot and cold running water, and such utilities as necessary. Equipment for washing glassware and other materials, and facilities for drying shall be maintained.

6.1.1.1 The venting system shall exit to the outside of the building, in order to prevent contamination of the manufacturing areas within the building.

6.1.1.2 Safety devices, such as showers, blankets, first-aid kits, fire extinguishers, etc., shall be available for immediate use.

6.1.1.3 Special rooms requiring isolation, such as sterility testing rooms, conditioning rooms, etc., shall be maintained in appropriate operating conditions.

6.1.2 Personnel staffing

The Laboratory staff shall be of a size and technical competence necessary for the testing performed. Supervision shall be maintained to the extent necessary, depending upon the education and experience of the personnel performing the tests, analyses, and examinations. The work performed shall be reviewed by the Laboratory Head or a Qualified Professional Person on the Laboratory Staff.

6.1.3 Equipment and Supplies

Equipment shall be in good working order, suitable for the intended testing and analyses. Sufficient supplies of chemicals, reagents, glassware, apparatus, etc. shall be maintained. Distilled or deionized water shall be available in sufficient quantity.

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6. QUALITY CONTROL TESTING LABORATORY (Cont'd)

6.1.4 Testing methods and procedures

The testing methods and procedures, and the techniques employed shall be in accordance with good analytical practices designed to give accurate and reproducible results.

The accuracy, sensitivity, and reproducibility of company-developed tests shall be established and documented.

Methods and procedures employed shall be obtained from technical publications, or maintained by the company in the form of written procedures.

6.1.5 Calibration and standardization

See Par. 7.7.

6.1.6 Laboratory log

Records shall be maintained of samples, quantities, lot number, and date received.

6.1.7 Test records

Test record shall include:

(a) Name and lot number of product.

(b) All test results and methods of analyses; methods of analyses may be reported by reference.

(c) Permitted tolerances and limits.

(d) Endorsement of individual obtaining sample.

(e) Calculations; (NOTE: Permanent records shall be maintained of weights, volumetric titrations, calculations, and all raw data which can be similarly recorded.)

(f) Date and identification of person(s) performing the tests.

(g) Statement of compliance or noncompliance.

(h) Approval, release, or rejection by the Laboratory Head or designated Qualified Professional Persons on the Laboratory Staff.

(i) When animals are used in testing products, the animals shall be identified and records maintained as to date, use, and time.

6.1.8 Library

A library of books and periodicals shall be maintained. It shall contain at least the following: The latest USP and NF with all interim revisions and supplements, and a compilation of chemical and pharmaceutical publications necessary for the testing performed. The location of the publications need not be limited to the laboratory proper.

6.2 COMMERCIAL LABORATORIES

Commercial laboratories may be used to augment the testing capability or capacity of the company laboratory.

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6.2.1 Commercial laboratories shall comply with the requirements for a company laboratory.

6.2.2 The test reports submitted by the commercial laboratory shall include:

(1) Name and lot number of product.

(2) Name of manufacturer of product.

(3) Test results and methods of analyses may be reported by reference. Actual calculations shall be included in the report or retained in work books as part of a permanent file.

(4) Required standards and limits.

(5) Reference to the purchase description or specification applicable to the item tested.

(6) Statement of compliance or noncompliance.

(7) Date and signature of the Commercial Laboratory Head or designated Qualified Professional Person.

6.2.3 The company's (manufacturer's) Laboratory Head or designated Qualified Professional Person shall evaluate the report from the commercial laboratory, and shall annotate approval or disapproval.

6.3 ANIMAL ROOMS

Animal Rooms shall be in a separated, walled-off area.

6.3.1 Animal room facilities

6.3.1.1 HOUSING

Housing facilities shall be structurally sound and shall be maintained in good repair to protect the animals from injury. The surfaces of the rooms shall be substantially impervious to moisture and readily sanitized.

6.3.1.2 WATER

Adequate potable water shall be available to the animals. Watering receptacles shall be placed so that when splashed out, the water does not mix with food or excreta. Watering receptacles shall be kept clean and shall be sanitized at regular intervals.

6.3 1.3 STORAGE

Supplies of food and bedding shall be stored in facilities which adequately protect such supplies against infestation or contamination by vermin. Perishable supplies requiring refrigeration shall be refrigerated.

6.3.1.4 WASTE DISPOSAL

Provision shall be made for the removal and disposal of animal and food wastes, bedding, dead animals, and debris. Disposal facilities shall be provided and suitably operated to minimize vermin infestation, odors, and disease hazards.

