21 CFR - SELECTED PARTS

PART 7, Subpart C - Recalls (Including Product Corrections) - Guidance on Policy, Procedures, and Industry Responsibilities

SOURCE: 43 FR 26218, June 16, 1978, unless otherwise noted.

7.40 Recall policy.

(a) Recall is an effective method of removing or correcting consumer products that are in violation of laws administered by the Food and Drug Administration. Recall is a voluntary action that takes place because manufacturers and distributors carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise defective. This section and 7.41 through 7.59 recognize the voluntary nature of recall by providing guidance so that responsible firms may effectively discharge their recall responsibilities. These sections also recognize that recall is an alternative to a Food and Drug Administration-initiated court action for removing or correcting violative, distributed products by setting forth specific recall procedures for the Food and Drug Administration to monitor recalls and assess the adequacy of a firm's efforts in recall.

(b) Recall may be undertaken voluntarily and at any time by manufacturers and distributors, or at the request of the Food and Drug Administration. A request by the Food and Drug Administration that a firm recall a product is reserved for urgent situations and is to be directed to the firm that has primary responsibility for the manufacture and marketing of the product that is to be recalled.

(c) Recall is generally more appropriate and affords better protection for consumers than seizure, when many lots of product have been widely distributed.

Seizure, multiple seizure, or other court action is indicated when a firm refuses to undertake a recall requested by the Food and Drug Administration, or where the agency has reason to believe that a recall would not be effective, determines that a recall is ineffective, or discovers that a violation is continuing.

[43CFR26218, June 16, 1978, as amended at 65 FR 56476, Sept. 19, 2000]

7.41 Health hazard evaluation and recall classification.

(a) An evaluation of the health hazard presented by a product being recalled or considered for recall will be conducted by an ad hoc committee of Food and Drug Administration scientists and will take into account, but need not be limited to, the following factors:

(1) Whether any disease or injuries have already occurred from the use of the product.

(2) Whether any existing conditions could contribute to a clinical situation that could expose humans or animals to a health hazard. Any conclusion shall be supported as completely as possible by scientific documentation and/or statements that the conclusion is the opinion of the individual(s) making the health hazard determination.

(3) Assessment of hazard to various segments of the population, e.g., children, surgical patients, pets, livestock, etc., who are expected to be exposed to the product being considered, with particular attention paid to the hazard to those individuals who may be at greatest risk.

(4) Assessment of the degree of seriousness of the health hazard to which the populations at risk would be exposed.

(5) Assessment of the likelihood of occurrence of the hazard.

(6) Assessment of the consequences (immediate or long-range) of occurrence of the hazard.

(b) On the basis of this determination, the Food and Drug Administration will assign the recall a classification, i.e., Class I, Class II, or Class III, to indicate the relative degree of health hazard of the product being recalled or considered for recall.

7.42 Recall strategy.

(a) General.

(1) A recall strategy that takes into account the following factors will be developed by the agency for a Food and Drug Administration-requested recall and by the recalling firm for a firm-initiated recall to suit the individual circumstances of the particular recall:

(i) Results of health hazard evaluation.

(ii) Ease in identifying the product.

(iii) Degree to which the product's deficiency is obvious to the consumer or user.

(iv) Degree to which the product remains unused in the market place.

(v) Continued availability of essential products.

(2) The Food and Drug Administration will review the adequacy of a proposed recall strategy developed by a recalling firm and recommend changes as appropriate. A recalling firm should conduct the recall in accordance with an approved recall strategy but need not delay initiation of a recall pending review of its recall strategy.

(b) Elements of a recall strategy. A recall strategy will address the following elements regarding the conduct of the recall:

(1) Depth of recall. Depending on the product's degree of hazard and extent of distribution, the recall strategy will specify the level in the distribution chain to which the recall is to extend, as follows:

(i) Consumer or user level, which may vary with product, including any intermediate wholesale or retail level; or

(ii) Retail level, including any intermediate wholesale level; or

(iii) Wholesale level.

(2) Public warning. The purpose of a public warning is to alert the public that a product being recalled presents a serious hazard to health. It is reserved for urgent situations where other means for preventing use of the recalled product appear inadequate. The Food and Drug Administration in consultation with the recalling firm will ordinarily issue such publicity. The recalling firm that decides to issue its

own public warning is requested to submit its proposed public warning and plan for distribution of the warning for review and comment by the Food and Drug Administration. The recall strategy will specify whether a public warning is needed and whether it will issue as:

(i) General public warning through the general news media, either national or local as appropriate, or

(ii) Public warning through specialized news media, e.g., professional or trade press, or to specific segments of the population such as physicians, hospitals, etc.

(3) Effectiveness checks. The purpose of effectiveness checks is to verify that all consignees at the recall depth specified by the strategy have received notification about the recall and have taken appropriate action. The method for contacting consignees may be accomplished by personal visits, telephone calls, letters, or a combination thereof. A guide entitled "Method for Conducting Recall Effectiveness Checks" that describes the use of these different methods is available upon request from the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. The recalling firm will ordinarily be responsible for conducting effectiveness checks, but the Food and Drug Administration will assist in this task where necessary and appropriate. The recall strategy will specify the method(s) to be used for and the level of effectiveness checks that will be conducted, as follows:

(i) Level A - 100 percent of the total number of consignees to be contacted;

(ii) Level B - Some percentage of the total number of consignees to be contacted, which percentage is to be determined on a case-by-case basis, but is greater that 10 percent and less than 100 percent of the total number of consignees;

(iii) Level C - 10 percent of the total number of consignees to be contacted;

(iv) Level D - 2 percent of the total number of consignees to be contacted; or

(v) Level E - No effectiveness checks.

[43 FR 26218, June 16, 1978, as amended at 46 FR 8455, Jan. 27, 1981; 59 FR 14363, Mar. 28, 1994]

7.45 Food and Drug Administration - requested recall.

(a) The Commissioner of Food and Drugs or his designee under 5.20 of this chapter may request a firm to initiate a recall when the following determinations have been made:

(1) That a product that has been distributed presents a risk of illness or injury or gross consumer deception.

(2) That the firm has not initiated a recall of the product.

(3) That an agency action is necessary to protect the public health and welfare.

(b) The Commissioner or his designee will notify the firm of this determination and of the need to begin immediately a recall of the product. Such notification will be by letter or telegram to a responsible official of the firm, but may be preceded by oral communication or by a visit from an authorized representative of the local Food and Drug Administration district office, with formal, written confirmation from the Commissioner or his designee afterward. The notification will specify the violation, the health hazard classification of the violative product, the recall strategy, and other appropriate instructions for conducting the recall.

(c) Upon receipt of a request to recall, the firm may be asked to provide the Food and Drug Administration any or all of the information listed in 7.46(a). The firm, upon agreeing to the recall request, may also provide other information relevant to the agency's determination of the need for the recall or how the recall should be conducted.

7.46 Firm-initiated recall.

(a) A firm may decide of its own volition and under any circumstances to remove or correct a distributed product. A firm that does so because it believes the product to be violative is requested to notify immediately the appropriate Food and Drug Administration district office listed in 5.115 of this chapter. Such removal or correction will be considered a recall only if the Food and Drug Administration regards the product as involving a violation that is subject to legal action, e.g., seizure. In such cases, the firm will be asked to provide the Food and Drug Administration the following information:

(1) Identity of the product involved.

(2) Reason for the removal or correction and the date and circumstances under which the product deficiency or possible deficiency was discovered.

(3) Evaluation of the risk associated with the deficiency or possible deficiency.

(4) Total amount of such products produced and/or the time span of the production.

(5) Total amount of such products estimated to be in distribution channels.

(6) Distribution information, including the number of direct accounts and, where necessary, the identity of the direct accounts.

(7) A copy of the firm's recall communication if any has issued, or a proposed communication if none has issued.

(8) Proposed strategy for conducting the recall.

(9) Name and telephone number of the firm official who should be contacted concerning the recall.

(b) The Food and Drug Administration will review the information submitted, advise the firm of the assigned recall classification, recommend any appropriate changes in the firm's strategy for the recall, and advise the firm that its recall will be placed in the weekly FDA Enforcement Report. Pending this review, the firm need not delay initiation of its product removal or correction.

(c) A firm may decide to recall a product when informed by the Food and Drug Administration that the agency has determined that the product in question violates the law, but the agency has not specifically requested a recall. The firm's action also is considered a firm-initiated recall and is subject to paragraphs (a) and (b) of this section.

(d) A firm that initiates a removal or correction of its product which the firm believes is a market withdrawal should consult with the appropriate Food and Drug Administration district office when the reason for the removal or correction is not obvious or clearly understood but where it is appar-

ent, e.g., because of complaints or adverse reactions regarding the product, that the product is deficient in some respect. In such cases, the Food and Drug Administration will assist the firm in determining the exact nature of the problem.

7.49 Recall communications.

(a) General. A recalling firm is responsible for promptly notifying each of its affected direct accounts about the recall. The format, content, and extent of a recall communication should be commensurate with the hazard of the product being recalled and the strategy developed for that recall. In general terms, the purpose of a recall communication is to convey:

(1) That the product in question is subject to a recall.

(2) That further distribution or use of any remaining product should cease immediately.

(3) Where appropriate, that the direct account should in turn notify its customers who received the product about the recall.

(4) Instructions regarding what to do with the product.

(b) Implementation. A recall communication can be accomplished by telegrams, mailgrams, or first class letters conspicuously marked, preferably in bold red type, on the letter and the envelope: "DRUG [or FOOD, BIOLOGIC, etc.] RECALL [or CORRECTION]". The letter and the envelope should be also marked: "URGENT" for class I and class II recalls and, when appropriate, for class III recalls. Telephone calls or other personal contacts should ordinarily be confirmed by one of the above methods and/or documented in an appropriate manner.

(c) Contents.

(1) A recall communication should be written in accordance with the following guidelines:

(i) Be brief and to the point;

(ii) Identify clearly the product, size, lot number(s), code(s) or serial number(s) and any other pertinent descriptive information to enable accurate and immediate identification of the product;

(iii) Explain concisely the reason for the recall and the hazard involved, if any;

(iv) Provide specific instructions on what should be done with respect to the recalled products; and

(v) Provide a ready means for the recipient of the communication to report to the recalling firm whether it has any of the product, e.g., by sending a postage-paid, self-addressed postcard or by allowing the recipient to place a collect call to the recalling firm.

(2) The recall communication should not contain irrelevant qualifications, promotional materials, or any other statement that may detract from the message. Where necessary, follow up communications should be sent to those who fail to respond to the initial recall communication.

(d) Responsibility of recipient. Consignees that receive a recall communication should immediately carry out the instructions set forth by the recalling firm and, where necessary, extend the recall to its consignees in accordance with paragraphs (b) and (c) of this section.

7.50 Public notification of recall.

The Food and Drug Administration will promptly make available to the public in the weekly FDA Enforcement Report a descriptive listing of each new recall according to its classification, whether it was Food and Drug Administration-requested or firm-initiated, and the specific action being taken by the recalling firm. The Food and Drug Administration will intentionally delay public notification of recalls of certain drugs and devices where the agency determines that public notification may cause unnecessary and harmful anxiety in patients and that initial consultation between patients and their physicians is essential. The report will not include a firm's product removals or corrections which the agency determines to be market withdrawals or stock recoveries. The report, which also includes other Food and Drug Administration regulatory actions, e.g., seizures that were effected and injunctions and prosecutions that were filed, is available upon request from the Office of Public Affairs (HFI-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

7.53 Recall status reports.

(a) The recalling firm is requested to submit periodic recall status reports to the appropriate Food and Drug Administration district office so that the agency may assess the progress of the recall. The frequency of such reports will be determined by the relative urgency of the recall and will be specified by the Food and Drug Administration in each recall case; generally the reporting interval will be between 2 and 4 weeks.

(b) Unless otherwise specified or inappropriate in a given recall case, the recall status report should contain the following information:

(1) Number of consignees notified of the recall, and date and method of notification.

(2) Number of consignees responding to the recall communication and quantity of products on hand at the time it was received.

(3) Number of consignees that did not respond (if needed, the identity of non-responding consignees may be requested by the Food and Drug Administration).

(4) Number of products returned or corrected by each consignee contacted and the quantity of products accounted for.

(5) Number and results of effectiveness checks that were made.

(6) Estimated time frames for completion of the recall.

(c) Recall status reports are to be discontinued when the recall is terminated by the Food and Drug Administration.

7.55 Termination of a recall.

(a) A recall will be terminated when the Food and Drug Administration determines that all reasonable efforts have been made to remove or correct the product in accordance with the recall strategy, and when it is reasonable to assume that the product subject to the recall has been removed and proper disposition or correction has been made commensurate with the degree of hazard of the recalled product. Written notification that a recall is termi-

nated will be issued by the appropriate Food and Drug Administration district office to the recalling firm.

(b) A recalling firm may request termination of its recall by submitting a written request to the appropriate Food and Drug Administration district office stating that the recall is effective in accordance with the criteria set forth in paragraph (a) of this section, and by accompanying the request with the most current recall status report and a description of the disposition of the recalled product.

7.59 General industry guidance.

A recall can be disruptive of a firm's operation and business, but there are several steps a prudent firm can take in advance to minimize this disruptive effect. Notwithstanding similar specific requirements for certain products in other parts of this chapter, the following is provided by the Food and Drug Administration as guidance for a firm's consideration:

(a) Prepare and maintain a current written contingency plan for use in initiating and effecting a recall in accordance with 7.40 through 7.49, 7.53, and 7.55.

(b) Use sufficient coding of regulated products to make possible positive lot identification and to facilitate effective recall of all violative lots.

(c) Maintain such product distribution records as are necessary to facilitate location of products that are being recalled. Such records should be maintained for a period of time that exceeds the shelf life and expected use of the product and is at least the length of time specified in other applicable regulations concerning records retention.

PART 19 - STANDARDS OF CONDUCT AND CONFLICTS OF INTEREST

Subpart A - General Provisions

AUTHORITY: 21 U.S.C. 371. SOURCE: 42FR 15615; Mar 22, 1977 unless otherwise noted.

19.1 Scope.

This part governs the standards of conduct for, and establishes regulations to prevent conflicts of interest by, all Food and Drug Administration employees.

19.5 Reference to Department regulations.

(a) The provisions of 45 CFR part 73, establishing standards of conduct for all Department employees, are fully applicable to all Food and Drug Administration employees, except that such regulations shall be applicable to special government employees, i.e., consultants to the Food and Drug Administration, only to the extent stated in subpart L of 45 CFR part 73.

(b) The provisions of 45 CFR part 73a supplement the Department standards of conduct and apply only to Food and Drug Administration employees except special government employees.

19.6 Code of ethics for government service.

The following code of ethics, adopted by Congress on July 11, 1958, shall apply to all Food and Drug Administration employees:

CODE OF ETHICS FOR GOVERNMENT SERVICE

Any person in Government service should:

1. Put loyalty to the highest moral principles and to country above loyalty to persons, party, or Government department.
2. Uphold the Constitution, laws, and legal regulations of the United States and of all governments therein and never be a party to their evasion.
3. Give a full day's labor for a full day's pay; giving to the performance of his duties his earnest effort and best thought.
4. Seek to find and employ more efficient and economical ways of getting tasks accomplished.
5. Never discriminate unfairly by the dispensing of special favors or privileges to anyone, whether for remuneration or not; and never accept, for himself or his family, favors or benefits under circumstances which might be construed by reasonable persons as influencing the performance of his governmental duties.
6. Make no private promises of any kind binding upon the duties of office, since a Government employee has no private word which can be binding on public duty.
7. Engage in no business with the Government, either directly or indirectly, which is inconsistent with the conscientious performance of his governmental duties.
8. Never use any information coming to him confidentially in the performance of governmental duties as a means for making private profit.
9. Expose corruption wherever discovered.
10. Uphold these principles, ever conscious that public office is a public trust.

19.10 Food and Drug Administration Conflict of Interest Review Board.

(a) The Commissioner shall establish a permanent five-member Conflict of Interest Review Board, which shall review and make recommendations to the Commissioner on all specific or policy matters relating to conflicts of interest arising within the Food and Drug Administration that are forwarded to it by: (1) The Associate Commissioner for Management and Operations or (2) anyone who is the subject of an adverse determination by the Associate Commissioner for Management and Operations on any matter arising under the conflict of interest laws, except a determination of an apparent violation of law. The Director, Division of Ethics and Program Integrity, Office of Management and Operations, shall serve as executive secretary of the Review Board.

(b) It shall be the responsibility of every Food and Drug Administration employee with whom any specific or policy issue relating to conflicts of interest is raised, or who otherwise wishes to have any such matter resolved, to forward the matter to the Associate Commissioner for Management and Operations for resolution, except that reporting of apparent violations of law are governed by 19.21.

(c) All general policy relating to conflicts of interest shall be established in guidance pursuant to the provisions of

10.90(b) of this chapter and whenever feasible shall be incorporated in regulations in this subpart.

(d) All decisions relating to specific individuals shall be placed in a public file established for this purpose by the Freedom of Information Staff, e.g., a determination that a consultant may serve on an advisory committee with specific limitations or with public disclosure of stock holdings, except that such determination shall be written in a way that does not identify the individual in the following situations:

(1) A determination that an employee must dispose of prohibited financial interests or refrain from incompatible outside activities in accordance with established Department or agency regulations.

(2) A determination that a proposed consultant is not eligible for employment by the agency.

(3) A determination that public disclosure of any information would constitute an unwarranted invasion of personal privacy in violation of 20.63 of this chapter.

[42 FR 15615, Mar.22, 1977, as amended at 46 FR 8456, Jan. 27, 1981, 50 FR 52278, Dec. 23, 1985; 55 FR 1404, Jan. 16, 1990; 65 FR 56479, Sept. 19, 2000]

Subpart B - Reporting of Violations

19.21 Duty to report violations.

(a) The Office of Internal Affairs, Office of the Commissioner, is responsible for obtaining factual information for the Food and Drug Administration on any matter relating to allegations of misconduct, impropriety, conflict of interest, or other violations of Federal statutes by agency personnel.

(b) Any Food and Drug Administration employee who has factual information showing or who otherwise believes that any present or former Food and Drug Administration employee has violated or is violating any provision of this subpart or of 45 CFR parts 73 or 73a or of any statute listed in Appendix A to 45 CFR part 73 should report such information directly to the Office of Internal Affairs. Any such reports shall be in writing or shall with the assistance of the Office of Internal Affairs, be reduced to writing, and shall be promptly investigated.

(c) Any report pursuant to paragraph (b) of this section and any records relating to an investigation of such reports shall be maintained in strict confidence in the files of the Office of Internal Affairs, shall be exempt from public disclosure, and may be reviewed only by authorized Food and Drug Administration employees who are required to do so in the performance of their duties.