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6.3.1.5 WASHROOMS AND SINKS

Facilit s, such as washrooms, basins, or sinks, shall be provided to maintain cleanliness.

6.3.1.6 TEMPERATURE CONTROL

Temperature shall be controlled, as necessary, within appropriate ranges.

6.3.1.7 VENTILATION

Adequate ventilation shall be provided by means of windows, vents, air conditioning, etc., in order to minimize drafts, odors, and moisture condensation.

6.3.1.8 LIGHTING

Ample light, by natural or artificial means, shall be uniformly distributed to permit routine inspection and cleaning during the work day.

6.3.1.9 DRAINAGE

A suitable method shall be provided to rapidly eliminate excess water. When drains are used, they shall be properly constructed and kept in good repair to avoid foul odors therefrom. When closed drainage systems are used, they shall be equipped with traps and properly installed to prevent any backup of sewage into the room.

6.3.2 *Sanitation*

Rooms, cages, and hard-surfaced pens or runs shall be kept clean, and adequately sanitized at regular intervals. Several methods of sanitizing are:

(a) Wash with hot water (180°F) and soap or detergent.

(b) Wash all soiled surfaces with a detergent solution followed by a safe and effective disinfectant.

(c) Clean all soiled surfaces with live steam.

Pens or runs using gravel, sand, or dirt shall be sanitized by removing the soiled gravel, sand, or dirt and replacing it as necessary.

Premises shall be free of accumulations of trash.

6.3.2.1 PEST CONTROL

An effective program for the control of insects and pests shall be established and maintained.

6.3.3 *Employees*

A sufficient number of employees shall be utilized to maintain the prescribed level for care. Animal rooms shall be under the supervision of a caretaker who has adequate experience in the care of animals.

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7. OPERATIONAL STANDARDS

7.1 WRITTEN PROCEDURES

Written procedures shall be established, maintained, and applied for the operations performed. Written procedures shall cover, but are not limited to, receipt of raw materials through all phases of manufacture, quality control, packaging, and packing; inspection through final release of the material; care and cleaning of equipment and facilities; and plant maintenance and sanitation. Operating units shall maintain, in their possession, written procedures applicable to their functions.

7.2 TEST PROCEDURES

Test procedures, as conducted by the company for official and non-official drugs, shall yield accurate and reproducible results, as demonstrated by company data.

7.3 PREPARATION OF RECORDS

7.3.1 Preparation of records

Records shall be prepared concurrently with the performance of each step of manufacture, quality control, maintenance, sanitation, etc., in accordance with the requirements of the written procedures and this document. Records of tests and inspections shall include the number of samples, the nature and number of observations made, the number and type of deficiencies found, the quantities approved and reviewed, and the nature of corrective action taken, as appropriate. Records from recording devices shall also be retained. The records shall be legible and permanent. They shall identify the dates and persons performing and supervising the operations (as required herein). The records shall be sufficiently detailed and accurate to allow retracing of each step in the history of the products.

7.3.2 Sterilization records

Records shall be maintained of sterilization operations, including the mode of sterilization, date, duration, temperature, and other conditions relating to sterilization of equipment and materials used in the processing of products. The sterilization records shall be developed by means of automatic recording devices, or by other means which give equivalent assurance of the accuracy and reliability of the sterilization. These sterilization records shall be maintained in a manner that permits identification of the lot.

7.4 RETENTION OF RECORDS

Records required in subparagraphs 7.3.1 and 7.3.2 above shall be retained from each lot for at least 5 years after manufacture, or, for dated products, for 1 year after expiration date.

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7. OPERATIONAL STANDARDS (Cont'd)

7.5 LOT NUMBER AND LOT NUMBERING SYSTEM

7.5.1 Lot number

Lot (batch or control) number shall be a number (or other designation) assigned to a single, uniform, and homogeneous quantity of a product from one formulation which has received entirely the same processing and treatment. The lot number of products manufactured by automation or continuous process shall represent a unit of time and/or quantity. During such manufacture the product shall continue to be produced within a manner that shall assure uniformity of product. The complete history of the product shall be traceable by reference to the lot number.

7.5.2 Lot numbering system

A lot numbering system shall be employed which reveals, for each lot of finished products, ready access to all information required in establishing the integrity of the lot. Relabeled or repackaged products shall also be subjected to a lot numbering system which reveals product history.