[42 FR 15615, Mar. 22, 1977, as amended at 46 FR 8456, Jan. 27, 1981; 50 FR 52278, Dec. 23, 1985; 60 FR 47478, Sept. 13, 1995]

Subpart C - Disqualification Conditions

19.45 Temporary disqualification of former employees.

Within 1 year after termination of employment with the Food and Drug Administration, no former Food and Drug Administration employee, including a special government employee, shall appear personally before the Food and Drug Administration or other federal agency or court as agent or attorney for any person other than the United States in connection with any proceeding or matter in which the United States is a party or has a direct and substantial interest and which was under his official responsibility at any time within one year preceding termination of such responsibility. The term official responsibility means the direct administrative or operating authority, whether intermediate or final, and either exercisable alone or with others, and either personally or through subordinates, to approve, disapprove, or otherwise direct government action.

19.55 Permanent disqualification of former employees.

No former Food and Drug Administration employee, including a special government employee, shall knowingly act as agent or attorney for anyone other than United States in connection with any judicial or other proceeding, application, request for a ruling or other determination, contract, claim, controversy, charge, accusation, or other particular matter involving a specific party or parties in which the United States is a party or has a direct and substantial interest and in which he participated personally and substantially through decision, approval, disapproval, recommendation, rendering of advice, investigation, or otherwise as a Food and Drug Administration employee.

PART 110-CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PACKING, OR HOLDING HUMAN FOOD

AUTHORITY: 21 U.S.C. 342, 371, 374; 42 U.S.C. 264. SOURCE: 51 FR 24475, June 19, 1986, unless otherwise noted

Subpart A - General Provisions

110.3 Definitions.

The definitions and interpretations of terms in section 201 of the Federal Food, Drug, and Cosmetic Act (the act) are applicable to such terms when used in this part. The following definitions shall also apply:

(a) Acid foods or acidified foods means foods that have an equilibrium pH of 4.6 or below.

(b) Adequate means that which is needed to accomplish the intended purpose in keeping with good public health practice.

(c) Batter means a semi-fluid substance, usually composed of flour and other ingredients, into which principal components of food are dipped or with which they are coated, or which may be used directly to form bakery foods.

(d) Blanching, except for tree nuts and peanuts, means a prepackaging heat treatment of foodstuffs for a sufficient time and at a sufficient temperature to partially or completely inactivate the naturally occurring enzymes and to effect other physical or biochemical changes in the food.

(e) Critical control point means a point in a food process where there is a high probability that improper control may cause, allow, or contribute to a hazard or to filth in the final food or decomposition of the final food.

(f) Food means food as defined in section 201(f) of the act and includes raw materials and ingredients.

(g) Food-contact surfaces are those surfaces that contact human food and those surfaces from which drainage onto the food or onto surfaces that contact the food ordinarily occurs during the normal course of operations. Food-contact surfaces includes utensils and food-contact surfaces of equipment.

(h) Lot means the food produced during a period of time indicated by a specific code.

(i) Microorganisms means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance. The term "undesirable microorganisms" includes those microorganisms that are of public health significance, that subject food to decomposition, that indicate that food is contaminated with filth, or that otherwise may cause food to be adulterated within the meaning of the act. Occasionally in these regulations, FDA used the adjective ``microbial'' instead of using an adjectival phrase containing the word microorganism.

(j) Pest refers to any objectionable animals or insects including, but not limited to, birds, rodents, flies, and larvae.

(k) Plant means the building or facility or parts thereof, used for or in connection with the manufacturing, packaging, labeling, or holding of human food.

(l) Quality control operation means a planned and systematic procedure for taking all actions necessary to prevent food from being adulterated within the meaning of the act.

(m) Rework means clean, unadulterated food that has been removed from processing for reasons other than insanitary conditions or that has been successfully reconditioned by reprocessing and that is suitable for use as food.

(n) Safe-moisture level is a level of moisture low enough to prevent the growth of undesirable microorganisms in the finished product under the intended conditions of manufacturing, storage, and distribution. The maximum safe moisture level for a food is based on its water activity (a_w). An a_w will be considered safe for a food if adequate data are available that demonstrate that the food at or below the given a_w will not support the growth of undesirable microorganisms.

(o) Sanitize means to adequately treat food-contact surfaces by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms, but without adversely affecting the product or its safety for the consumer.

(p) Shall is used to state mandatory requirements.

(q) Should is used to state recommended or advisory procedures or identify recommended equipment.

(r) Water activity (a_w) is a measure of the free moisture in a food and is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature.

110.5 Current good manufacturing practice.

(a) The criteria and definitions in this part shall apply in determining whether a food is adulterated (1) within the meaning of section 402(a)(3) of the act in that the food has been manufactured section 402(a)(4) of the act in that the food has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. The criteria and definitions in this part also apply in determining whether a food is in violation of section 361 of the Public Health Service Act (42 U.S.C. 264).

(b) Food covered by specific current good manufacturing practice regulations also is subject to the requirements of those regulations.

110.10 Personnel.

The plant management shall take all reasonable measures and precautions to ensure the following:

(a) Disease control. Any person who, by medical examination or supervisory observation, is shown to have, or appears to have, an illness, open lesion, including boils, sores, or infected wounds, or any other abnormal source of microbial contamination by which there is a reasonable possibility of food, food-contact surfaces, or food-packaging materials becoming contaminated, shall be excluded from any operations which may be expected to result in such contamination until the condition is corrected. Personnel shall be instructed to report such health conditions to their supervisors.

(b) Cleanliness. All persons working in direct contact with food, food-contact surfaces, and food-packaging materials shall conform to hygienic practices while on duty to the extent necessary to protect against contamination of food. The methods for maintaining cleanliness include, but are not limited to:

(1) Wearing outer garments suitable to the operation in a manner that protects against the contamination of food, food-contact surfaces, or food-packaging materials.

(2) Maintaining adequate personal cleanliness.

(3) Washing hands thoroughly (and sanitizing if necessary to protect against contamination with undesirable microorganisms) in an adequate hand-washing facility before starting work, after each absence from the work station, and at any other time when the hands may have become soiled or contaminated.

(4) Removing all unsecured jewelry and other objects that might fall into food, equipment, or containers, and removing hand jewelry that cannot be adequately sanitized during periods in which food is manipulated by hand. If such hand jewelry cannot be removed, it may be covered by material which can be maintained in an intact, clean, and sanitary condition and which effectively protects against the contamination by these objects of the food, food-contact surfaces, or food-packaging materials.

(5) Maintaining gloves, if they are used in food handling, in an intact, clean, and sanitary condition. The gloves should be of an impermeable material.

(6) Wearing, where appropriate, in an effective manner, hair nets, headbands, caps, beard covers, or other effective hair restraints.

(7) Storing clothing or other personal belongings in areas other than where food is exposed or where equipment or utensils are washed.

(8) Confining the following to areas other than where

food may be exposed or where equipment or utensils are washed: eating food, chewing gum, drinking beverages, or using tobacco.

(9) Taking any other necessary precautions to protect against contamination of food, food-contact surfaces, or food-packaging materials with microorganisms or foreign substances including, but not limited to, perspiration, hair, cosmetics, tobacco, chemicals, and medicines applied to the skin.

(c) Education and training. Personnel responsible for identifying sanitation failures or food contamination should have a background of education or experience, or a combination thereof, to provide a level of competency necessary for production of clean and safe food. Food handlers and supervisors should receive appropriate training in proper food handling techniques and food-protection principles and should be informed of the danger of poor personal hygiene and insanitary practices.

(d) Supervision. Responsibility for assuring compliance by all personnel with all requirements of this part shall be clearly assigned to competent supervisory personnel.

[51 FR 24475, June 19, 1986, as amended at 54 FR 24892, June 12, 1989]

110.19 Exclusions.

(a) The following operations are not subject to this part: Establishments engaged solely in the harvesting, storage, or distribution of one or more "raw agricultural commodities," as defined in section 201(r) of the act, which are ordinarily cleaned, prepared, treated, or otherwise processed before being marketed to the consuming public.

(b) FDA, however, will issue special regulations if it is necessary to cover these excluded operations.

Subpart B - Buildings and Facilities

110.20 Plant and grounds.

(a) Grounds. The grounds about a food plant under the control of the operator shall be kept in a condition that will protect against the contamination of food. The methods for adequate maintenance of grounds include, but are not limited to:

(1) Properly storing equipment, removing litter and waste, and cutting weeds or grass within the immediate vicinity of the plant buildings or structures that may constitute an attractant, breeding place, or harborage for pests.

(2) Maintaining roads, yards, and parking lots so that they do not constitute a source of contamination in areas where food is exposed.

(3) Adequately draining areas that may contribute contamination to food by, foot-borne filth, or providing a breeding place for pests.

(4) Operating systems for waste treatment and disposal in an adequate manner so that they do not constitute a source of contamination in areas where food is exposed. If the plant grounds are bordered by grounds not under the operator's control and not maintained in the manner described in paragraph (a) (1) through (3) of this section, care shall be exercised in the plant by inspection, extermination, or other means to exclude pests, dirt, and filth that may be a source of food contamination.

(b) Plant construction and design. Plant buildings and structures shall be suitable in size, construction, and design to facilitate maintenance and sanitary operations for food-manufacturing purposes. The plant and facilities shall:

(1) Provide sufficient space for such placement of equipment and storage of materials as is necessary for the maintenance of sanitary operations and the production of safe food.

(2) Permit the taking of proper precautions to reduce the potential for contamination of food, food-contact surfaces, or food-packaging materials with microorganisms, chemicals, filth, or other extraneous material. The potential for contamination may be reduced by adequate food safety controls and operating practices or effective design, including the separation of operations in which contamination is likely to occur, by one or more of the following means: location, time, partition, air flow, enclosed systems, or other effective means.

(3) Permit the taking of proper precautions to protect food in outdoor bulk fermentation vessels by any effective means, including:

(i) Using protective coverings.

(ii) Controlling areas over and around the vessels to eliminate harborages for pests.

(iii) Checking on a regular basis for pests and pest infestation.

(iv) Skimming the fermentation vessels, as necessary.

(4) Be constructed in such a manner that floors, walls, and ceilings may be adequately cleaned and kept clean and kept in good repair; that drip or condensate from fixtures, ducts and pipes does not contaminate food, food-contact surfaces, or food-packaging materials; and that aisles or working spaces are provided between equipment and walls and are adequately unobstructed and of adequate width to permit employees to perform their duties and to protect against contaminating food or food-contact surfaces with clothing or personal contact.

(5) Provide adequate lighting in hand-washing areas, dressing and locker rooms, and toilet rooms and in all areas where food is examined, processed, or stored and where equipment or utensils are cleaned; and provide safety-type light bulbs, fixtures, skylights, or other glass suspended over exposed food in any step of preparation or otherwise protect against food contamination in case of glass breakage.

(6) Provide adequate ventilation or control equipment to minimize odors and vapors (including steam and noxious fumes) in areas where they may contaminate food; and locate and operate fans and other air-blowing equipment in a manner that minimizes the potential for contaminating food, food-packaging materials, and food-contact surfaces.

(7) Provide, where necessary, adequate screening or other protection against pests.

110.35 Sanitary operations.

(a) General maintenance. Buildings, fixtures, and other physical facilities of the plant shall be maintained in a sanitary condition and shall be kept in repair sufficient to pre-

vent food from becoming adulterated within the meaning of the act. Cleaning and sanitizing of utensils and equipment shall be conducted in a manner that protects against contamination of food, food-contact surfaces, or food-packaging materials.

(b) Substances used in cleaning and sanitizing; storage of toxic materials.

(1) Cleaning compounds and sanitizing agents used in cleaning and sanitizing procedures shall be free from undesirable microorganisms and shall be safe and adequate under the conditions of use. Compliance with this requirement may be verified by any effective means including purchase of these substances under a supplier's guarantee or certification, or examination of these substances for contamination. Only the following toxic materials may be used or stored in a plant where food is processed or exposed:

(i) Those required to maintain clean and sanitary conditions;

(ii) Those necessary for use in laboratory testing procedures;

(iii) Those necessary for plant and equipment maintenance and operation; and

(iv) Those necessary for use in the plant's operations.

(2) Toxic cleaning compounds, sanitizing agents, and pesticide chemicals shall be identified, held, and stored in a manner that protects against contamination of food, food-contact surfaces, or food-packaging materials. All relevant regulations promulgated by other Federal, State, and local government agencies for the application, use, or holding of these products should be followed.

(c) Pest control. No pests shall be allowed in any area of a food plant. Guard or guide dogs may be allowed in some areas of a plant if the presence of the dogs is unlikely to result in contamination of food, food-contact surfaces, or food-packaging materials. Effective measures shall be taken to exclude pests from the processing areas and to protect against the contamination of food on the premises by pests. The use of insecticides or rodenticides is permitted only under precautions and restrictions that will protect against the contamination of food, food-contact surfaces, and food-packaging materials.

(d) Sanitation of food-contact surfaces. All food-contact surfaces, including utensils and food-contact surfaces of equipment, shall be cleaned as frequently as necessary to protect against contamination of food.

(1) Food-contact surfaces used for manufacturing or holding low-moisture food shall be in a dry, sanitary condition at the time of use. When the surfaces are wet-cleaned, they shall, when necessary, be sanitized and thoroughly dried before subsequent use.

(2) In wet processing, when cleaning is necessary to protect against the introduction of microorganisms into food, all food-contact surfaces shall be cleaned and sanitized before use and after any interruption during which the food-contact surfaces may have become contaminated. Where equipment and utensils are used in a continuous production operation, the utensils and food-contact surfaces of the equipment shall be cleaned and sanitized as necessary.

(3) Non-food-contact surfaces of equipment used in the operation of food plants should be cleaned as frequently as necessary to protect against contamination of food.

(4) Single-service articles (such as utensils intended for one-time use, paper cups, and paper towels) should be stored in appropriate containers and shall be handled, dispensed, used, and disposed of in a manner that protects against contamination of food or food-contact surfaces.

(5) Sanitizing agents shall be adequate and safe under conditions of use. Any facility, procedure, or machine is acceptable for cleaning and sanitizing equipment and utensils if it is established that the facility, procedure, or machine will routinely render equipment and utensils clean and provide adequate cleaning and sanitizing treatment.

(e) Storage and handling of cleaned portable equipment and utensils. Cleaned and sanitized portable equipment with food-contact surfaces and utensils should be stored in a location and manner that protects food-contact surfaces from contamination.

[51 FR 24475, June 19, 1986, as amended at 54 FR 24892, June 12, 1989]

110.37 Sanitary facilities and controls.

Each plant shall be equipped with adequate sanitary facilities and accommodations including, but not limited to:

(a) Water supply. The water supply shall be sufficient for the operations intended and shall be derived from an adequate source. Any water that contacts food or food-contact surfaces shall be safe and of adequate sanitary quality. Running water at a suitable temperature, and under pressure as needed, shall be provided in all areas where required for the processing of food, for the cleaning of equipment, utensils, and food-packaging materials, or for employee sanitary facilities.

(b) Plumbing. Plumbing shall be of adequate size and design and adequately installed and maintained to:

(1) Carry sufficient quantities of water to required locations throughout the plant.

(2) Properly convey sewage and liquid disposable waste from the plant.

(3) Avoid constituting a source of contamination to food, water supplies, equipment, or utensils or creating an unsanitary condition.

(4) Provide adequate floor drainage in all areas where floors are subject to flooding-type cleaning or where normal operations release or discharge water or other liquid waste on the floor.

(5) Provide that there is not backflow from, or cross-connection between, piping systems that discharge waste water or sewage and piping systems that carry water for food or food manufacturing.

(c) Sewage disposal. Sewage disposal shall be made into an adequate sewerage system or disposed of through other adequate means.

(d) Toilet facilities. Each plant shall provide its employees with adequate, readily accessible toilet facilities. Compliance with this requirement may be accomplished by:

(1) Maintaining the facilities in a sanitary condition.

(2) Keeping the facilities in good repair at all times.

(3) Providing self-closing doors.

(4) Providing doors that do not open into areas where

food is exposed to airborne contamination, except where alternate means have been taken to protect against such contamination (such as double doors or positive air-flow systems).

(e) Hand-washing facilities. Hand-washing facilities shall be adequate and convenient and be furnished with running water at a suitable temperature. Compliance with this requirement may be accomplished by providing:

(1) Hand-washing and, where appropriate, hand-sanitizing facilities at each location in the plant where good sanitary practices require employees to wash and/or sanitize their hands.

(2) Effective hand-cleaning and sanitizing preparations.

(3) Sanitary towel service or suitable drying devices.

(4) Devices or fixtures, such as water control valves, so designed and constructed to protect against recontamination of clean, sanitized hands.

(5) Readily understandable signs directing employees handling unprotected food, unprotected food-packaging materials, or food-contact surfaces to wash and, where appropriate, sanitize their hands before they start work, after each absence from post of duty, and when their hands may have become soiled or contaminated. These signs may be posted in the processing room(s) and in all other areas where employees may handle such food, materials, or surfaces.

(6) Refuse receptacles that are constructed and maintained in a manner that protects against contamination of food.

(f) Rubbish and offal disposal. Rubbish and any offal shall be so conveyed, stored, and disposed of as to minimize the development of odor, minimize the potential for the waste becoming an attractant and harborage or breeding place for pests, and protect against contamination of food, food-contact surfaces, water supplies, and ground surfaces.

Subpart C - Equipment

110.40 Equipment and utensils.

(a) All plant equipment and utensils shall be so designed and of such material and workmanship as to be adequately cleanable, and shall be properly maintained. The design, construction, and use of equipment and utensils shall preclude the adulteration of food with lubricants, fuel, metal fragments, contaminated water, or any other contaminants. All equipment should be so installed and maintained as to facilitate the cleaning of the equipment and of all adjacent spaces. Food-contact surfaces shall be corrosion-resistant when in contact with food. They shall be made of nontoxic materials and designed to withstand the action of food, and, if applicable, cleaning compounds and sanitizing agents. Food-contact surfaces shall be maintained to protect food from being contaminated by any source, including unlawful indirect food additives.

(b) Seams on food-contact surfaces shall be smoothly bonded or maintained so as to minimize accumulation of food particles, dirt, and organic matter and thus minimize the opportunity for growth of microorganisms.

(c) Equipment that is in the manufacturing or food-handling area and that does not come into contact with food shall be so constructed that it can be kept in a clean condition.

(d) Holding, conveying, and manufacturing systems, including gravimetric, pneumatic, closed, and automated systems, shall be of a design and construction that enables them to be maintained in an appropriate sanitary condition.