7.6 INSPECTION AND CONTROL OF LABELS AND LABELING

7.6.1 Inspection of labels and labeling

Printed supplies such as labels, brochures, inserts, labeled cartons, etc., shall be inspected by a Qualified Professional Person for comparison to a standard copy of the text. The printed supplies shall be further inspected for compliance with specifications for type and grade of paper stock, quality of printing, workmanship, and dimensional tolerances when applicable.

The correctness of lot numbers shall be checked by a Qualified Professional Person.

7.6.2 Controls of labels and labeling

Written procedures shall be established, maintained, and applied for the control of printed supplies such as labels, brochures, inserts, labeled cartons, etc. Procedures and controls of labels and labeling shall be under the supervision of a Qualified Professional Person and shall include:

(a) Receipt, review, and proof reading prior to release to inventory.

(b) Storage of labels and labeling material in a manner that avoids mixups. Each label representing different product, strength, or potency or dosage form, and related labeling shall be stored in separate compartments and suitably identified.

(c) Perpetual inventory records including the date, quantity, and identity of person issuing the materials and quantity returned. Access to label and labeling storage area shall be restricted to designated persons.

(d) Disposition of unused and waste labeling.

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7.0.2 Controls of labels and labeling (Cont'd)

(e) Obsolete and outdated labels and labeling shall be destroyed.

(f) Actions to be taken when discrepancies in labeling exceed the limits designated in company procedures. Discrepancies shall be resolved with the approval and consent of Quality Control Director before distribution of the lot in question. All discrepancies shall be fully described on the Batch-Production Record and criteria for action explained.

(g) Inventory records and accountability of containers which are labeled prior to receipt, and containers which are labeled by printing applied directly on the containers.

7.7 CALIBRATION AND STANDARDIZATION

Instruments, apparatus, gages, and recording devices shall be calibrated at predetermined intervals in accordance with good scientific practices and instructions from the manufacturers. Balances and scales, and weights for these, shall be calibrated at least every year. Calibrated thermometers shall be employed for precise temperature measurements.

Each operator shall be instructed to watch for possible malfunctions of balances, scales, etc. When malfunction exists, the balance, scale, etc., shall not be used until repaired. Appropriate records or tags shall be maintained to show date of last calibration and identification of person or company performing the calibration.

Calibrations shall be performed by an outside organization qualified to perform such work, or may be accomplished by company employees who are specifically trained and proficient at such assignments. The calibration equipment shall be traceable to the National Bureau of Standards when applicable.

Volumetric solutions used in analyses shall be re-calibrated at least every six months.

7.8 DISPOSITION OF REJECTED MATERIAL

Rejected material shall be disposed of or reworked in accordance with written procedures. These procedures shall include but are not limited to the following:

(a) For raw materials, the rejected items shall remain in a quarantine area and the containers shall be clearly marked to show they are rejected. These raw materials shall be either destroyed, reworked, or returned to the vendor. Records shall be maintained to show the disposition, reworking, or return of the raw materials.

(b) For intermediates and finished products, the rejected items shall be immediately impounded, clearly marked to show they are rejected, and maintained in a segregated area, preferably under lock and key. The rejected materials shall be either disposed of or reworked. Approval of reworking material shall be given only by the Quality Control Director. Records shall be maintained to show the disposition of the rejected material.

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7. OPERATIONAL STANDARDS (Cont'd)

7.9 PRODUCT COMPLAINTS

All product complaint reports concerning quality of material shall be retained for at least 5 years. The information shall contain the full history of the complaint, including the nature of the complaint, the quantities and lot numbers of the material involved, and the dates the complaints were reported. All such complaints shall be reported as required, investigated to a sound scientific conclusion, and the results shall be filed. Records available to the procuring activity may be limited to: complaints involving quality control or housekeeping received during the prior year; and complaints dealing with the item under procurement.

7.10 RETURNED GOODS

All returned goods, regardless of reason, shall be impounded to prevent integration with other material. No such material shall be released without approval by Quality Control. Records shall be maintained of quantity and date received and actual disposition of the product.

7.11 STABILITY OF FINISHED PRODUCT

Data shall be developed for finished drug products showing stability test results which shall be scientifically determined to be reliable and specific. Such data shall demonstrate the stability of the product and the immediate container and closure, as required in Par. 5.2, by:

(a) Storage as stated in the labeling

(b) A combination of accelerated aging and storage under conditions stated in the labeling

The data shall substantiate the shelf-life or expiration date, as required by the procuring activity and shall also include and substantiate conditions of storage, and any preparation for use which is prepared at the time of dispensing.