(e) Each freezer and cold storage compartment used to store and hold food capable of supporting growth of microorganisms shall be fitted with an indicating thermometer, temperature-measuring device, or temperature-recording device so installed as to show the temperature accurately within the compartment, and should be fitted with an automatic control for regulating temperature or with an automatic alarm system to indicate a significant temperature change in a manual operation.

(f) Instruments and controls used for measuring, regulating, or recording temperatures, pH, acidity, water activity, or other conditions that control or prevent the growth of undesirable microorganisms in food shall be accurate and adequately maintained, and adequate in number for their designated uses.

(g) Compressed air or other gases mechanically introduced into food or used to clean food-contact surfaces or equipment shall be treated in such a way that food is not contaminated with unlawful indirect food additives.

110.80 Processes and controls.

All operations in the receiving, inspecting, transporting, segregating, preparing, manufacturing, packaging, and storing of food shall be conducted in accordance with adequate sanitation principles. Appropriate quality control operations shall be employed to ensure that food is suitable for human consumption and that food-packaging materials are safe and suitable. Overall sanitation of the plant shall be under the supervision of one or more competent individuals assigned responsibility for this function. All reasonable precautions shall be taken to ensure that production procedures do not contribute contamination from any source. Chemical, microbial, or extraneous-material testing procedures shall be used where necessary to identify sanitation failures or possible food contamination. All food that has become contaminated to the extent that it is adulterated within the meaning of the act shall be rejected, or if permissible, treated or processed to eliminate the contamination.

(a) Raw materials and other ingredients.

(1) Raw materials and other ingredients shall be inspected and segregated or otherwise handled as necessary to ascertain that they are clean and suitable for processing into food and shall be stored under conditions that will protect against contamination and minimize deterioration. Raw materials shall be washed or cleaned as necessary to remove soil or other contamination. Water used for washing, rinsing, or conveying food shall be safe and of adequate sanitary quality. Water may be reused for washing, rinsing, or conveying food if it does not increase the level of contamination of the food. Containers and carriers of raw materials should be inspected on receipt to ensure that their condition has not contributed to the contamination or deterioration of food.

(2) Raw materials and other ingredients shall either not contain levels of microorganisms that may produce food poisoning or other disease in humans, or they shall be pasteurized or otherwise treated during manufacturing operations so that they no longer contain levels that would cause the product to be adulterated within the meaning of the act. Compliance with this requirement may be verified by any effective means, including purchasing raw materials and other ingredients under a supplier's guarantee or certification.

(3) Raw materials and other ingredients susceptible to contamination with aflatoxin or other natural toxins shall comply with current Food and Drug Administration regulations, and action levels for poisonous or deleterious substances before these materials or ingredients are incorporated into finished food. Compliance with this requirement may be accomplished by purchasing raw materials and other ingredients under a supplier's guarantee or certification, or may be verified by analyzing these materials and ingredients for aflatoxins and other natural toxins.

(4) Raw materials, other ingredients, and rework susceptible to contamination with pests, undesirable microorganisms, or extraneous material shall comply with applicable Food and Drug Administration regulations, and defect action levels for natural or unavoidable defects if a manufacturer wishes to use the materials in manufacturing food. Compliance with this requirement may be verified by any effective means, including purchasing the materials under a supplier's guarantee or certification, or examination of these materials for contamination.

(5) Raw materials, other ingredients, and rework shall be held in bulk, or in containers designed and constructed so as to protect against contamination and shall be held at such temperature and relative humidity and in such a manner as to prevent the food from becoming adulterated within the meaning of the act. Material scheduled for rework shall be identified as such.

(6) Frozen raw materials and other ingredients shall be kept frozen. If thawing is required prior to use, it shall be done in a manner that prevents the raw materials and other ingredients from becoming adulterated within the meaning of the act.

(7) Liquid or dry raw materials and other ingredients received and stored in bulk form shall be held in a manner that protects against contamination.

(b) Manufacturing operations.

(1) Equipment and utensils and finished food containers shall be maintained in an acceptable condition through appropriate cleaning and sanitizing, as necessary. Insofar as necessary, equipment shall be taken apart for thorough cleaning.

(2) All food manufacturing, including packaging and storage, shall be conducted under such conditions and controls as are necessary to minimize the potential for the growth of microorganisms, or for the contamination of food. One way to comply with this requirement is careful monitoring of physical factors such as time, temperature, humidity, a_W, pH, pressure, flow rate, and manufacturing operations such as freezing, dehydration, heat processing, acidification, and refrigeration to ensure that mechanical breakdowns, time delays, temperature fluctuations, and other factors do not contribute to the decomposition or contamination of food.

(3) Food that can support the rapid growth of undesirable microorganisms, particularly those of public health significance, shall be held in a manner that prevents the food from becoming adulterated within the meaning of the act. Compliance with this requirement may be accomplished by any effective means, including:

(i) Maintaining refrigerated foods at 45 deg.F (7.2 deg.C) or below as appropriate for the particular food involved.

(ii) Maintaining frozen foods in a frozen state.

(iii) Maintaining hot foods at 140 deg.F (60 deg.C) or above.

(iv) Heat treating acid or acidified foods to destroy mesophilic microorganisms when those foods are to be held in hermetically sealed containers at ambient temperatures.

(4) Measures such as sterilizing, irradiating, pasteurizing, freezing, refrigerating, controlling pH or controlling pH or controlling a_W that are taken to destroy or prevent the growth of undesirable microorganisms, particularly those of public health significance, shall be adequate under the conditions of manufacture, handling, and distribution to prevent food from being adulterated within the meaning of the act.

(5) Work-in-process shall be handled in a manner that protects against contamination.

(6) Effective measures shall be taken to protect finished food from contamination by raw materials, other ingredients, or refuse. When raw materials, other ingredients, or refuse are unprotected, they shall not be handled simultaneously in a receiving, loading, or shipping area if that handling could result in contaminated food. Food transported by conveyor shall be protected against contamination as necessary.

(7) Equipment, containers, and utensils used to convey, hold, or store raw materials, work-in-process, rework, or food shall be constructed, handled, and maintained during manufacturing or storage in a manner that protects against contamination.

(8) Effective measures shall be taken to protect against the inclusion of metal or other extraneous material in food. Compliance with this requirement may be accomplished by using sieves, traps, magnets, electronic metal detectors, or other suitable effective means.

(9) Food, raw materials, and other ingredients that are adulterated within the meaning of the act shall be disposed of in a manner that protects against the contamination of other food. If the adulterated food is capable of being reconditioned, it shall be reconditioned using a method that has been proven to be effective or it shall be reexamined and found not to be adulterated within the meaning of the act before being incorporated into other food.

(10) Mechanical manufacturing steps such as washing, peeling, trimming, cutting, sorting and inspecting, mashing, dewatering, cooling, shredding, extruding, drying, whipping, defatting, and forming shall be performed so as to protect food against contamination. Compliance with this requirement may be accomplished by providing adequate physical protection of food from contaminants that may drip, drain, or be drawn into the food. Protection may be provided by

adequate cleaning and sanitizing of all food-contact surfaces, and by using time and temperature controls at and between each manufacturing step.

(11) Heat blanching, when required in the preparation of food, should be effected by heating the food to the required temperature, holding it at this temperature for the required time, and then either rapidly cooling the food or passing it to subsequent manufacturing without delay. Thermophilic growth and contamination in blanchers should be minimized by the use of adequate operating temperatures and by periodic cleaning. Where the blanched food is washed prior to filling, water used shall be safe and of adequate sanitary quality.

(12) Batters, breading, sauces, gravies, dressings, and other similar preparations shall be treated or maintained in such a manner that they are protected against contamination. Compliance with this requirement may be accomplished by any effective means, including one or more of the following:

(i) Using ingredients free of contamination.

(ii) Employing adequate heat processes where applicable.

(iii) Using adequate time and temperature controls.

(iv) Providing adequate physical protection of components from contaminants that may drip, drain, or be drawn into them.

(v) Cooling to an adequate temperature during manufacturing.

(vi)Disposing of batters at appropriate intervals to protect against the growth of microorganisms.

(13) Filling, assembling, packaging, and other operations shall be performed in such a way that the food is protected against contamination. Compliance with this requirement may be accomplished by any effective means, including:

(i) Use of a quality control operation in which the critical control points are identified and controlled during manufacturing.

(ii) Adequate cleaning and sanitizing of all food-contact surfaces and food containers.

(iii) Using materials for food containers and food- packaging materials that are safe and suitable, as defined in Sec. 130.3(d) of this chapter.

(iv) Providing physical protection from contamination, particularly airborne contamination.

(v) Using sanitary handling procedures.

(14) Food such as, but not limited to, dry mixes, nuts, intermediate moisture food, and dehydrated food, that relies on the control of aw for preventing the growth of undesirable microorganisms shall be processed to and maintained at a safe moisture level.

(15) Compliance with this requirement may be accomplished by any effective means, including employment of one or more of the following practices:

(i) Monitoring the a_W of food.

(ii) Controlling the soluble solids-water ratio in finished food.

(iii) Protecting finished food from moisture pickup, by use of a moisture barrier or by other means, so that the a_W of the food does not increase to an unsafe level.

(16) Food such as, but not limited to, acid and acidified food, that relies principally on the control of pH for preventing the growth of undesirable microorganisms shall be monitored and maintained at a pH of 4.6 or below. Compliance with this requirement may be accomplished by any effective means, including employment of one or more of the following practices:

(i) Monitoring the pH of raw materials, food in process, and finished food.

(ii) Controlling the amount of acid or acidified food added to low-acid food.

(17) When ice is used in contact with food, it shall be made from water that is safe and of adequate sanitary quality, and shall be used only if it has been manufactured in accordance with current good manufacturing practice as outlined in this part.

(18) Food-manufacturing areas and equipment used for manufacturing human food should not be used to manufacture nonhuman food-grade animal feed or inedible products, unless there is no reasonable possibility for the contamination of the human food.

[51 FR 24475, June 19, 1986, as amended at 65 FR 56479, Sept. 19, 2000]

110.93 Warehousing and distribution.

Storage and transportation of finished food shall be under conditions that will protect food against physical, chemical, and microbial contamination as well as against deterioration of the food and the container.

Subpart F-[Reserved]

Subpart G-Defect Action Levels

110.110 Natural or unavoidable defects in food for human use that present no health hazard.

(a) Some foods, even when produced under current good manufacturing practice, contain natural or unavoidable defects that at low levels are not hazardous to health. The Food and Drug Administration establishes maximum levels for these defects in foods produced under current good manufacturing practice and uses these levels in deciding whether to recommend regulatory action.

(b) Defect action levels are established for foods whenever it is necessary and feasible to do so. These levels are subject to change upon the development of new technology or the availability of new information.

(c) Compliance with defect action levels does not excuse violation of the requirement in section 402(a)(4) of the act that food not be prepared, packed, or held under unsanitary conditions or the requirements in this part that food manufacturers, distributors, and holders shall observe current good manufacturing practice. Evidence indicating that such a violation exists causes the food to be adulterated within the meaning of the act, even though the amounts of natural or unavoidable defects are lower than the currently established defect action levels. The manufacturer, distributor, and holder of food shall at all times utilize quality control operations that reduce natural or unavoidable defects to the lowest level currently feasible.

(d) The mixing of a food containing defects above the current defect action level with another lot of food is not permitted and renders the final food adulterated within the meaning of the act, regardless of the defect level of the final food.

(e) A compilation of the current defect action levels for natural or unavoidable defects in food for human use that present no health hazard may be obtained upon request from the Center for Food Safety and Applied Nutrition (HFS-565), Food and Drug Administration, 5100 Paint Branch Pkwy., Colege Park, MD 20740.

[51 FR 24475, June 19,1986, as amended at 61 CFR 14480, Apr. 2, 1996; 66 FR 56035, Nov. 6, 2001]

PART 210-CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374.
SOURCE: 43 FR 45076, Sept, 29, 1978, unless otherwise noted.

210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in Parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in Parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

210.2 Applicability of current good manufacturing practice regulations.

(a) The regulations in this part and in Parts 211 through 226 of this chapter as they may pertain to a drug and in Parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in Parts 211 through 226 and Parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

210.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in Parts 211 through 226 of this chapter.

(b) The following definitions of terms apply to this part and to Parts 211 through 226 of this chapter.

(1) Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 U.S.C. 301 et seq.).

(2) Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

(3) Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

(4) Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.

(5) Fiber means any particulate contaminant with a length at least three times greater than its width.

(6) Non-fiber-releasing filter means any filter, which after any appropriate pre-treatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos are deemed to be fiber-releasing filters.

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

(8) Inactive ingredient means any component other than an active ingredient.

(9) In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

(10) Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

(11) Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.

(12) Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products.

(13) The term medicated feed means any Type B or Type C medicated feed as defined in 558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of Part 225 of this chapter.

(14) The term medicated premix means a Type A medicated article as defined in 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of Part 226 of this chapter.

(15) Quality control unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

(16) Strength means:

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

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

(17) Theoretical yield means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

(18) Actual yield means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.

(19) Percentage of theoretical yield means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.

(20) Acceptance criteria means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(21) Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

(22) Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

[43 FR 45076, Sept. 29, 1978, as amended at 51 FR 7389, Mar. 3, 1986; 58 FR 41353, Aug. 3, 1993]

PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

AUTHORITY: 21 U.S.C. 321, 351, 352, 355, 360b, 371, 374.
SOURCE: 43 FR 45077, Sept. 29; 1978, unless otherwise noted.

Subpart A - General Provisions

211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter, as they pertain to drug products, and in Parts 600 through 680 of this chapter, as they pertain to biological products for human use, shall be considered to supplement, not supersede, the regulations in this part unless the regulations explicitly provide otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter or in Parts 600 through 680 of this chapter, the regulation specifically supersede the regulation in this part.

(c) Pending consideration of a proposed exemption, published in the FEDERAL REGISTER of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under Part 110 of this chapter, and where applicable, Parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.

[FR 45077, Sept. 29, 1978, as amended at 62 FR 66522, Dec. 19, 1997]

211.3 Definitions.

The definitions set forth in 210.3 of this chapter apply in this part.

Subpart B - Organization and Personnel

211.22 Responsibilities of quality control unit.

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

211.25 Personnel qualifications.

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

211.28 Personnel responsibilities.

(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.

(b) Personnel shall practice good sanitation and health habits.

(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

211.34 Consultants.

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C - Buildings and Facilities

211.42 Design and construction features.

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.

(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

(c) Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;

(2) Holding rejected components, drug product containers, closures, and labeling before disposition;

(3) Storage of released components, drug product containers, closures, and labeling;

(4) Storage of in-process materials;

(5) Manufacturing and processing operations;

(6) Packaging and labeling operations;

(7) Quarantine storage before release of drug products;

(8) Storage of drug products after release;

(9) Control and laboratory operations;

(10) Aseptic processing, which includes as appropriate:

(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;

(ii) Temperature and humidity controls;

(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;

(iv) A system for monitoring environmental conditions;

(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions;

(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

211.44 Lighting.

Adequate lighting shall be provided in all areas.

211.46 Ventilation, air filtration, air heating and cooling.

(a) Adequate ventilation shall be provided.

(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.

(c) Air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.

(d) Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

211.48 Plumbing.

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR Part 141. Water not meeting such standards shall not be permitted in the potable water system.

(b) Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back-siphonage.

[43 FR 45077, Sept. 29, 1978, as amended at 48 FR 11426, Mar. 18, 1983!]

211.50 Sewage and refuse.

Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

211.52 Washing and toilet facilities.

Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

211.56 Sanitation.

(a) Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.

(b) There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 135).

(d) Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

211.58 Maintenance.

Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Subpart D-Equipment

211.63 Equipment design, size, and location.

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

211.65 Equipment construction.

(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

211.67 Equipment cleaning and maintenance.

(a) Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

(1) Assignment of responsibility for cleaning and maintaining equipment;

(2) Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;

(3) A description in sufficient detail of the methods, equipment, and materials used in cleaning and mainte-

nance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;

(4) Removal or obliteration of previous batch identification;

(5) Protection of clean equipment from contamination prior to use;

(6) Inspection of equipment for cleanliness immediately before use.

(c) Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in 211.180 and 211.182.

211.68 Automatic, mechanical, and electronic equipment.

(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

211.72 Filters.

Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non-fiber-releasing filter of 0.22 micron maximum mean porosity (0.45 micron if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. Use of an asbestos-containing filter, with or without subsequent use of a specific non-fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the Food and Drug Administration that use of a non-fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the injectable drug product.

[51 FR 24475, June 19,1986, as amended at 61 CFR 14480, Apr. 2, 1996]

Subpart E - Control of Components and Drug Product Containers and Closures

211.80 General requirements.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.

(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.

(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.

(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

211.82 Receipt and storage of untested components, drug product containers, and closures.

(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.

(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of 211.80.

211.84 Testing and approval or rejection of components, drug product containers, and closures.

(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.

(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by 211.170.

(c) Samples shall be collected in accordance with the following procedures:

(1) The containers of components selected shall be cleaned where necessary, by appropriate means.

(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.

(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.

(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.

(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the data on which the sample was taken, and the name of the person who collected the sample.

(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.

(d) Samples shall be examined and tested as follows:

(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.

(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

(3) Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.

(4) When appropriate, components shall be microscopically examined.

(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.

(6) Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

[43 FR 45077, Sept. 29, 1978, as amended at 63 FR 14356, Mar. 25, 1998]

211.86 Use of approved components, drug product containers, and closures.

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

211.87 Retesting of approved components, drug product containers, and closures.

Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure.

211.89 Rejected components, drug product containers, and closures.

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.94 Drug product containers and closures.

(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

Subpart F-Production and Process Controls

211.100 Written procedures; deviations.

(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

(b) Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

211.101 Charge - in of components.

Written production and control procedures shall include the following, which are designed to assure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess:

(a) The batch shall be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient.

(b) Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information:

(1) Component name or item code;

(2) Receiving or control number;

(3) Weight or measure in new container;

(4) Batch for which component was dispensed, including its product name, strength, and lot number.

(c) Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to assure that:

(1) The component was released by the quality control unit;

(2) The weight or measure is correct as stated in the batch production records;

(3) The containers are properly identified.

(d) Each component shall be added to the batch by one person and verified by a second person.

211.103 Calculation of yield.

Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

211.105 Equipment identification.

(a) All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.

(b) Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation;

(2) Disintegration time;

(3) Adequacy of mixing to assure uniformity and homogeneity;

(4) Dissolution time and rate;

(5) Clarity, completeness, or pH of solutions.

(b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.

(c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

(d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.111 Time limitations on production.

When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

211.113 Control of microbiological contamination.

(a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

(b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

211.115 Reprocessing.

(a) Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics.

(b) Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G-Packaging and Labeling Control

211.122 Materials examination and usage criteria.

(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

(b) Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

(c) Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

(d) Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.