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8. QUALITY EVALUATION PROGRAM (SELF-INSPECTION PROGRAM)

An effective Quality Evaluation Program shall be planned, developed, and established in consonance with the company's operations. The program, representing a self-inspection concept, shall insure adequate quality throughout all phases of manufacture, quality control, and handling of materials and products by demonstrating compliance with all applicable requirements.

Management shall regularly review the status and adequacy of the company operations. Such review shall include but not be limited to the evaluation of procedures, processes, methods, controls, and operations in order to determine applicability, currentness, accuracy, and effectiveness of the procedures and company operations.

The Quality Evaluation Program shall detect promptly and correct assignable conditions adverse to quality. Corrective action shall extend to all operations and shall be responsive to data developed by the company, and products and product complaints forwarded from users. Corrective action shall include as a minimum:

(a) Analysis of data and examination of product scrapped or reworked to determine extent and causes

(b) Analysis of trends in processes or performance of work to prevent nonconforming product

(c) Introduction of required improvements and corrections, and initial review of the adequacy of such measures and monitoring of the effectiveness of correction action taken

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9. PLANT MAINTENANCE AND SANITATION

9.1 PROCEDURES

Plant maintenance and sanitation procedures shall be established (written) and enforced for maintenance and sanitation of plant and equipment. These procedures shall cover all areas and operations of the plant. They shall: delineate methods for assuring adequate cleanliness or asepsis; designate specific areas, cleaning intervals, cleaning periods, and equipment and materials used; and include necessary provisions for preventing the potential for contamination of material, equipment, or areas.

9.2 PLANT CONDITIONS

Plant conditions shall comply with the following:

(a) The plant shall be in good state of repair, being orderly, clean, well lighted, well ventilated, and free from insects, rodents, pests, vermin, dampness, mustiness, foreign odor, contamination, dirt, filth, and any refuse not in containers provided for the purpose.

(b) There shall be no excessive vibration in the floor when equipment is in use. Excessive vibration may result in stratification of bulk powders, disturbance of scales, balances, and delicate instruments or apparatus, etc.

(c) All vents, drains, and openings shall be protected to prevent entrance of rodents or other pests.

(d) All drains shall be equipped with traps and constructed to insure proper drainage, elimination of odors, and prevent clogging and back-siphonage. Drains shall be covered in sterile, aseptic and other critical areas.

(e) All outside windows in the manufacturing areas shall be screened to prevent the entrance of flies and other insects, unless permanently closed. Air-conditioned areas need not be screened, providing windows are not opened and doors are kept closed except for entrance and exit.

(f) Toilet, Dressing Room, and Handwashing Facilities

Toilet, dressing room, and handwashing facilities shall be provided near working areas and shall be kept clean and in good repair. The toilet room shall not open directly into any manufacturing area except through an enclosed vestibule or passageway. All toilet room doors shall be self-closing. The toilet room shall be well lighted, and ventilated to the outside. Convenient handwashing facilities shall be provided, including hot and cold running water, soap, and single-service towels or blower-type hand dryers.

(g) There shall be a water supply with adequate pressure which shall meet all requirements for potable water. Sanitary water fountains used to supply drinking water shall be in good working order and conveniently located. Non-potable water shall be restricted to closed systems such as cooling jackets, condensers, etc. All outlets and pipelines shall be marked to show the water is non-potable. There shall be no cross-connecting between potable and non-potable water.

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9.2 PLANT CONDITIONS (Cont'd)

(h) Lunch Rooms

Facilities shall be maintained in a sanitary condition. Food shall not be stored, prepared, or eaten in the manufacturing areas or where packaging materials are stored.

(i) Extermination Program

An extermination program shall be maintained for control of insects, rodents, and pest habitations. Periodic extermination shall be conducted, consistent with the particular needs of the various areas. Extermination applications shall be made by professional exterminators or by a company employee(s) trained in extermination of insects, rodents, and pests. It is of utmost importance that extreme precautionary measures be taken to prevent contamination of material and equipment. Information regarding the rodenticides, insecticides, etc., shall be maintained for record purposes. Exterminating materials shall be stored in a separate, closed area, clearly identified for the purpose.

(j) Janitorial Service

Janitorial service shall be maintained daily to remove rubbish and waste, and keep the plant in a clean and orderly condition. Cleaning operations shall be conducted in a manner to prevent the potential for contamination of drug substances. Soiled cleaning rags and uniforms shall be kept in closed containers until laundered.

(k) Trash, Waste, and Sewage Disposal

Adequate sewage and waste disposal facilities shall be maintained.