(e) Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

(f) Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape or color.

(g) If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:

(1) Dedication of labeling and packaging lines to each different strength of each different drug product;

(2) Use of appropriate electronic or electromechanical equipment to conduct a 100-percent examination for correct labeling during or after completion of finishing operations; or

(3) Use of visual inspection to conduct a 100-percent examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

(h) Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to assure that all imprinting conforms to the print specified in the batch production record.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41353, Aug. 3, 1993]

211.125 Labeling issuance.

(a) Strict control shall be exercised over labeling issued for use in drug product labeling operations.

(b) Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

(c) Procedures shall be utilized to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with 211.192. Labeling reconciliation is waived for cut or roll a labeling if a 100-percent examination for correct labeling is performed in accordance with 211.122(g)(2).

(d) All excess labeling bearing lot or control numbers shall be destroyed.

(e) Returned labeling shall be maintained and stored in a manner to prevent mixups and provide proper identification.

(f) Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

211.130 Packaging and labeling operations.

There shall be written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be followed. These procedures shall incorporate the following features:

(a) Prevention of mixups and cross-contamination by physical or spatial separation from operations on other drug products.

(b) Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.

(c) Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.

(d) Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.

(e) Inspection of the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

[43 FR 45077, Sept. 29, 1978, as amended at 58 FR 41354, Aug. 3, 1993]

211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

(a) General. The Food and Drug Administration has the authority under the Federal Food, Drug, and Cosmetic Act

(the act) to establish a uniform national requirement for tamper-evident packaging of OTC drug products that will improve the security of OTC drug packaging and help assure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or throat lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.

(b) Requirements for tamper-evident package.

(1) Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale shall package the product in a tamper-evident package, if this product is accessible to the public while held for sale. A tamper-evident package is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo or picture). For purposes of this section, the term "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper evident package may involve an immediate-container and closure system or secondary-container or carton system or any combination of systems intended to provide visual indication of package integrity. The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution and retail display.

(2) In addition to the tamper-evident packaging feature described in paragraph (b)(1) of this section, any two-piece, hard gelatin capsule, covered by this section must be sealed using an acceptable tamper-evident technology.

(c) Labeling.

(1) In order to alert consumers to the specific tamper-evident feature(s) used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampules, containers of compressed medical oxygen, or aerosol products that depend upon the power of liquefied or compressed gas to expel the contents from the container) is required to bear a statement that:

(i) Identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section;

(ii) Is prominently placed on the package; and

(iii) Is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.

(2) If the tamper-evident feature chosen to meet the requirements in paragraph (b) of this section uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say, "For your protection, this bottle has an imprinted seal around the neck."

(d) Request for exemptions from packaging and labeling requirements. A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for exemption is required to be submitted in the form of a citizen petition under 10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from the Tamper-Evident Packaging Rule". The petition is required to contain the following:

(1) The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class.

(2) The reasons that the drug product's compliance with the tamper-evident packaging or labeling requirements of this section is unnecessary or can't be achieved.

(3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration.

(4) Other information justifying an exemption.

(e) OTC drug products subject to approved new drug applications. Holders of approved new drug applications for OTC drug products are required under 314.70 of this chapter to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under 314. 70 of this chapter. Manufacturing changes by which capsules are to be sealed require prior FDA approval under 314. 70(b) of this chapter.

(f) Poison Prevention Packaging Act of 1970. This section does not affect any requirements for "special packaging" as defined under 310.3(l) of this chapter and required under the Poison Prevention Packaging Act of 19707.

(Approved by the Office of Management and Budget under OMB control number 0910-0149)
[54 FR 5228, Feb. 2, 1989, as amended at 63 FR 59470, Nov. 4, 1998]

211.134 Drug product inspection.

(a) Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.

(b) A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.

(c) Results of these examinations shall be recorded in the batch production or control records.

211.137 Expiration dating.

(a) To assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166.

(b) Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in 211.166.

(c) If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and unreconstituted drug products.

(d) Expiration dates shall appear on labeling in accordance with the requirements of 201.17 of this chapter.

(e) Homeopathic drug products shall be exempt from the requirements of this section.

(f) Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

(g) New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.

(h) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981; 60 FR 4091, Jan. 20, 1995]

Subpart H - Holding and Distribution

211.142 Warehousing procedures.

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

211.150 Distribution procedures.

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

(a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

(b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart I - Laboratory Controls

211.160 General requirements.

(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

211.165 Testing and release for distribution.

(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing con-

ducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

211.166 Stability testing.

(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods;

(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;

(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.

(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt from the requirements of this section.

[43 FR 45077, Sept. 29, 1978, as amended at 46 FR 56412, Nov. 17, 1981]

211.167 Special testing requirements.

(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.

(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.

(c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

211.170 Reserve samples.

(a) An appropriately identified shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:

(1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.

(2) For an active ingredient in a radioactive drug product, except for non-radioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.

(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.

(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical

procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve samples. Any evidence of reserve sample deterioration shall be investigated in accordance with 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.

(2) For a radioactive drug product, except for non-radioactive reagent kits, the reserve sample shall be retained for:

(i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or

(ii) Six months after the expiration date of the drug product if the expiration more than 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

[48 FR 13025, Mar. 29, 1983, as amended at 60 FR 4091, Jan 20, 1995]

211.173 Laboratory animals.

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

211.176 Penicillin contamination.

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD-470), Center for Drug Evaluation and Research, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the Office of the Federal Register, 800 North Capitol Street, NW, Suite 700, Washington, DC 20408.

[43 FR 45077, Sept. 29, 1978, as amended at 47 FR 9396, Mar. 5, 1982; 50 FR 8996, Mar. 6, 1985; 55 FR 11577, Mar. 29, 1990, Nov 6, 2001]

Subpart J - Records and Reports

211.180 General requirements.

(a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch.

(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.

(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.

(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

(1) A review of representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under 211.192 for each drug product.

(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.

[43 FR 45077, Sept. 29, 1978, as amended at 60 FR 4091, Jan. 20, 1995]

211.182 Equipment cleaning and use log.

A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to man-

ufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

211.184 Component, drug product container, closure, and labeling records.

These records shall include the following:

(a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.

(b) The results of any test or examination performed (including those performed as required by 211.82(a), 211.84(d), or 211.122(a)) and the conclusions derived therefrom.

(c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.

(d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with 211.122(c) and 211.130(c).

(e) The disposition of rejected components, drug product containers, closure, and labeling.

211.186 Master production and control records.

(a) To assure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.

(b) Master production and control records shall include:

(1) The name and strength of the product and a description of the dosage form;

(2) The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit;

(3) A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic;

(4) An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records;

(5) A statement concerning any calculated excess of component;

(6) A statement of theoretical weight or measure at appropriate phases of processing;

(7) A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 211.192 is required;

(8) A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling;

(9) Complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed.

211.188 Batch production and control records.

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

(a) An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed;

(b) Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:

(1) Dates;

(2) Identity of individual major equipment and lines used;

(3) Specific identification of each batch of component or in-process material used;

(4) Weights and measures of components used in the course of processing;

(5) In-process and laboratory control results;

(6) Inspection of the packaging and labeling area before and after use;

(7) A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing;

(8) Complete labeling control records, including specimens or copies of all labeling used;

(9) Description of drug product containers and closures;

(10) Any sampling performed;

(11) Identification of the persons performing and directly supervising or checking each significant step in the operation;

(12) Any investigation made according to 211.192.

(13) Results of examinations made in accordance with 211.134.

211.192 Production record review.

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures

before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow up.

211.194 Laboratory records.

(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

(2) A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopoeia, National Formulary, Association of Official Analytical Chemists, Book of Methods**, or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

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

(3) A statement of the weight or measure of sample used for each test, where appropriate.

(4) A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.

(5) A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.

(6) A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.

(7) The initials or signature of the person who performs each test and the date(s) the tests were performed.

(8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

(b) Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

(c) Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

(d) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by 211.160(b)(4).

(e) Complete records shall be maintained of all stability testing performed in accordance with 211.166.

[43 FR 45077, Sept. 29, 1978, as amended at 55 FR 11577, Mar. 29, 1990; 65 FR 1889, APR 10,2000]

211.196 Distribution records.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

(Approved by the Office of Management and Budget under control number 0910 0139) [49 FR 9865, Mar. 16, 1984]

211.198 Complaint files.

(a) Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with 310.305 and 514.80 of this chapter.

(b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, such written records shall be maintained for 3 years after distribution of the drug product.

(1) The written record shall include the following information, where known: the name and strength of the drug

product, lot number, name of complainant, nature of complaint, and reply to complainant.

(2) Where an investigation under 211.192 is conducted, the written record shall include the findings of the investigation and follow up. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with 211.180(c).

(3) Where an investigation under 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

[43 FR 45077, Sept. 29, 1978, as amended at 51 FR 24479, July 3, 1986]

EFFECTIVE DATE NOTE: At 68 FR 15364, Mar.31, 2003, 211.198 was amended in paragraph (a) in the last sentence by removing "in accordance with 310.305 of this chapter" and adding in its place "in accordance with 310.305 and 514.80 of this chapter," effective June 30,2003.

Subpart K - Returned and Salvaged Drug Products

211.204 Returned drug products.

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

211.208 Drug product salvaging.

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

PART 225 - CURRENT GOOD MANUFACTURING PRACTICE FOR MEDICATED FEEDS

AUTHORITY: 21 U.S.C. 351, 352 360b, 371, 374.
SOURCE: 41 FR 52618, Nov. 30, 1976, unless otherwise noted.

Subpart A-General Provisions

225.1 Current good manufacturing practice.

(a) Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act provides that a drug (including a drug contained in a medicated feed) shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirement of the act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

(b)(1) The provisions of this part set forth the criteria for determining whether the manufacture of a medicated feed is in compliance with current good manufacturing practice. These regulations shall apply to all types of facilities and equipment used in the production of medicated feeds, and they shall also govern those instances in which failure to adhere to the regulations has caused non-medicated feeds that are manufactured, processed, packed, or held to be adulterated. In such cases, the medicated feed shall be deemed to be adulterated within the meaning of section 501(a)(2)(B) of the act, and the non-medicated feed shall be deemed to be adulterated within the meaning of section 402(a)(2)(D) of the act.

(2) The regulations in 225.10 through 225.115 apply to facilities manufacturing one or more medicated feeds for which an approved medicated feed application is required. The regulations in 225.120 through 225.202 apply to facilities manufacturing solely medicated feeds for which an approved license is not required.

(c) In addition to the recordkeeping requirements in this part, Type B and Type C medicated feeds made from Type A articles or Type B feeds under approved NADA's and a medicated feed mill license are subject to the requirements of § 510.301 of this chapter.

[41 FR 52618, Nov. 30, 1976, as amended at 51 FR 7389, Mar. 3, 1986; 64 FR 63203, Nov. 19, 1999]

225.10 Personnel.

(a) Qualified personnel and adequate personnel training and supervision are essential for the proper formulation, manufacture, and control of medicated feeds. Training and experience leads to proper use of equipment, maintenance of accurate records, and detection and prevention of possible deviations from current good manufacturing practices.

(b)(1) All employees involved in the manufacture of medicated feeds shall have an understanding of the manufacturing or control operation(s) which they perform, including the location and proper use of equipment.

(2) The manufacturer shall provide an on-going program of evaluation and supervision of employees in the manufacture of medicated feeds.

[41 FR 52618, Nov. 30, 1976, as amended at 42 FR 12426, Mar. 4, 1977]

Subpart B - Construction and Maintenance of Facilities and Equipment

225.20 Buildings.

(a) The location, design, construction, and physical size of the buildings and other production facilities are factors important to the manufacture of medicated feed. The features of facilities necessary for the proper manufacture of medicated feed include provision for ease of access to structures and equipment in need of routine maintenance; ease of cleaning of equipment and work areas; facilities to promote personnel hygiene; structural conditions for control and prevention of vermin and pest infestation; adequate space for the orderly receipt and storage of drugs and feed ingredients and the controlled flow of these materials through the processing and manufacturing operations; and the equipment for the accurate packaging and delivery of a medicated feed of specified labeling and composition.

(b) The construction and maintenance of buildings in which medicated feeds are manufactured, processed, packaged, labeled, or held shall conform to the following:

(1) The building grounds shall be adequately drained and routinely maintained so that they are reasonably free from litter, waste, refuse, uncut weeds or grass, standing water, and improperly stored equipment.

(2) The building(s) shall be maintained in a reasonably clean and orderly manner.

(3) The building(s) shall be of suitable construction to minimize access by rodents, birds, insects, and other pests.

(4) The buildings shall provide adequate space and lighting for the proper performance of the following medicated feed manufacturing operations:

(i)The receipt, control, and storage of components.

(ii) Component processing.

(iii) Medicated feed manufacturing.

(iv) Packaging and labeling.

(v) Storage of containers, packaging materials, labeling and finished products.

(vi) Routine maintenance of equipment.

225.30 Equipment.

(a) Equipment which is designed to perform its intended function and is properly installed and used is essential to the manufacture of medicated feeds. Such equipment permits production of feeds of uniform quality, facilitates cleaning, and minimizes spillage of drug components and finished product.

(b)(1) All equipment shall possess the capability to produce a medicated feed of intended potency, safety, and purity.

(2) All equipment shall be maintained in a reasonably clean and orderly manner.

(3) All equipment, including scales and liquid metering devices, shall be of suitable size, design, construction, precision, and accuracy for its intended purpose.

(4) All scales and metering devices shall be tested for accuracy upon installation and at least once a year thereafter, or more frequently as may be necessary to insure their accuracy.

(5) All equipment maintained as to prevent lubricants and coolants from becoming unsafe additives in feed components or medicated feed.

(6) All equipment shall be designed, constructed, installed and maintained so as to facilitate inspection and use of clean out procedure(s).

225.35 Use of work areas, equipment, and storage areas for other manufacturing and storage purpose.

(a) Many manufacturers of medicated feeds are also involved in the manufacture, storage, or handling of products which are not intended for animal feed use, such as fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides. Manufacturing, storage, or handling of non-feed and feed products in the same facilities may cause adulteration of feed products with toxic or otherwise unapproved feed additives.

(b) Work areas and equipment used for the manufacture or storage of medicated feeds or components thereof shall not be used for, and shall be physically separated from, work areas and equipment used for the manufacture of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides unless such articles are approved drugs or approved food additives intended for use in the manufacture of medicated feed.

Subpart C-Product Quality Control

225.42 Components.

(a) A medicated feed, in addition to providing nutrients, is a vehicle for the administration of a drug, or drugs, to animals. To ensure proper safety and effectiveness, such medicated feeds must contain the labeled amounts of drugs. It is necessary that adequate procedures be established for the receipt, storage, and inventory control for all such drugs to aid in assuring their identity, strength, quality, and purity when incorporated into products.

(b) The receipt, storage, and inventory of drugs, including undiluted drug components, medicated premixes, and semi-processed (i.e., intermediate premixes, in plant premixes and concentrates) intermediate mixes containing drugs, which are used in the manufacture and processing

of medicated feeds shall conform to the following:

(1) Incoming shipments of drugs shall be visually examined for identity and damage. Drugs which have been subjected to conditions which may have adversely affected their identity, strength, quality, or purity shall not be accepted for use.

(2) Packaged drugs in the storage areas shall be stored in their original closed containers.

(3) Bulk drugs shall be identified and stored in a manner such that their identity, strength, quality, and purity will be maintained.

(4) Drugs in the mixing areas shall be properly identified, stored, handled, and controlled to maintain their integrity and identity. Sufficient space shall be provided for the location of each drug.

(5) A receipt record shall be prepared and maintained for each lot of drug received. The receipt record shall accurately indicate the identity and quantity of the drug, the name of the supplier, the supplier's lot number or an identifying number assigned by the feed manufacturer upon receipt which relates to the particular shipment, the date of receipt, the condition of the drug when received, and the return of any damaged drugs.

(6) A daily inventory record for each drug used shall be maintained and shall list by manufacturer's lot number or the feed manufacturer's shipment identification number at least the following information:

(i) The quantity of drug on hand at the beginning and end of the work day (the beginning amount being the same as the previous day's closing inventory if this amount has been established to be correct); the quantity shall be determined by weighing, counting, or measuring, as appropriate.

(ii) The amount of each drug used, sold, or otherwise disposed of.

(iii) The batches or production runs of medicated feed in which each drug was used.

(iv) When the drug is used in the preparation of a semi-processed intermediate mix intended for use in the manufacture of medicated feed, any additional information which may be required for the purpose of paragraph (b)(7) of this section.

(v) Action taken to reconcile any discrepancies in the daily inventory record.

(7) Drug inventory shall be maintained of each lot or shipment of drug by means of a daily comparison of the actual amount of drug used with the theoretical drug usage in terms of the semi-processed, intermediate and finished medicated feeds manufactured. Any significant discrepancy shall be investigated and corrective action taken. The medicated feed(s) remaining on the premises which are affected by this discrepancy shall be detained until the discrepancy is reconciled.

(8) All records required by this section shall be maintained on the premises for at least one year after complete use of a drug component of a specific lot number or feed manufacturer's shipment identification number.

225.58 Laboratory controls.

(a) The periodic assay of medicated feeds for drug components provides a measure of performance of the manufacturing process in manufacturing a uniform product of intended potency.

(b) The following assay requirements shall apply to medicated feeds:

(1) For feeds requiring approved Medicated Feed Applications (Form FDA 3448) for their manufacture and marketing, at least three representative samples of medicated feed containing each drug or drug combination used in the establishment shall be collected and assayed by approved official methods, at periodic intervals during the calendar year, unless otherwise specified in this chapter. At least one of these assays shall be performed on the first batch using the drug. If a medicated feed contains a combination of drugs, only one of the drugs need be subject to analysis each time, provided the one tested is different from the one(s) previously tested.

(2) Reserved

(c) The originals or copies of all results of assays, including those from State feed control officials and any other governmental agency, shall be maintained on the premises for a period of not less than 1 year after distribution of the medicated feed. The results of assays performed by State feed control officials may be considered toward fulfillment of the periodic assay requirements of this section.

(d) Where the results of assays indicate that the medicated feed is not in accord with label specifications or is not within permissible assay limits as specified in this chapter, investigation and corrective action shall be implemented and an original or copy of the record of such action maintained on the premises.

(e) Corrective action shall include provisions for discontinuing distribution where the medicated feed fails to meet the labeled drug potency. Distribution of subsequent production of the particular feed shall not begin until it has been determined that proper control procedures have been established.