(l) Exterior surroundings shall be free from fly-breeding accumulations, mosquito-breeding accumulations, and rodent harborage.

(m) Animal Rooms - See Par. 6.3 for requirements.

(n) Floors shall be free from pools, slush, and materials that can be tracked from one area to another.

(o) Where a mechanical ventilation system is used, it shall be designed to prevent the potential for disseminating contaminants from one machine to another, one manufacturing area to another, and to avoid conditions unfavorable to the safety of the product or personnel. The air disseminated by forced mechanical ventilation shall be filtered if the air is distributed to an area where internal medications are manufactured. The ventilation system shall have a capacity suitable for the purpose employed. Air ducts shall be cleaned according to established procedures and schedule. Filters shall be replaced regularly. The ventilation system shall be arranged so that outgoing air shall not be admixed with incoming air.

(p) Manufacturing areas, laboratories, and passageways shall not be used for storage of raw materials, intermediates, finished products, containers, or equipment.

(q) Dehumidifying agents may be used to prevent dampness and moistness.

(r) Special precautions shall be taken when radioactive materials are used. Filtration of air and reduction in dust particles are among the essential elements in such precautions.

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9.3 EQUIPMENT, MACHINES, AND ACCESSORIES

The condition of the equipment, machines, and accessories shall comply with the following:

(a) The equipment and machines shall be:

(1) Adequate for the operations performed

(2) Properly located and constructed to facilitate cleaning

(3) Arranged to avoid the potential for contamination

(4) Operated and maintained as described by the manufacturers of the equipment and machines

(5) Installed in a manner that eliminates excessive vibration

(b) Processing vessels, equipment, filtering and filling apparatus, storage containers, and all machines, pumps, apparatus, and accessory equipment (including pipes and tubes) used in manufacture shall be:

(1) Designed and constructed to permit thorough cleaning and inspection (when possible). Records of cleaning and inspection shall be maintained.

(2) Cleaned promptly after use, or tagged to show that cleaning is required. Uncleaned machines, equipment, etc. that may represent a potential source of contamination shall be covered to avoid such potential for contamination.

(3) Inspected before use to assure that there is no contaminating material in, on, or near the machines, equipment, etc.

(4) Tanks, hoppers, pipes, outlets, and other portions of liquid-fill and powder-fill equipment shall be cleaned (with the aid of steam, special solvent, or other suitable method) to remove any residual material from previous operations. The equipment shall be disassembled regularly to prevent the potential for contamination.

(5) Stills, lines, and tanks holding Water for Injection shall be routinely cleaned with detergent and steam or by equivalent means at predetermined intervals. Simultaneously, pipes shall be disassembled from tanks and stills, and similarly cleaned with detergent and steam or by equivalent means. Records shall be maintained showing dates of cleaning.

(6) Storage tanks holding the same raw material, and lines and pumps, shall be cleaned at least annually and records maintained.

(c) Hoppers shall be protected while machines, equipment, etc. are in operation, in order to prevent the potential for contamination.

(d) No utensils or containers (such as porcelain and crockery) shall be in contact with drugs or available for such use if they have chipped, cracked, or bare areas.

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9.3 EQUIPMENT, MACHINES, AND ACCESSORIES (Cont'd)

(e) Reuse of drums, cartons, and other containers shall be permitted only when cleaned and lined with unused paper bags or unused polyethylene or equivalent liners. Those drums and other containers that can be washed do not require liners, provided the drums and other containers are thoroughly washed and thoroughly cleaned after use, and inspected prior to reuse.

(f) When used for storage of drugs, freezers, refrigerators, and warm rooms shall be maintained at designated temperatures. Suitable temperature recording devices shall be employed, or temperature readings shall be recorded on a regular routine basis. Freezers, refrigerators, and warm rooms shall not be used to store extraneous material.

(g) Incubators shall be maintained at designated temperatures. Suitable temperature recording devices shall be employed, or temperature readings shall be recorded on a regular routine basis.