[41 FR 52618, Nov. 30, 1976, as amended at 51 FR 7390, Mar. 3, 1986; 55 FR 11577, Mar. 29, 1990;64FR 63203, Nov.19,1999]

225.65 Equipment cleanout procedures.

(a) Adequate clean out procedures for all equipment used in the manufacture and distribution of medicated feeds are essential to maintain proper drug potency and avoid unsafe contamination of feeds with drugs. Such procedures may consist of cleaning by physical means, e.g., vacuuming, sweeping, washing, etc. Alternatively, flushing or sequencing or other equally effective techniques may be used whereby the equipment is cleaned either through use of a feed containing the same drug(s) or through use of drug free feedstuffs.

(b) All equipment, including that used for storage, processing, mixing, conveying, and distribution that comes in contact with the active drug component, feeds in process, or finished medicated feed shall be subject to all reasonable and effective procedures to prevent unsafe contamination of manufactured feed. The steps used to prevent unsafe contamination of feeds shall include one or more of the following, or other equally effective procedures:

(1) Such procedures shall, where appropriate, consist of physical means (vacuuming, sweeping, or washing), flushing, and/or sequential production of feeds.

(2) If flushing is utilized, the flush material shall be properly identified, stored, and used in a manner to prevent unsafe contamination of other feeds.

(3) If sequential production of medicated feeds is utilized, it shall be on a predetermined basis designed to prevent unsafe contamination of feeds with residual drugs.

Subpart D - Packaging and Labeling

225.80 Labeling.

(a) Appropriate labeling identifies the medicated feed, and provides the user with directions for use which, if adhered to, will assure that the article is safe and effective for its intended purposes.

(b)(1) Labels and labeling, including placards, shall be received, handled, and stored labeling mixups and assures that correct labeling is employed for the medicated feed.

(2) Labels and labeling, including placards, upon receipt from the printer shall be proofread against the Master Record File to verify their suitability and accuracy. The proofread label shall be dated, initialed by a responsible individual, and kept for 1 year after all the labels from that batch have been used.

(3) In those instances where medicated feeds are distributed in bulk, complete labeling shall accompany the shipment and be supplied to the consignee at the time of delivery. Such labeling may consist of a placard or other labels attached to the invoice or delivery ticket, or manufacturer's invoice that identifies the medicated feed and includes adequate information for the safe and effective use of the medicated feed.

(4) Label stock shall be reviewed periodically and discontinued labels shall be discarded.

Subpart E-Records and Reports

225.102 Master record file and production records.

(a) The Master Record File provides the complete procedure for manufacturing a specific product, setting forth the formulation, theoretical yield, manufacturing procedures, assay requirements, and labeling of batches or production runs. The production record(s) includes the complete history of a batch or production run. This record includes the amounts of drugs used, the amount of medicated feed manufactured, and provides a check for the daily inventory record of drug components.

(b) The Master Record File and production records shall comply with the following provisions:

(1) A Master Record File shall be prepared, checked, dated, and signed or initialed by a qualified person and shall be retained for not less than 1 year after production of the last batch or production run of medicated feed to which it pertains. The Master Record File or card shall include at least the following:

(i) The name of the medicated feed.

(ii) The name and weight percentage or measure of each drug or drug combination and each non-drug ingredient to be used in manufacturing a stated weight of the medicated feed.

(iii) A copy or description of the label or labeling that will accompany the medicated feed.

(iv) Manufacturing instructions or reference thereto that have been determined to yield a properly mixed medicated feed of the specified formula for each medicated feed produced on a batch or continuous operation basis, including mixing steps, mixing times and, in the case of medicated feeds produced by continuous production run, any additional manufacturing directions including, when indicated, the settings of equipment.

(v) Appropriate control directions or reference thereto, including the manner and frequency of collecting the required number of samples for specified laboratory assay.

(2) The original production record or copy thereof shall be prepared by qualified personnel for each batch or run of medicated feed produced and shall be retained on the premises for not less than 1 year. The production record shall include at least the following:

(i) Product identification, date of production, and a written endorsement in the form of a signature or initials by a responsible individual.

(ii) The quantity and name of drug components used.

(iii) The theoretical quantity of medicated feed to be produced.

(iv) The actual quantity of medicated feed produced. In those instances where the finished feed is stored in bulk and actual yield cannot be accurately determined, the firm shall estimate the quantity produced and provide the basis for such estimate in the Master Record File.

(3) In the case of a custom formula feed made to the specifications of a customer, the Master Record File and production records required by this section shall consist either of such records or of copies of the customer's purchase orders and the manufacturer's invoices bearing the information required by this section. When a custom order is received by telephone, the manufacturer shall prepare the required production records.

(4) Batch production records shall be checked by a responsible individual at the end of the working day in which the product was manufactured to determine whether all required production steps have been performed. If significant discrepancies are noted, an investigation shall be instituted immediately, and the production record shall describe the corrective action taken.

(5) Each batch or production run of medicated feed shall be identified with its own individual batch or production run number, code, date, or other suitable identification applied to the label, package, invoice or shipping document. This identification shall permit the tracing of the complete and accurate manufacturing history of the product by the manufacturer.

225.110 Distribution records.

(a) Distribution records permit the manufacturer to relate complaints to specific batches and/or production runs of medicated feed. This information may be helpful in instituting a recall.

(b) Distribution records for each shipment of a medicated feed shall comply with the following provisions:

(1) Each distribution record shall include the date of shipment, the name and address of purchaser, the quantity shipped, and the name of the medicated feed. A lot or control number, or date of manufacture or other suitable identification shall appear on the distribution record or the label issued with each shipment.

(2) The originals or copies of the distribution records shall be retained on the premises for not less than one year after the date of shipment of the medicated feed.

225.115 Complaint files.

(a) Complaints and reports of experiences of product defects relative to the drug's efficacy or safety may provide an indicator as to whether or not medicated feeds have been manufactured in conformity with current good manufacturing practices. These complaints and experiences may reveal the existence of manufacturing problems not otherwise detected through the normal quality control procedures. Timely and appropriate follow-up action can serve to correct a problem and minimize future problems.

(b) The medicated feed manufacturer shall maintain on the premises a file which contains the following information:

(1) The original or copy of a record of each oral and written complaint received relating to the safety and effectiveness of the product produced. The record shall include the date of the complaint, the complainant's name and address, name and lot or control number or date of manufacture of the medicated feed involved, and the specific details of the complaint. This record shall also include all correspondence from the complainant and/or memoranda of conversations with the complainant, and a description of all investigations made by the manufacturer and of the method of disposition of the complaint.

(2) For medicated feeds whose manufacture require a feed mill license (Form FDA 3448), records and reports of clinical and other experience with the drug shall be maintained and reported, under section 510.301 of this chapter.

[41 FR 52618, Nov. 30, 1976, as amended at 51 FR 7390, Mar. 3, 1986; 57 FR 6475, Feb. 25, 1992; 64 FR 63203, Nov.19,1999]

Subpart F - Facilities and Equipment

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

225.120 Buildings and grounds.

Buildings used for production of medicated feed shall provide adequate space for equipment, processing, and orderly receipt and storage of medicated feed. Areas shall include access for routine maintenance and cleaning of equipment. Buildings and grounds shall be constructed and maintained in a manner to minimize vermin and pest infestation.

225.130 Equipment.

Equipment shall be capable of producing a medicated feed of intended potency and purity, and shall be maintained in a reasonably clean and orderly manner. Scales and liquid metering devices shall be accurate and of suitable size, design, construction, precision, and accuracy for their intended purposes. All equipment shall be designed, constructed, installed, and maintained so as to facilitate inspection and use of clean out procedure(s).

225.135 Work and storage areas.

Work areas and equipment used for the production or storage of medicated feeds or components thereof shall not be used for, and shall be physically separated from, work areas and equipment used for the manufacture and storage of fertilizers, herbicides, insecticides, fungicides, rodenticides, and other pesticides unless such articles are approved for use in the manufacture of animal feed.

Subpart G - Product Quality Assurance

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

225.142 Components.

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

225.158 Laboratory assays.

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

225.165 Equipment clean out procedures.

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

Subpart H - Labeling

225.180 Labeling.

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

[51 FR 7390, Mar. 3, 1986]

Subpart I - Records

225.202 Formula, production, and distribution records.

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

(Approved by the Office of Management and Budget under control number 0910- 0152) [51 FR 7390, Mar. 3, 1986]

226 - CURRENT GOOD MANUFACTURING PRACTICE FOR TYPE A MEDICATED ARTICLES

AUTHORITY: 21 U.S.C. 351, 352, 360b, 371, 374.
SOURCE: 40 FR 14031, Mar. 27, 1975, unless otherwise noted. Editorial Note: Nomenclature change to Part 226 appears at 51 FR 7390, Mar. 3, 1986.

Subpart A - General Provisions

226.1 Current good manufacturing practice.

The criteria in 226.10 through 226.115, inclusive, shall apply in determining whether the methods used in, or the facilities and controls used for the manufacture, processing, packing, or holding of a Type A medicated article(s) conform to or are operated or administered in conformity with current good manufacturing practice to assure that a Type A medicated article(s) meets the requirements of the act as to safety, and has the identity and strength, and meets the quality and purity characteristics which it purports or is represented to possess, as required by section 501(a) (2)(B) of the act. The regulations in this Part 226 permit the use of precision, automatic, mechanical, or electronic equipment in the production of a Type A medicated article(s) when adequate inspection and checking procedures or other quality control procedures are used to assure proper performance.

Effective Date Note: At 68 FR 15364, Mar. 31, 2003, Sec. 226.1 was amended by redesignating the existing text as paragraph (a) and by adding paragraph (b), effective June 30, 2003. For the convenience of the user, the added text is set forth as follows:

Sec. 226.1 Current good manufacturing practice.

* * * * *

(b) In addition to maintaining records and reports required in this part, Type A medicated articles requiring approved NADAs are subject to the requirements of Sec. 514.80 of this chapter.

226.10 Personnel.

The key personnel and any consultants involved in the manufacture and control of the Type A medicated article(s) shall have a background of appropriate education or appropriate experience or combination thereof for assuming responsibility to assure that the Type A medicated article(s) has the proper labeling and the safety, identity, strength, quality, and purity that it purports to possess.

Subpart B - Construction and Maintenance of Facilities and Equipment

226.20 Buildings.

Buildings in which Type A medicated article(s) are manufactured, processed, packaged, labeled, or held shall be maintained in a clear and orderly manner and shall be of suitable size, construction and location in relation to surroundings to facilitate maintenance and operation for their intended purpose. The building shall:

(a) Provide adequate space for the orderly placement of equipment and materials used in any of the following operations for which they are employed to minimize risk of mixups between different Type A medicated article(s), their components, packaging, or labeling:

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

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

(3) Packaging and labeling operations.

(4) Storage of containers, packaging materials, labeling, and finished products.

(5) Control laboratory operations.

(b) Provide adequate lighting and ventilation, and when necessary for the intended production or control purposes, adequate screening, dust and temperature controls, to avoid contamination of Type A medicated article(s), and to avoid other conditions unfavorable to the safety, identity, strength, quality, and purity of the raw materials and Type A medicated article(s) before, during, and after production.

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

Work areas and equipment used for the production of Type A medicated article(s) or for the storage of the components of Type A medicated article(s) shall not be used for the production, mixing or storage of finished or unfinished insecticides, fungicides, rodenticides, or other pesticides or their components unless such materials are recognized as approved drugs intended for use in animal feeds.

226.30 Equipment.

Equipment used for the manufacture, processing, packaging, bulk shipment, labeling, holding, or control of Type A medicated article(s) or their components shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction, and location to facilitate maintenance and operation for its intended purpose. The equipment shall:

(a) Be so constructed that any surfaces that come into contact with Type A medicated article(s) are suitable, in that they are not reactive, additive, or absorptive to an extent that significantly affects the identity, strength, quality, or purity of the Type A medicated article(s) or its components.

(b) Be so constructed that any substance required for the operation of the equipment, such as lubricants, coolants, etc., may be employed without hazard of becoming an unsafe additive to the Type A medicated article(s).

(c) Be constructed to facilitate adjustment, cleaning, and maintenance, and to assure uniformity of production and reliability of control procedures and to assure the exclusion from Type A medicated article(s) of contamination, including cross-contamination from manufacturing operations.

(d) Be suitably grounded electrically to prevent lack of uniform mixing due to electrically charged particles.

(e) Be of suitable size and accuracy for use in any intended measuring, mixing, or weighing operations.

Subpart C - Product Quality Control

226.40 Production and control procedures.

Production and control procedures shall include all reasonable precautions, including the following, to assure that the Type A medicated article(s) produced have the identity, strength, quality, and purity they purport to possess:

(a) Each critical step in the process, such as the selection, weighing, and measuring of components; the addition of drug components during the process; weighing and measuring during various stages of the processing; and the determination of the finished yield, shall be performed by one or more competent, responsible individuals. If such are controlled by precision, automatic, mechanical, or electronic equipment, their proper performance shall be adequately checked by one or more competent, responsible individuals.

(b) All containers to be used for undiluted drugs, drug components, intermediate mixtures thereof, and Type A medicated article(s) shall be received, adequately identified, and properly stored and handled in a manner adequate to avoid mixups and contamination.

(c) Equipment, including dust-control and other equipment, such as that used for holding and returning recovered or flush-out materials back into production, shall be maintained and operated in a manner to avoid contamination of the Type A medicated article(s) and to insure the integrity of the finished product.

(d) Competent and responsible personnel shall check actual against theoretical yield of a batch of Type A medicated article(s), and, in the event of any significant discrepancies, key personnel shall prevent distribution of the batch in question and other associated batches of Type A medicated article(s) that may have been involved in a mixup with it.

(e) Adequate procedures for cleaning of those parts of storage, mixing conveying and other equipment coming in contact with the drug component of the Type A medicated article(s) shall be used to avoid contamination of Type A medicated article(s).

(f) If there is sequential production of batches of a Type A medicated article(s) containing the same drug component (or components) at the same or lower levels, there shall be sufficient safeguards to avoid any build up above the specified levels of the drug components in any of the batches of the Type A medicated article(s).

(g) Production and control procedures shall include provision for discontinuing distribution of any Type A medicated article(s) found by the assay procedures, or other controls performed to fail to conform to appropriate specifications. Distribution of subsequent production of such Type A medicated article(s) shall not begin until it has been determined that proper control procedures have been established.

226.42 Components.

(a) Drug components, including undiluted drugs and any intermediate mixes containing drugs used in the manufacture and processing of Type A medicated article(s), shall be received, examined or tested, stored, handled, and otherwise controlled in a manner to maintain the integrity and identification of such articles. Appropriate receipt and inventory records shall be maintained for 2 years, and such records shall show the origin of any drug components, the manufacturer's control number (if any), the dates and batches in which they were used, and the results of any testing of them.

(b) Non-drug components shall be stored and otherwise handled in a manner to avoid contamination, including cross-contamination from manufacturing operations.

226.58 Laboratory controls.

Laboratory controls shall include the establishment of adequate specifications and test procedures to assure that the drug components and the Type A medicated article(s) conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(a) The establishment of master records containing appropriate specifications and a description of the test procedures used to check them for each kind of drug component used in the manufacture of Type A medicated article(s). This may consist of the manufacturer's or supplier's statement of specifications and methods of analyses.

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

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

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

(2) In the case of Type A medicated article(s) which are manufactured by dilution of Type A medicated article(s) assayed in accordance with paragraph (c)(1) of this section, each batch shall be assayed for its drug component(s) with the first five consecutive batches assaying within the limitations, followed thereafter by assay of representative samples of not less than 5 percent of all batches produced. When any batch does not assay within limitations, each batch should again be assayed until five consecutive batches are within limitations.

(d) A determination establishing that the drug components remain uniformly dispersed and stable in the Type A medicated article(s) under ordinary conditions of shipment, storage, and use. This may consist of a determination on a Type A medicated article(s) of substantially the same formula and characteristics. Suitable expiration dates shall appear on the labels of the Type A medicated article(s) to assure that the articles meet the appropriate standards of

identity, strength, quality, and purity at the time of use.

(e) Adequate provision to check the reliability, accuracy, and precision of any laboratory test procedure used. The official methods in "Methods of Analysis of the Association of Official Analytical Chemists,"** methods described in an official compendium, and any method submitted as a part of a food additive petition or new-drug application that has been accepted by the Food and Drug Administration shall be regarded as meeting this provision.

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

(f) Provisions for the maintenance of the results of any assays, including dates and endorsement of analysts. Such records shall be retained in the possession of the manufacturer and shall be maintained for a period of at least 2 years after distribution by the manufacturer of the Type A medicated article(s) has been completed.

[40 FR 14031, Mar. 27, 1975, as amended at 55 FR 11577, Mar. 29, 1990 5; 55 FR 23703, June 12, 1990]

Subpart D-Packaging and Labeling

226.80 Packaging and labeling.

(a) Packaging and labeling operations shall be adequately controlled:

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

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

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

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

(b) Packaging and labeling operations shall provide:

(1) For storage of labeling in a manner to avoid mixups.

(2) For careful checking of labeling for identity and conformity to the labeling specified in the batch-production records.

(3) For adequate control of the quantities of labeling issued for use with the Type A medicated article(s).

(c) Type A medicated article(s) shall be distributed in suitable containers to insure the safety, identity, strength, and quality of the finished product.

Subpart E - Records and Reports

226.102 Master-formula and batch-production records.

(a) For each Type A medicated article(s) master-formula records shall be prepared, endorsed, and dated by a competent and responsible individual and shall be independently checked, reconciled, endorsed, and dated by a second competent and responsible individual. The record shall include:

(1) The name of the Type A medicated article(s) and a specimen copy of its label.

(2) The weight or measure of each ingredient, adequately identified, to be used in manufacturing a stated weight of the Type A medicated article(s).

(3) A complete formula for each batch size, or of appropriate size in the case of continuous systems to be produced from the master-formula record, including a complete list of ingredients designated by names or codes sufficiently specific to indicate any special quality characteristics; an accurate statement of the weight or measure of each ingredient, except that reasonable variations may be permitted in the amount of ingredients necessary in the preparation of the Type A medicated article(s), provided that the variations are stated in the master formula; an appropriate statement concerning any calculated excess of an ingredient; and a statement of the theoretical yield.

(4) Manufacturing instructions for each type of Type A medicated article(s) produced on a batch or continuous operation basis, including mixing steps and mixing times that have been determined to yield an the case of Type A medicated article(s) produced by continuous production run, any additional manufacturing directions including, when indicated, the settings of equipment that have been determined to yield an adequately mixed Type A medicated article(s) of the specified formula.

(5) Control instructions, procedures, specifications, special notations, and precautions to be followed.

(b) A separate batch-production and control record shall be prepared for each batch or run of Type A medicated article(s) produced and shall be retained for at least 2 years after distribution by the manufacturer has been completed. The batch-production and control record shall include:

(1) Product identification, date of production, and endorsement by a competent and responsible individual.

(2) Records of each step in the manufacturing, packaging, labeling, and controlling of the batch, including dates, specific identification of drug components used, weights or measures of all components, laboratory-control results, mixing times, and the endorsements of the individual actively performing or the individual actively supervising or checking each step in the operation.

(3) A batch number that permits determination of all laboratory-control procedures and results on the batch and all lot or control numbers appearing on the labels of the Type A medicated article(s).

226.110 Distribution records.

Complete records shall be maintained for each shipment of Type A medicated article(s) in a manner that will facilitate the recall, diversion, or destruction of the Type A medicated article(s), if necessary. Such records shall be retained for at least 2 years after the date of the shipment by the manufacturer and shall include the name and address of the consignee, the date and quantity shipped, and the manufacturing dates, control numbers, or marks identifying the Type A medicated article(s) shipped.

226.115 Complaint files.

Records shall be maintained for a period of 2 years of all written or verbal complaints concerning the safety or effica-

cy of each Type A medicated article(s). Complaints shall be evaluated by competent and responsible personnel and, where indicated, appropriate action shall be taken. The record shall indicate the evaluation and the action.

PART 589 - SUBSTANCES PROHIBITED FROM USE IN ANIMAL FOOD OR FEED

AUTHORITY: 21 U.S.C. 321, 342, 343, 348, 371

Subpart A-General Provisions

589.1 Substances prohibited from use in animal food or feed.

(a) The substances listed in this part have been prohibited from use in animal food or feed by the Food and Drug Administration because of a determination that they present a potential risk to the public health or have not been shown by adequate scientific data to be safe for use in such food or feed. Use of any of these substances in violation of this part causes the animal food or feed involved to be adulterated and in violation of the Act.

(b) This part includes only a partial list of substances prohibited from use in animal food or feed; it is for easy reference purposes and is not a complete list of substances that may not lawfully be used in such animal food or feed. No substance may be used in animal food or feed unless it meets all applicable requirements of the Act.

(c) The Food and Drug Administration either on its own initiative or on behalf of any interested person who has submitted a petition, may publish a proposal to establish, amend, or repeal a regulation under this part on the basis of new scientific evaluation or information. Any such petition shall include an adequate scientific basis to support the petition, shall be the form set forth in Sec. 571.1 of this chapter, and will be published in the FEDERAL REGISTER for comment if it contains reasonable ground.

[45 FR 28319, Apr. 29, 1980]

Subpart B-Listing of Specific Substances Prohibited from Use in Animal Food or Feed

Sec. 589.1000 Gentian violet.

The Food and Drug Administration has determined that gentian violet has not been shown by adequate scientific data to be safe for use in animal feed. Use of gentian violet in animal feed causes the feed to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (the act), in the absence of a regulation providing for its safe uses s a food additive under section 409 of the act, unless it is subject to an effective notice of claimed investigational exemption for a food additive under Sec. 570.17 of this chapter, or unless the substance is intended for use as a new animal drug and is subject to an approved application under section 512 of the act or an effective notice of claimed investigational exemption for a new animal drug under part 511 of this chapter.

[56 FR 40507, Aug. 15, 1991]

Sec. 589.1001 Propylene glycol in or on cat food.

The Food and Drug Administration has determined that propylene glycol in or on cat food has not been shown by adequate scientific data to be safe for use. Use of propylene glycol in or on cat food causes the feed to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (the act), in the absence of a regulation providing for its safe use as a food additive under section 409 of the act, unless it is subject to an effective notice of claimed investigational exemption for a food additive under Sec. 570.17 of this chapter, or unless the substance is intended for use as a new animal drug and is subject to an approved application under section 512 of the act or an effective notice of claimed investigational exemption for a new animal drug under part 511 of this chapter.

[61 FR 19544, May 2, 1996

589.2000 Animal proteins prohibited in ruminant feed.

(a) Definitions

(1) Protein derived from mammalian tissues means any protein-containing portion of mammalian animals, excluding: Blood and blood products; gelatin; inspected meat products which have been cooked and offered for human food and further heat processed for feed (such as plate waste and used cellulosic food casings); milk products (milk and milk proteins); and any product whose only mammalian protein consists entirely of porcine or equine protein.

(2) Renderer means any firm or individual that processes slaughter byproducts, animals unfit for human consumption, or meat scraps. The term includes persons who collect such materials and subject them to minimal processing, or distribute them to firms other than renderers (as defined here) whose intended use for the products may include animal feed. The term includes renderers that also blend animal protein products.

(3) Blender means any firm or individual which obtains processed animal protein from more than one source or from more than one species, and subsequently mixes (blends) or redistributes an animal protein product.

(4) Feed manufacturer includes manufacturers of complete and intermediate feeds intended for animals, and includes on-farm in addition to off-farm feed manufacturing and mixing operations.

(5) Nonmammalian protein includes proteins from nonmammalian animals.

(6) Distributor includes persons who distribute or transport feeds or feed ingredients intended for animals.

(7) Ruminant includes any member of the order of animals which has a stomach with four chambers (rumen, reticulum, omasum, and abomasum) through which feed passes in digestion. The order includes, but is not limited to, cattle, buffalo, sheep, goats, deer, elk, and antelopes.

(b) Food additive status. The Food and Drug Administration has determined that protein derived from mammalian tissues for use in ruminant feed is a food additive subject to section 409 of the Federal Food, Drug, and Cosmetic Act (the act). The use or intended use in ruminant

feed of any material that contains protein derived from mammalian tissues causes the feed to be adulterated and in violation of the act, unless it is the subject of an effective notice of claimed investigational exemption for a food additive under Sec. 570.17 of this chapter.

(c) Requirements for renderers that are not included in paragraph (e) of this section.

(1) Renderers that manufacture products that contain or may contain protein derived from mammalian tissues and that are intended for use in animal feed shall take the following measures to ensure that materials identified in paragraph (b) of this section are not used in the feed of ruminants:

(i) Label the materials as follows: "Do not feed to cattle or other ruminants"; and

(ii) Maintain records sufficient to track the materials throughout their receipt, processing, and distribution, and make the copies available for inspection and copying by the Food and Drug Administration.

(2) Renderers described in paragraph (c)(1) of this section will be exempted from the requirements of paragraphs (c)(1)(i) and (c)(1)(ii) of this section if they:

(i) Use exclusively a manufacturing method that has been validated by the Food and Drug Administration to deactivate the agent that causes transmissible spongiform encephalopathy (TSE) and whose design has been made available to the public;

(ii) Use routinely a test method that has been validated by the Food and Drug Administration to detect the presence of the agent that causes TSE's and whose design has been made available to the public. Renderers whose products test positive for agents that cause TSE's must comply with paragraphs (c)(1)(i) and (c)(1)(ii) of this section. Records of the test results shall be made available for inspection by the Food and Drug Administration; or

(iii) Use exclusively a method for controlling the manufacturing process that minimizes the risk of the TSE agent entering the product and whose design has been made available to the public and validated by the Food and Drug Administration.

(3) Renderers described in paragraph (c)(1) of this section will be exempted from the requirements of paragraph (c)(1)(ii) of this section if they use a permanent method, approved by FDA, to make a mark indicating that the product contains or may contain protein derived from mammalian tissue. If the marking is by the use of an agent that cannot be detected on visual inspection, the renderer must use an agent whose presence can be detected by a method that has been validated by the Food and Drug Administration and whose design has been made available to the public.

(d) Requirements for protein blenders, feed manufacturers, and distributors that are not included in paragraph (e) of this section.

(1) Protein blenders, feed manufacturers, and distributors that manufacture, blend, process, and distribute products that contain or may contain protein derived from mammalian tissues shall comply with paragraph (c)(1) of this section.

(2) Protein blenders, feed manufacturers, and distributors, shall be exempt from paragraphs (d)(1) of this section if they:

(i) Purchase animal products from renderers that certified compliance with paragraph (c)(2) of this section or purchase such materials from parties that certify that the materials were purchased from renderers that certified compliance with paragraph (c)(2) of this section; or

(ii) Comply with the requirements of paragraph (c)(2) of this section where appropriate.

(3) Protein blenders, feed manufacturers, and distributors, shall be exempt from paragraph (c)(1)(ii) of this section if they:

(i) Purchase animal protein products that are marked in accordance with paragraph (c)(3) of this section or purchase such materials from renderers that certified compliance with paragraph (c)(3) of this section, or purchase such materials from parties that certify that the materials were purchased from renderers that certified compliance with paragraph (c)(3) of this section; or

(ii) Comply with the requirements of paragraph (c)(3) of this section where appropriate.

(4) Pet food products that are sold or are intended for sale at retail and feeds for nonruminant laboratory animals are exempt from the labeling requirements in paragraphs (c) and (d) of this section. However, if the pet food products or feeds for nonruminant laboratory animals are sold or are intended for sale as distressed or salvage items, then such products shall be labeled in accordance with paragraph (c) or (d) of this section, as appropriate.

(5) Copies of certifications as described in paragraphs (d)(2) and (d)(3) of this section, shall be made available for inspection and copying by the Food and Drug Administration.

(e) Requirements for persons that intend to separate mammalian and nonmammalian materials.

(1) Renderers, protein blenders, feed manufacturers, distributors, and others that manufacture, process, blend and distribute both products that contain or may contain protein derived from mammalian tissues or feeds containing such products, and protein products from other animal tissues or feeds containing such products, and that intend to keep those products separate shall:

(i) Comply with paragraphs (c)(1) or (d)(1) of this section as appropriate except that the labeling requirement shall apply only to products that contain or may contain protein derived from mammalian tissues or feeds containing such products;

(ii) In the case of a renderer, obtain nonmammalian or pure porcine or pure equine materials only from single-species slaughter facilities;

(iii) Provide for measures to avoid commingling or cross-contamination;

(A) Maintain separate equipment or facilities for the manufacture, processing, or blending of such materials; or

(B) Use clean-out procedures or other means adequate to prevent carry-over of products that contain or may contain protein derived from mammalian tissues into animal protein or feeds that may be used for ruminants; and

(iv) Maintain written procedures specifying the clean-out procedures or other means, and specifying the procedures

for separating products that contain or may contain protein derived from mammalian tissue from all other protein products from the time of receipt until the time of shipment.

(2) Renderers, blenders, feed manufacturers, and distributors will be exempted from applicable requirements of paragraph (e)(1) of this section, if they meet the criteria for exemption under paragraphs (c)(2) or (c)(3) of this section, and (d)(2) or (d)(3) of this section.

(f) Requirements for establishments and individuals that are responsible for feeding ruminant animals. Establishments and individuals that are responsible for feeding ruminant animals shall maintain copies of purchase invoices and labeling for all feeds containing animal protein products received, and make the copies available for inspection and copying by the Food and Drug Administration.

(g) Adulteration and misbranding.

(1) Animal protein products, and feeds containing such products, that are not in compliance with paragraphs (c) through (f) of this section, excluding labeling requirements, will be deemed adulterated under section 402(a)(2)(C) or 402(a)(4) of the act.

(2) Animal protein products, and feeds containing such products, that are not in compliance with the labeling requirements of paragraphs (c) through (f) of this section will be deemed misbranded under section 403(a)(1) or 403(f) of the act.

(h) Inspection; records retention.

(1) Records that are to be made available for inspection and copying, as required by this section, shall be kept for a minimum of 1 year.

(2) Written procedures required by this section shall be made available for inspection and copying by the Food and Drug Administration.

[62 FR 30976, June 5, 1997] Effective Date Note: At 62 FR 30976, June 5, 1997, Sec. 589.2000 was added. Paragraph (e)(1)(iv) of this section contains information collection and recordkeeping requirements and will not become effective until approval has been given by the Office of Management and Budget.

PART 606 - CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

AUTHORITY: 21 U.S.C. 321, 331,351,352,355,360,360j, 371,374; 42 U.S.C. 216,262,263a,264. SOURCE: 40 FR 53532, Nov. 18, 1975, unless otherwise noted.

Subpart A - General Provisions

606.3 Definitions.

As used in this part:

(a) Blood means whole blood collected from a single donor and processed either for transfusion or further manufacturing.

(b) Unit means the volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood from one donor.

(c) Component means that part of a single-donor unit of blood separated by physical or mechanical means.

(d) Plasma for further manufacturing means that liquid portion of blood separated and used as material to prepare another product.

(e) Plasmapheresis means the procedure in which blood is removed from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor. This process may be immediately repeated, once.

(f) Plateletpheresis means the procedure in which blood is removed from the donor, a platelet concentrate is separated, and the remaining formed elements are returned to the donor along with a portion of the residual plasma.

(g) Leukapheresis means the procedure in which blood is removed from the donor, a leukocyte concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

(h) Facilities means any area used for the collection, processing, compatibility testing, storage or distribution of blood and blood components.

(i) Processing means any procedure employed after collection and before compatibility testing of blood and includes the identification of a unit of donor blood, the preparation of components from such unit of donor blood, serological testing, labeling and associated recordkeeping.

(j) Compatibility testing means the procedures performed to establish the matching of a donor's blood or blood components with that of a potential recipient.

(k) Distributed means:

(1) The blood or blood components have left the control of the licensed manufacturer, unlicensed registered blood establishment, or transfusion service; or

(2) The licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed biological product.

(l) Control means having responsibility for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with current good manufacturing practices.

[40 FR 53532, Nov. 18, 1975, as amended at 64 FR 45370, Aug. 19, 1999; 65 FR 66635, Nov. 7, 2000; 66 FR 1835, Jan. 10, 2001; 66 FR 40889, Aug. 6, 2001]

Subpart B - Organization and Personnel

606.20 Personnel.

(a) [Reserved]

(b) The personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood or blood components shall be adequate in number, educational background, training and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions, and to ensure that the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to possess. All personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the procedures or control operations they perform, the necessary training or experience, and adequate information concerning the application of pertinent provisions of this part to their respective functions.

(c) Persons whose presence can adversely affect the safety and purity of the products shall be excluded from areas where the collection, processing, compatibility testing, storage or distribution of blood or blood components is conducted.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11014, Mar. 26, 1990; 62 FR 53538, Oct.15, 1997]

Subpart C - Plant and Facilities

606.40 Facilities.

Facilities shall be maintained in a clean and orderly manner, and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operations. The facilities shall:

(a) Provide adequate space for the following when applicable:

(1) Private and accurate examinations of individuals to determine their suitability as blood donors.

(2) The withdrawal of blood from donors with minimal risk of contamination, or exposure to activities and equipment unrelated to blood collection.

(3) The storage of blood or blood components pending completion of tests.

(4) The quarantine storage of blood or blood components in a designated location pending repetition of those tests that initially gave questionable serological results.

(5) The storage of finished products prior to distribution.

(6) The quarantine storage, handling and disposition of products and reagents not suitable for use.

(7) The orderly collection, processing, compatibility testing, storage and distribution of blood and blood components to prevent contamination.

(8) The adequate and proper performance of all steps in plasmapheresis, plateletpheresis and leukapheresis procedures.

(9) The orderly conduction of all packaging, labeling and other finishing operations.

(b) Provide adequate lighting, ventilation and screening of open windows and doors.

(c) Provide adequate, clean, and convenient handwashing facilities for personnel, and adequate, clean, and convenient toilet facilities for donors and personnel. Drains shall be of adequate size and, where connected directly to a sewer, shall be equipped with traps to prevent back-siphonage.

(d) Provide for safe and sanitary disposal for the following:

(1) Trash and items used during the collection, processing and compatibility testing of blood and blood components.

(20 Blood and blood components not suitable for use or distribution.

Subpart D - Equipment

606.60 Equipment.

(a) Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and shall perform in the manner for which it was designed so as to assure compliance with the official requirements prescribed in this chapter for blood and blood products.

(b) Equipment that shall be observed, standardized and calibrated with at least the following frequency, include but are not limited to:

Equipment	Performance check	Frequency	Frequency of Calibration
Temp. Recorder	Compare to thermometer	Daily	As necessary
Refrigerated Centrifuge	Check speed & temperature	Each day of use	As necessary.
Hematocrit Centrifuge	----------	----------	Standardize before initial use, after repairs or adjustments, and annually. Timer every 3 months
General lab centrifuge	----------	----------	Tachometer every 6 mo.
Automated blood-typing machine	Observe controls for correct results	Each day of use	
Hemoglobinometer	Standardize against cyanmethemoglobin standard	Each day of use	
Refractometer	Standardize against distilled water	Each day of use	
Blood container scale	Standardize against container of known weight	Each day of use	As necessary
Water Bath	Observe temperature	Each day of use	As necessary
Rh view box	Observed temperature	Each day of use	As necessary
Autoclave	Observe temperature	Each time of use	As necessary
Serologic rotators	Observe controls for correct results	Each day of use	Speed as necessary
Laboratory thermometers	----------	----------	Before initial use.
Electronic thermometers	----------	----------	Monthly
Vacuum blood agitator	Observe weight of the first container of blood filled for correct results	Each day of use	Standardize with container of known mass or volume before initial use, and after repairs or adjustments.

(c) Equipment employed in the sterilization of materials used in blood collection or for disposition of contaminated products shall be designed, maintained and utilized to ensure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5 C (251 F) maintained for 20 minutes by saturated steam or by an attained temperature of 170 C (338 F) maintained for 2 hours with dry heat.

[40 FR 53532, Nov. 18, 1975; 40 FR 55849, Dec. 2, 1975, as amended at 45 FR 9261, Feb 12, 1980; 57 FR 11263, Apr. 2, 1992; 57 FR 12862, Apr. 13, 1992]

606.65 Supplies and reagents.

All supplies and reagents used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be stored in a safe, sanitary and orderly manner.

(a) All surfaces coming in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product. All final containers and closures for blood and blood components not intended for transfusion shall be clean and free of surface solids and other contaminants.

(b) Each blood collecting container and its satellite container(s), if any, shall be examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination shall include inspection for breakage of seals, when indicated, and abnormal discoloration. Where any defect is observed, the container shall not be used, or, if detected after filling, shall be properly discarded.

(c) Representative samples of each lot of the following reagents or solutions shall be tested on a regularly scheduled basis by methods described in the Standard Operating Procedures Manual to determine their capacity to perform as required:

Reagent or Solution	Frequency of "Testing"
Anti-human globulin	Each day of use
Blood grouping reagents	Each day of use
Lectins	Each day of use
Antibody screening and reverse grouping cells	Each day of use
Hepatitis test reagents	Each run
Syphilis serology reagents	Each run
Enzymes	Each day of use

(d) Supplies and reagents that do not bear an expiration date shall be stored in such a manner that the oldest is used first.

(e) Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

(f) Items that are required to be sterile and come into contact with blood should be disposable whenever possible.