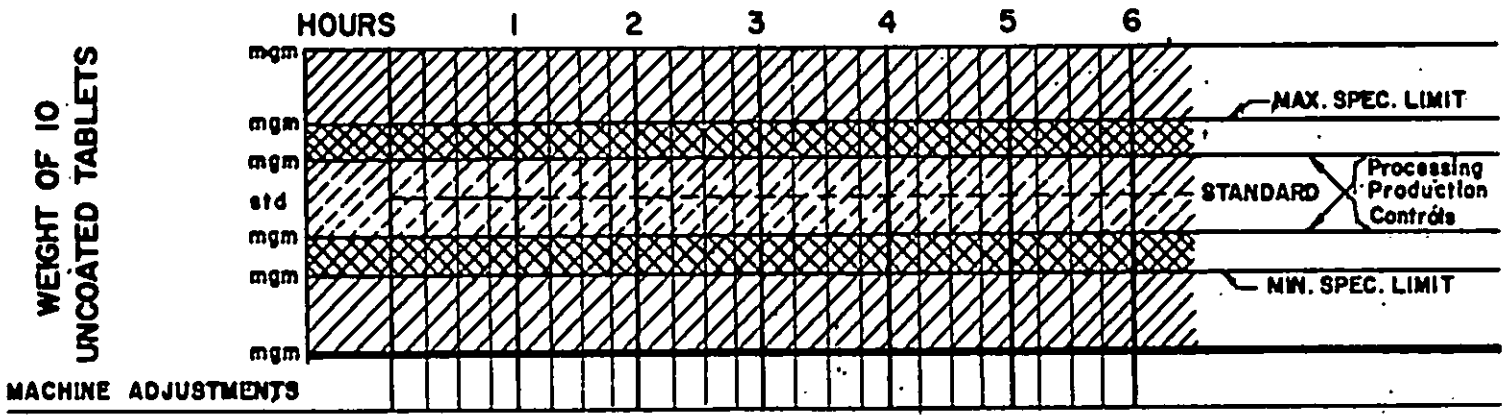
(h) Drying ovens shall be maintained at designated temperatures. Suitable recording devices shall be employed, or temperature readings shall be recorded on a regular routine basis. The interior of the ovens, including the trays, racks, base, walls, doors, and other surfaces, shall be cleaned after use. Forced air systems shall include adequate filters which shall be routinely replaced or cleaned to prevent the potential for contamination, in accordance with procedures and schedules. The intake of air shall originate from an area which is free from odors, fumes, and dust or vapor contaminants. The exhaust shall be released where it will not contaminate other products or be harmful to personnel.

(i) Sterilizers and method of sterilization shall insure the destruction of contaminating micro-organisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5°C maintained for 20 minutes by saturated steam, or by an attained temperature of 170°C maintained uninterruptedly for 2 hours with dry heat. Specifications describing the required characteristics for each sterilizer model shall be maintained. Periodic verifications shall be made to insure that the equipment is operating within the specified limits, and that there is adequate proof for effectiveness of the procedure.

IN PROCESS TABLETING DATA

NAME OF PRODUCT

LOT NO.	WT. PER TAB.	DATE STARTED DAY/HOUR	DATE ENDED DAY/HOUR	MACHINE NO.	SPEED OF PRODUCTION	SUPERVISED BY



OTHER INFORMATION

CHARACTERISTICS	LIMITS
DISINTEGRATION	
DISSOLUTION	
HARDNESS	
THICKNESS	
OTHER	

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APPENDIX II

LEAKAGE TEST

Leakage Test for Flame-Sealed Ampuls

All flame-sealed ampuls shall be tested by the manufacturer for leakage in accordance with A, B, or C below:

A. Thoroughly wash all ampuls with a suitable detergent and then rinse. The ampuls are completely immersed in a hydroalcoholic solution (containing about 10 percent denatured alcohol) that is highly colored with a suitable dye or combination of dyes, yielding a color that is different from the injection. The solution containing the ampuls is heated between 105°F, and 110°F. for 10 minutes, and then allowed to cool to room temperature. The contents of each ampul is examined for color change or presence of dye. Ampuls showing color change or presence of dye are rejected.

B. Thoroughly wash all ampuls with a suitable detergent and then rinse. The ampuls are completely immersed in an aqueous solution that is highly colored with a suitable dye or combination of dyes, yielding a color that is different from the injection. A vacuum of at least 25 inches is applied on the vessel containing the ampuls and dye solution, and the vacuum is maintained for at least 5 minutes. After releasing the vacuum, the contents of each ampul is examined for color change or presence of dye. Ampuls showing color change or presence of dye are rejected.

C. The ampuls are completely immersed in water that is highly colored with a suitable dye or combination of dyes, yielding a color that is different from the injection. Apply at least 10 inches of vacuum for at least 5 minutes and follow with 35 pounds air pressure for 15 minutes. After releasing the air pressure, the contents of each ampul is examined for color change or presence of dye. Ampuls showing color change or presence of dye are rejected.

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Review Activities:

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OMB Approval
No. 22-R255

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