[40 FR 53532, Nov. 18, 1975, as amended at 59 FR 23636, May 6, 1994]

Subpart E - [Reserved]

Subpart F - Production and Process Controls

606.100 Standard operating procedures.

(a) In all instances, except clinical investigations, standard operating procedures shall comply with published additional standards in Part 640 of this chapter for the products being processed; except that, references in Part 640 relating to licenses, licensed establishments and submission of material or data to or approval by the Director, Center for Biologics Evaluation and Research, are not applicable to establishments not subject to licensure under section 351 of the Public Health Service Act.

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage and distribution of blood and blood components for transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed. The written standard operating procedures shall include, but are not limited to, descriptions of the following, when applicable:

(1) Criteria used to determine donor suitability, including acceptable medical history criteria.

(2) Methods of performing donor qualifying tests and measurements, including minimum and maximum values for a test or procedure when a factor in determining acceptability.

(3) Solutions and methods used to prepare the site of phlebotomy to give maximum assurance of a sterile container of blood.

(4) Method of accurately relating the product(s) to the donor.

(5) Blood collection procedure, including in-process precautions taken to measure accurately the quantity of blood removed from the donor.

(6) Methods of component preparation, including any time restrictions for specific steps in processing.

(7) All tests and repeat tests performed on blood and blood components during manufacturing.

(8) Pretransfusion testing, where applicable, including precautions to be taken to identify accurately the recipient blood samples and crossmatched donor units.

(9) Procedures for investigating adverse donor and recipient reactions.

(10) Storage temperatures and methods of controlling storage temperatures for all blood products and reagents as prescribed in 600.15 and 610.53 of this chapter.

(11) Length of expiration dates, if any, assigned for all final products as prescribed in 610.53 of this chapter.

(12) Criteria for determining whether returned blood is suitable for reissue.

(13) Procedures used for relating a unit of blood or blood component from the donor to its final disposition.

(14) Quality control procedures for supplies and reagents employed in blood collection, processing and pretransfusion testing.

(15)Schedules and procedures for equipment maintenance and calibration.

(16) Labeling procedures, including safeguards to avoid labeling mixups.

(17) Procedures of plasmapheresis, plateletpheresis, and leukapheresis, if performed, including precautions to be taken to ensure reinfusion of a donor's own cells.

(18) Procedure for preparing recovered plasma, if performed, including details of separation, pooling, labeling, storage and distribution.

(19) Procedures in accordance with 610.46 of this chapter to look at prior donations of Whole Blood, blood components, Source Plasma and Source Leukocytes from a donor who has donated blood and subsequently tests repeatedly reactive for antibody to human immunodeficiency virus (HIV) or otherwise is determined to be unsuitable when tested in accordance with 610.45 of this chapter. Procedures to quarantine in-house Whole Blood, blood components, Source Plasma and Source Leukocytes intended for further manufacture into injectable products that were obtained from such donors; procedures to notify consignees regarding the need to quarantine such products; procedures to determine the suitability for release of such products from quarantine; procedures to notify consignees of Whole Blood, blood components, Source Plasma and Source Leukocytes from such donors of the results of the antibody testing of such donors; and procedures in accordance with 610.47 of this chapter to notify attending physicians so that transfusion recipients are informed that they may have received Whole Blood and, blood components at increased risk for transmitting human immunodeficiency virus.

(20) Procedures for donor deferral as prescribed in 610.41 of this chapter; and procedures for donor notification and autologous donor referring physician notification, including procedures for the appropriate followup if the initial attempt at notification fails, as prescribed in 630.6 of this chapter.

(c) All records pertinent to the lot or unit maintained pursuant to these regulations shall be reviewed before the release or distribution of a lot or unit of final product. The review or portions of the review may be performed at appropriate periods during or after blood collecting, processing, compatibility testing and storing. A thorough investigation, including the conclusions and follow up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded.

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize current standard operating procedures such as the manuals of the following organizations, as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part.

(1) American Association of Blood Banks.

(2) American National Red Cross.

(3) Other organizations or individual blood banks, subject to approval by the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990; 61FR47422, Sept.9, 1996; 64 FR 45370,Aug. 19, 1999; 66FR 31176, June 11, 2001]

606.110 Plateletpheresis, leukapheresis, and plasmapheresis.

(a) The use of plateletpheresis and leukapheresis procedures to obtain a product for a specific recipient may be at variance with the additional standards for specific products prescribed in this part provided that:

(1) A physician has determined that the recipient must be transfused with the leukocytes or platelets from a specific donor, and

(2) the procedure is performed under the supervision of a qualified licensed physician who is aware of the health status of the donor, and the physician has certified in writing that the donor's health permits plateletpheresis or leukapheresis.

(b) Plasmapheresis of donors who do not meet the donor requirements of 640.63, 640.64 and 640.65 of this chapter for the collection of plasma containing rare antibodies shall be permitted only with the prior approval of the Director, Center for Biologics Evaluation and Research.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 55 FR 11013, Mar. 26, 1990]

Subpart G - Finished Product Control

606.120 Labeling, general requirements.

(a) Labeling operations shall be separated physically or spatially from other operations in a manner adequate to prevent mixups.

(b) The labeling operation shall include the following labeling controls:

(1) Labels shall be held upon receipt, pending review and proofing against an approved final copy, to ensure accuracy regarding identity, content, and conformity with the approved copy.

(2) Each type of label representing different products shall be stored and maintained in a manner to prevent mixups, and stocks of obsolete labels shall be destroyed.

(3) All necessary checks in labeling procedures shall be utilized to prevent errors in translating test results to container labels.

(c) All labeling shall be clear and legible.

[50 FR 35469, Aug. 30, 1985]

606.121 Container label.

(a) The container label requirements are designed to facilitate the use of a uniform container label for blood and blood components (except Source Plasma) by all blood establishments.

(b) The label provided by the collecting facility and the initial processing facility shall not be removed, altered, or obscured, except that the label may be altered to indicate the proper name and other information required to identify accurately the contents of a container after blood components have been prepared.

(c) The container label shall include the following information, as well as other specialized information as required in this section for specific products:

(1) The proper name of the product in a prominent posi-

tion, and modifier(s), if appropriate.

(2) The name, address, registration number, and, if a licensed product, the license number of each manufacturer.

(3) The donor, pool, or lot number relating the unit to the donor.

(4) The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, the hour of expiration.

(5) If the product is intended for transfusion, the appropriate donor classification statement, i.e., "paid donor" or "volunteer donor", in no less prominence than the proper name of the product.

(i) A paid donor is a person who receives monetary payment for a blood donation.

(ii) A volunteer donor is a person who does not receive monetary payment for a blood donation.

(iii) Benefits, such as time off from work, membership in blood assurance programs, and cancellation of nonreplacement fees that are not readily convertible to cash, do not constitute monetary payment within the meaning of this paragraph.

(6) For Whole Blood, Plasma, Platelets, and partial units of Red Blood Cells, the volume of the product, accurate to within plus or minus 10 percent; or optionally for Platelets, the volume range within reasonable limits.

(7) The recommended storage temperature (in degrees Celsius).

(8) If the product is intended for transfusion, the statements:

(i) "Rx only."

(ii) "See circular of information for indications, contraindications, cautions, and methods of infusion."

(iii) "Properly identify intended recipient."

(9) The statement: "This product may transmit infectious agents."

(10) Where applicable, the name and volume of source material.

(11) The statement: "Caution: For Manufacturing Use Only", when applicable.

(12) If the product is intended for transfusion, the ABO and Rh groups of the donor shall be designated conspicuously. For Cryoprecipitated AHF, the Rh group may be omitted. The Rh group shall be designated as follows:

(i) If the test using Anti-D Blood Grouping Reagent is positive, the product shall be labeled: "Rh positive."

(ii) If the test using Anti-D Blood Grouping Reagent is negative but the test for Du is positive, the product shall be labeled: "Rh positive."

(iii) If the test using Anti-D Blood Grouping Reagent is negative and the test for Du is negative, the product shall be labeled: "Rh negative."

(13) The container label may bear encoded information in the form of machine-readable symbols approved for use by the Director, Center for Biologics Evaluation and Research (HFB 1).

(d) Except for recovered plasma intended for manufacturing use or as otherwise approved by the Director, Center for Biologics Evaluation and Research (HFB 1), the paper of the container label shall be white and print shall be solid black, with the following additional exceptions:

(1) The Rh blood group shall be printed as follows:

(i) Rh positive: Use black print on white background.

(ii) Rh negative: Use white print on black background.

(2) The proper name of the product, any appropriate modifier(s), the donor classification statement, and the statement "properly identify intended recipient" shall be printed in solid red or in solid black.

(3) The following color scheme may be used optionally for differentiating ABO Blood groups:

Blood Group	Color of label paper
O	Blue
A	Yellow
B	Pink
AB	White

(4) Ink colors used for the optional color coding system described in paragraph (d)(3) of this section shall be a visual match to specific color samples designated by the Director, Center for Biologics Evaluation and Research (HFB 1).

(5) Special labels, such as those described in paragraphs (h) and (i) of this section, may be color coded using the colors recommended in the guideline (see paragraph (a) of this section), or colors otherwise approved for use by the Director, Center for Biologics Evaluation and Research (HFB 1).

(e) Container label requirements for particular products or groups of products.

(1) Whole Blood labels shall include:

(i) The volume of anticoagulant.

(ii) The name of the applicable anticoagulant immediately preceding and of no less prominence than the proper name approved for use by the Director, Center for Biologics Evaluation and Research.

(iii) If tests for unexpected antibodies are positive, blood intended for transfusion shall be labeled: "Contains (name of antibody)."

(2) Except for frozen, deglycerolized, or washed Red Blood Cell products, red blood cell labels shall include:

(i) The volume and kind of Whole Blood, including the type of anticoagulant, from which the product was prepared.

(ii) If tests for unexpected antibodies are positive and the product is intended for transfusion, the statement: "Contains (name of antibody)."

(3) Labels for products with a dating period of 72 hours or less, including any product prepared in a system that may compromise sterility, shall bear the hour of expiration.

(4) If tests for unexpected antibodies are positive, Plasma intended for transfusion shall be labeled: "Contains (name of antibody)."

(5) Recovered plasma labels shall include:

(i) In lieu of an expiration date, the date of collection of the oldest material in the container.

(ii) The statement: "Caution: For Manufacturing Use Only"; or "Caution: For Use in Manufacturing Noninjectable Products Only", as applicable. If the recovered plasma has a reactive screening test for evidence of infection due to a communicable disease agent(s) under Sec. 610.40 of this chapter, or is collected from a donor with a previous record

of a reactive screening test for evidence of infection due to a communicable disease agent(s) under Sec. 610.40 of this chapter, the recovered plasma must be labeled as required under Sec. 610.40(h)(2)(ii)(E) of this chapter.

(iii) For recovered plasma not meeting the requirements for manufacture into licensable products, the statement: "Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act."

(f) Blood and blood components determined to be unsuitable for transfusion shall be prominently labeled: "NOT FOR TRANSFUSION", and the label shall state the reason the unit is considered unsuitable. The provision does not apply to recovered plasma labeled according to paragraph (e)(5) of this section.

(g) [Reserved]

(h) The following additional information shall appear on the label for blood or blood components shipped in an emergency, prior to completion of required tests, in accordance with 640.2(f) of this chapter:

(1) The statement: "FOR EMERGENCY USE ONLY BY _____"

(2) Results of any tests prescribed under 610.40, and 640.5 (a), (b), or (c) of this chapter completed before shipment.

(3) Indication of any tests prescribed under 610.40, and 640.5 (a), (b) or (c) of this chapter and not completed before shipment.

(i) The following additional information shall appear on the label for Whole Blood or Red Blood Cells intended for autologous infusion:

(1) Information adequately identifying the patient, e.g., name, blood group, hospital, and identification number.

(2) Date of donation.

(3) The statement: "FOR AUTOLOGOUS USE ONLY."

(4) In place of the blood group label, each container of blood intended for autologous use and obtained from a donor who fails to meet any of the donor suitability requirements under 640.3 of this chapter or who is reactive in the hepatitis tests prescribed under 610.40 of this chapter shall be prominently and permanently labeled: "FOR AUTOLOGOUS USE ONLY."

(5) Units of blood originally intended for autologous use, except those labeled as prescribed under paragraph (i)(4) of this section, may be issued for homologous transfusion provided the container label complies with all applicable provisions of paragraphs (b) through (e) of this section. In such case, the special label required under paragraph (i)(1), (2), and (3) of this section shall be removed or otherwise obscured.

(j) A tie-tag attached to the container may be used for providing the information required by paragraph (e) (1)(iii), (2)(ii), and (4), (h), or (i)(1), (2), and (3) of this section.

[50 FR 35469, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988; 55 FR 11014, Mar. 26, 1990; 57 FR 10814, Mar. 31, 1992; 59 FR 23636, May 6, 1994, 63 FR 16685, Apr. 6, 1998; 64 FR 45371, Aug. 19, 1999; 66 FR 31162, June 11, 2001; 67 FR 4907, Feb. 1, 2002]

EFFECTIVE DATE NOTE: The information collection requirements contained in 606.121 will not become effective until OMB approval has been obtained. FDA will publish a notice of OMB approval in the FEDERAL REGISTER.

606.122 Instruction circular.

An instruction circular shall be available for distribution if the product is intended for transfusion. The instruction circular shall provide adequate directions for use, including the following information:

(a) Instructions to mix the product before use.

(b) Instructions to use a filter in the administration equipment.

(c) The statement "Do Not Add Medications" or an explanation concerning allowable additives.

(d) A description of the product, its source, and preparation, including the name and proportion of the anticoagulant used in collecting the Whole Blood from each product is prepared.

(e) Statements that the product was prepared from blood that was negative when tested for antibody to Human Immunodeficiency Virus (HIV) and nonreactive for hepatitis B surface antigen by FDA required tests and nonreactive when tested for syphilis by a serologic test for syphilis (STS).

(f) The statements: "Warning. The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard."

(g) The names of cryoprotective agents and other additives that may still be present in the product.

(h) The names and results of all tests performed when necessary for safe and effective use.

(i) The use of the product, indications, contraindications, side effects and hazards, dosage and administration recommendations.

(j) [Reserved]

(k) For Red Blood Cells, the instruction circular shall contain:

(1) Instructions to administer a suitable plasma volume expander if Red Blood Cells are substituted when Whole Blood is the indicated product.

(2) A warning not to add Lactated Ringer's Injection U.S.P. solution to Red Blood Cell products.

(l) For Platelets, the instruction circular shall contain:

(1) The approximate volume of plasma from which a sample unit of Platelets is prepared.

(2) Instructions to begin administration as soon as possible, but not more than 4 hours after entering the container.

(m) For Plasma, the instruction circular shall contain:

(1) A warning against further processing of the frozen product if there is evidence of breakage or thawing.

(2) Instructions to thaw the frozen product at a temperature between 30 degrees and 37 degrees C.

(3) When applicable, instructions to begin administration of the product within 6 hours after thawing.

(4) Instructions to administer to ABO-group-compatible recipients.

(5) A statement that this product has the same hepatitis risk as Whole Blood; other plasma volume expanders without this risk are available for treating hypovolemia.

(n) For Cryoprecipitated AHF, the instruction circular shall contain:

(1) A statement that the average potency is 80 or more International Units of antihemophilic factor.

(2) The statement: "Usually contains at least 150 milligrams of fibrinogen''; or, alternatively, the average fibrinogen level determined by assay of representative units.

(3) A warning against further processing of the product if there is evidence of breakage or thawing.

(4) Instructions to thaw the product for no more than 15 minutes at a temperature between 30 and 37 degrees C.

(5) Instructions to store at room temperature after thawing and to begin administration as soon as possible but no more than 4 hours after entering the container or after pooling and within 6 hours after thawing.

(6) A statement that 0.9 percent Sodium Chloride Injection U.S.P. is the preferred diluent.

(7) Adequate instructions for pooling to ensure complete removal of all concentrated material from each container.

(8) The statement: "Good patient management requires monitoring treatment responses to Cryoprecipitated AHF transfusions with periodic plasma factor VIII or fibrinogen assays in hemophilia A and hypofibrinogenemic recipients, respectively."

[50 FR 35470, Aug. 30, 1985, as amended at 53 FR 116, Jan. 5, 1988; 64 FR 45371, Aug. 19, 1999]

EFFECTIVE DATE NOTE: The information collection requirements contained in 606.122 will not become effective until OMB approval has been obtained. FDA will publish a notice of OMB approval in the FEDERAL REGISTER .

Subpart H - Laboratory Controls

606.140 Laboratory controls.

Laboratory control procedures shall include:

(a) The establishment of scientifically sound and appropriate specifications, standards and test procedures to assure that blood and blood components are safe, pure, potent and effective.

(b) Adequate provisions for monitoring the reliability, accuracy, precision and performance of laboratory test procedures and instruments.

(c) Adequate identification and handling of all test samples so that they are accurately related to the specific unit of product being tested, or to its donor, or to the specific recipient, where applicable.

606.151 Compatibility testing.

Standard operating procedures for compatibility testing shall include the following:

(a) A method of collecting and identifying the blood samples of recipients to ensure positive identification.

(b) The use of fresh recipient serum samples less than 3-days old for all pretransfusion testing if the recipient has been pregnant or transfused within the previous 3 months.

(c) The testing of the donor's cell type with the recipient's serum type by a method that will demonstrate incompatibility.

(d) A provision that, if the unit of donor's blood has not been screened by a method that will demonstrate agglutinating, coating and hemolytic antibodies, the recipient's cells shall be tested with the donor's serum (minor cross-match) by a method that will so demonstrate.

(e) Procedures to expedite transfusions in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by a physician.

40 FR 53532, Nov. 18, 1975, as amended at 64 FR 45371, Aug. 19, 1999; 66 FR 1835, Jan 10, 2001;66 FR 40889, Aug.6, 2001]

Subpart I - Records and Reports

606.160 Records.

(a)(1) Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced. All records shall be legible and indelible, and shall identify the person performing the work, include dates of the various entries, show test results as well as the interpretation of the results, show the expiration date assigned to specific products, and be as detailed as necessary to provide a complete history of the work performed.

(2) Appropriate records shall be available from which to determine lot numbers of supplies and reagents used for specific lots or units of the final product.

(b) Records shall be maintained that include, but are not limited to, the following when applicable:

(1) Donor records:

(i) Donor selection, including medical interview and examination and where applicable, informed consent.

(ii) Permanent and temporary deferrals for health reasons including reason(s) for deferral.

(iii) Donor adverse reaction complaints and reports, including results of all investigations and follow up.

(iv) Therapeutic bleedings, including signed requests from attending physicians, the donor's disease and disposition of units.

(v) Immunization, including informed consent, identification of the antigen, dosage and route of administration.

(vi) Blood collection, including identification of the phlebotomist.

(vii) Records to relate the donor with the unit number of each previous donation from that donor.

(viii) Records of quarantine, notification, testing and disposition performed pursuant to 610.46 and 610.47 of this chapter.

(ix) Records of notification of donors deferred or determined not to be suitable for donation, including appropriate followup if the initial attempt at notification fails, performed under 630.6 of this chapter.

(x) The donor's address provided at the time of donation where the donor may be contacted within 8 weeks after donation.

(xi) Records of notification of the referring physician of a deferred autologous donor, including appropriate followup if

the initial notification attempt fails, performed under 630.6 of this chapter.

(2) Processing records:

(i) Blood processing, including results and interpretation of all tests and retests.

(ii) Component preparation, including all relevant dates and times.

(iii) Separation and pooling of recovered plasma.

(iv) Centrifugation and pooling of source plasma.

(v) Labeling, including initials of person(s) performing the procedure.

(3) Storage and distribution records:

(i) Distribution and disposition, as appropriate, of blood and blood products.

(ii) Visual inspection of whole blood and red blood cells during storage and immediately before distribution.

(iii) Storage temperature, including initialed temperature recorder charts.

(iv) Reissue, including records of proper temperature maintenance.

(v) Emergency release of blood, including signature of requesting physician obtained before or after release.

(4) Compatibility test records:

(i) Results of all compatibility tests, including crossmatching, testing of patient samples, antibody screening and identification.

(ii) Results of confirmatory testing.

(5) Quality control records:

(i) Calibration and standardization of equipment.

(ii) Performance checks of equipment and reagents.

(iii) Periodic check on sterile technique.

(iv) Periodic tests of capacity of shipping containers to maintain proper temperature in transit.

(v) Proficiency test results.

(6) Transfusion reaction reports and complaints, including records of investigations and follow up.

(7) General records:

(i) Sterilization of supplies and reagents prepared within the facility, including date, time interval, temperature and mode.

(ii) Responsible personnel.

(iii) Biological product deviations.

(iv) Maintenance records for equipment and general physical plant.

(v) Supplies and reagents, including name of manufacturer or supplier, lot numbers, expiration date and date of receipt.

(vi) Disposition of rejected supplies and reagents used in the collection, processing and compatibility testing of blood and blood components.

(c) A donor number shall be assigned to each accepted donor, which relates the unit of blood collected to that donor, to his medical record, to any component or blood product from that donor's unit of blood, and to all records describing the history and ultimate disposition of these products.

(d) Records shall be retained for such interval beyond the expiration date for the blood or blood component as necessary to facilitate the reporting of any unfavorable clinical reactions. The retention period shall be no less than 5 years after the records of processing have been completed or 6 months after the latest expiration date for the individual product, whichever is a later date. When there is no expiration date, records shall be retained indefinitely.

(e) A record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed.

[40 FR 53532, Nov.18, 1975, as amended at 61 FR 47422, Sept. 9, 1996; 64 FR 45371, Aug 19, 1999; 69 FR 66635, Nov. 7, 2000; 66 FR 31176, June 11, 2001]]

606.165 Distribution and receipt; procedures and records.

(a) Distribution and receipt procedures shall include a system by which the distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary.

(b) Distribution records shall contain information to readily facilitate the identification of the name and address of the consignee, the date and quantity delivered, the lot number of the unit(s), the date of expiration or the date of collection, whichever is applicable, or for crossmatched blood and blood components, the name of the recipient.

(c) Receipt records shall contain the name and address of the collecting facility, date received, donor or lot number assigned by the collecting facility and the date of expiration or the date of collection, whichever is applicable.

606.170 Adverse reaction file.

(a) Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion. A thorough investigation of each reported adverse reaction shall be made. A written report of the investigation of adverse reactions, including conclusions and follow up, shall be prepared and maintained as part of the record for that lot or unit of final product by the collecting or transfusing facility. When it is determined that the product was at fault in causing a transfusion reaction, copies of all such written reports shall be forwarded to and maintained by the manufacturer or collecting facility.

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, shall be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible; a written report of the investigation shall be submitted to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

[40 FR 53532, Nov. 18, 1975, as amended at 49 FR 23833, June 8, 1984; 50 FR 35471, Aug. 30, 1985; 55 FR 11014, Mar. 26, 1990; 64 FR 45371, Aug. 19, 1999; 67 FR 9586, Mar. 4, 2002]

606.171 Reporting of product deviations by licensed manufacturers, unlicensed registered blood establishmkents, and transfusion services.

(a) Who must report under this section? You, a licensed manufacturer of blood and blood components, including Source Plasma; an unlicensed registered blood establishment; or a transfusion service who had control over the product when the deviation occurred, must report under this section. If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

(b) What do I report under this section? You must report any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of both licensed and unlicensed blood or blood components, including Source Plasma, if that event meets all the following criteria:

(1) Either:

(i) Represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or

(ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and

(2) Occurs in your facility or another facility under contract with you; and

(3) Involves distributed blood or blood components.

(c) When do I report under this section? You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.

(d) How do I report under this section? You must report on Form FDA-3486.

(e) Where do I report under this section? You must send the completed Form FDA-3486 to the Director, Office of Compliance and Biologics Quality (HFM-600), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, by either a paper or electronic filing:

(1) If you make a paper filing, you should identify on the envelope that a BPDR (biological product deviation report) is enclosed; or

(2) If you make an electronic filing, you may submit the completed Form FDA-3486 electronically through CBER's website at www.fda.gov/cber.

(f) How does this regulation affect other FDA regulations? This part supplements and does not supersede other provisions of the regulations in this chapter. All biological product deviations, whether or not they are required to be reported under this section, should be investigated in accordance with the applicable provisions of parts 211, 606, and 820 of this chapter.

[65 FR 66635, Nov. 7, 2000]

PART 803 - MEDICAL DEVICE REPORTING

AUTHORITY: 21 U.S.C. 352, 360, 360i, 360j, 371, 374. SOURCE: 60 FR 63597, Dec. 11, 1995, unless otherwise noted.

Subpart A - General Provisions

803.1 Scope

(a) This part establishes requirements for medical device reporting. Under this part, medical device user facilities, importers, and manufacturers, as defined in 803.3, must report deaths and serious injuries to which a device has or may have caused or contributed, must establish and maintain adverse event files, and must submit to FDA specified followup and summary reports. Medical device distributors, as defined in 803.3, are also required to maintain records of incidents (files). Furthermore, manufacturers and importers are also required to report certain device malfunctions. These reports will assist FDA in protecting the public health by helping to ensure that devices are not adulterated or misbranded and are safe and effective for their intended use.

(b) This part supplements and does not supersede other provisions of this subchapter, including the provisions of part 820 of this chapter.

(c) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of title 21 unless otherwise noted.

[60 FR 63597, Dec 11, 1995, as amended at 62 FR 13306, Mar 20, 1997; 65 FR 4118, Jan. 26, 2000]

803.3 Definitions.

(a) Act means the Federal Food, Drug, and Cosmetic Act.

(b) Ambulatory surgical facility (ASF) means a distinct entity that operates for the primary purpose of furnishing same day outpatient surgical services to patients. An ASF may be either an independent entity (i.e., not a part of a provider of services or any other facility) or operated by another medical entity (e.g., under the common ownership, licensure or control of an entity). An ASF is subject to this regulation regardless of whether it is licensed by a Federal, State, municipal, or local government or regardless of whether it is accredited by a recognized accreditation organization. If an adverse event meets the criteria for reporting, the ASF must report that event regardless of the nature or location of the medical service provided by the ASF.

(c) Become aware means that an employee of the entity required to report has acquired information reasonably suggesting a reportable adverse event has occurred.

(1) Device user facilities are considered to have "become aware" when medical personnel, as defined in paragraph (s) of this section, who are employed by or otherwise formally affiliated with the facility, acquire such information about a reportable event.

(2) Manufacturers are considered to have become aware of an event when:

(i) Any employee becomes aware of a reportable event that is required to be reported within 30 days or that is required to be reported within 5 days under a written request from FDA under Sec. 803.53(b); and

(ii) Any employee, who is a person with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or a person whose duties relate to the collection and reporting of adverse events, becomes aware that a reportable MDR event or events, from any information, including any trend analysis, necessitate remedial action to prevent an unreasonable risk of substantial harm to the public health.

(3) Importers are considered to have become aware of an event when any employee becomes aware of a reportable event that is required to be reported by an importer within 30 days.

(d) Caused or contributed means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of:

(1) Failure;

(2) Malfunction;

(3) Improper or inadequate design;

(4) Manufacture;

(5) Labeling; or

(6) User error.

(e)(1) Device family means a group of one or more devices manufactured by or for the same manufacturer and having the same:

(i) Basic design and performance characteristics related to device safety and effectiveness,

(ii) Intended use and function, and

(iii) Device classification and product code.

(2) Devices that differ only in minor ways not related to safety or effectiveness can be considered to be in the same device family. Factors such as brand name and common name of the device and whether the devices were introduced into commercial distribution under the same 510(k) or premarket approval application (PMA), may be considered in grouping products into device families.

(f) Device user facility means a hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility as defined in paragraphs (b), (l), (t), (u), and (v), respectively, of this section, which is not a "physician`s office," as defined in paragraph (x) of this section. School nurse offices and employee health units are not device user facilities.

(g) Distributor means, for the purposes of this part, any person (other than the manufacturer or importer) who furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user, but who does not repackage or otherwise change the container, wrapper or labeling of the device or device package. One who repackages or otherwise changes the container, wrapper, or labeling, is a manufacturer under paragraph (o) of this section.

(h) [Reserved]

(i) Expected life of a device (required on the manufacturer`s baseline report) means the time that a device is expected to remain functional after it is placed into use. Certain implanted devices have specified "end of life" (EOL) dates. Other devices are not labeled as to their respective EOL, but are expected to remain operational through maintenance, repair, upgrades, etc., for an estimated period of time.

(j) FDA means the Food and Drug Administration.

(k) Five-day report means a medical device report that must be submitted by a manufacturer to FDA pursuant to Sec. 803.53, on FDA Form 3500A or electronic equivalent as approved under Sec. 803.14, within 5 work days.

(l) Hospital means a distinct entity that operates for the primary purpose of providing diagnostic, therapeutic (medical, occupational, speech, physical, etc.), surgical and other patient services for specific and general medical conditions. Hospitals include general, chronic disease, rehabilitative, psychiatric, and other special-purpose facilities. A hospital may be either independent (e.g., not a part of a provider of services or any other facility) or may be operated by another medical entity (e.g., under the common ownership, licensure or control of another entity). A hospital is covered by this regulation regardless of whether it is licensed by a Federal, State, municipal or local government or whether it is accredited by a recognized accreditation organization. If an adverse event meets the criteria for reporting, the hospital must report that event regardless of the nature or location of the medical service provided by the hospital.

(m) Importer means, for the purposes of this part, any person who imports a device into the United States and who furthers the marketing of a device from the original place of manufacture to the person who makes final delivery or sale to the ultimate user, but who does not repackage or otherwise change the container, wrapper, or labeling of the device or device package. One who repackages or otherwise changes the container, wrapper, or labeling, is a manufacturer under paragraph (o) of this section.

(n) Malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed, as defined in Sec. 801.4 of this chapter.

(o) Manufacturer means any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological, or other procedure. The term includes any person who:

(1) Repackages or otherwise changes the container, wrapper or labeling of a device in furtherance of the distribution of the device from the original place of manufacture;

(2) Initiates specifications for devices that are manufactured by a second party for subsequent distribution by the person initiating the specifications;

(3) Manufactures components or accessories which are devices that are ready to be used and are intended to be commercially distributed and intended to be used as is, or are processed by a licensed practitioner or other qualified person to meet the needs of a particular patient; or

(4) Is the U.S. agent of a foreign manufacturer.

(p) Manufacturer or importer report number means the number that uniquely identifies each individual adverse event report submitted by a manufacturer or importer. This

number consists of three parts as follows:

(1) The FDA registration number for the manufacturing site of the reported device, or the registration number for the importer. (If the manufacturing site or the importer does not have a registration number, FDA will assign a temporary MDR reporting number until the site is officially registered. The manufacturer or importer will be informed of the temporary number.);

(2) The four-digit calendar year in which the report is submitted; and

(3) The five-digit sequence number of the reports submitted during the year, starting with 00001. (For example, the complete number will appear 1234567-1995-00001.)

(q) MDR means medical device report.

(r) MDR reportable event (or reportable event) means:

(1) An event about which user facilities become aware of information that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or

(2) An event about which manufacturers or importers have received or become aware of information that reasonably suggests that one of their marketed devices:

(i) May have caused or contributed to a death or serious injury; or

(ii) Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

(s) Medical personnel , as used in this part, means an individual who:

(1) Is licensed, registered, or certified by a State, territory, or other governing body, to administer health care;

(2) Has received a diploma or a degree in a professional or scientific discipline;

(3) Is an employee responsible for receiving medical complaints or adverse event reports; or

(4) Is a supervisor of such persons.

(t)(1) Nursing home means an independent entity (i.e., not a part of a provider of services or any other facility) or one operated by another medical entity (e.g., under the common ownership, licensure, or control of an entity) that operates for the primary purpose of providing:

(i) Skilled nursing care and related services for persons who require medical or nursing care;

(ii) Hospice care to the terminally ill; or

(iii) Services for the rehabilitation of the injured, disabled, or sick.

(2) A nursing home is subject to this regulation regardless of whether it is licensed by a Federal, State, municipal, or local government or whether it is accredited by a recognized accreditation organization. If an adverse event meets the criteria for reporting, the nursing home must report that event regardless of the nature, or location of the medical service provided by the nursing home.

(u)(1) Outpatient diagnostic facility means a distinct entity that:

(i) Operates for the primary purpose of conducting medical diagnostic tests on patients;

(ii) Does not assume ongoing responsibility for patient care; and

(iii) Provides its services for use by other medical personnel. (Examples include diagnostic radiography, mammography, ultrasonography, electrocardiography, magnetic resonance imaging, computerized axial tomography and invitro testing).

(2) An outpatient diagnostic facility may be either independent (i.e., not a part of a provider of services or any other facility) or operated by another medical entity (e.g., under the common ownership, licensure, or control of an entity). An outpatient diagnostic facility is covered by this regulation regardless of whether it is licensed by a Federal, State, municipal, or local government or whether it is accredited by a recognized accreditation organization. If an adverse event meets the criteria for reporting, the outpatient diagnostic facility must report that event regardless of the location of the medical service provided by the outpatient diagnostic facility.

(v)(1) Outpatient treatment facility means a distinct entity that operates for the primary purpose of providing nonsurgical therapeutic (medical, occupational, or physical) care on an outpatient basis or home health care setting. Outpatient treatment facilities include ambulance providers, rescue services, and home health care groups. Examples of services provided by outpatient treatment facilities include: Cardiac defibrillation, chemotherapy, radiotherapy, pain control, dialysis, speech or physical therapy, and treatment for substance abuse.

(2) An outpatient treatment facility may be either independent (i.e., not a part of a provider of services or any other facility) or operated by another medical entity (e.g., under the common ownership, licensure, or control of an entity). An outpatient treatment facility is covered by this regulation regardless of whether it is licensed by a Federal, State, municipal, or local government or whether it is accredited by a recognized accreditation organization. If an adverse event meets the criteria for reporting, the outpatient treatment facility must report that event regardless of the nature or location of the medical service provided by the outpatient treatment facility.

(w) Patient of the facility means any individual who is being diagnosed or treated and/or receiving medical care at or under the control or authority of the facility. For the purposes of this part, the definition encompasses employees of the facility or individuals affiliated with the facility, who in the course of their duties suffer a device-related death or serious injury that has or may have been caused or contributed to by a device used at the facility.

(x) Physician`s office means a facility that operates as the office of a physician or other health care professional (e.g., dentist, chiropractor, optometrist, nurse practitioner, school nurse offices, school clinics, employee health clinics, or free-standing care units) for the primary purpose of examination, evaluation, and treatment or referral of patients. A physician`s office may be independent, a group practice, or part of a Health Maintenance Organization.

(y) [Reserved]

(z) Remedial action means, for the purposes of this subpart, any action other than routine maintenance or servicing, of a device where such action is necessary to prevent recurrence of a reportable event.

(aa) [Reserved]

(bb)(1) Serious injury means an injury or illness that:

(i) Is life-threatening;

(ii) Results in permanent impairment of a body function or permanent damage to body structure; or

(iii) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

(2) Permanent means, for purposes of this subpart, irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

(cc) Shelf life , as required on the manufacturer`s baseline report, means the maximum time a device will remain functional from the date of manufacture until it is used in patient care. Some devices have an expiration date on their labeling indicating the maximum time they can be stored before losing their ability to perform their intended function.

(dd) [Reserved]

(ee)(1) User facility report number means the number that uniquely identifies each report submitted by a user facility to manufacturers and FDA. This number consists of three parts as follows:

(i) The user facility`s 10-digit Health Care Financing Administration (HCFA) number (if the HCFA number has fewer than 10 digits, fill the remaining spaces with zeros);

(ii) The four-digit calendar year in which the report is submitted; and

(iii) The four-digit sequence number of the reports submitted for the year, starting with 0001. (For example, a complete number will appear as follows: 1234560000-1995-0001.)

(2) If a facility has more than one HCFA number, it must select one that will be used for all of its MDR reports. If a facility has no HCFA number, it should use all zeros in the appropriate space in its initial report (e.g., 0000000000-1995-0001) and FDA will assign a number for future use. The number assigned will be used in FDA`s record of that report and in any correspondence with the user facility. All zeros should be used subsequent to the first report if the user does not receive FDA's assigned number before the next report is submitted. If a facility has multiple sites, the primary site can report centrally and use one reporting number for all sites if the primary site provides the name, address and HCFA number for each respective site.

(ff) Work day means Monday through Friday, excluding Federal holidays.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4118, Jan. 26, 2000; 66 FR 23156, May 8, 2001]

Effective Date Note: At 61 FR 38347, July 23, 1996, in Sec. 803.3, paragraph (n)(4) was stayed indefinitely.

803.9 Public availability of reports.

(a) Any report, including any FDA record of a telephone report, submitted under this part is available for public disclosure in accordance with part 20 of this chapter.

(b) Before public disclosure of a report, FDA will delete from the report:

(1) Any information that constitutes trade secret or confidential commercial or financial information under Sec. 20.61 of this chapter;

(2) Any personal, medical, and similar information (including the serial number of implanted devices), which would constitute an invasion of personal privacy under Sec. 20.63 of this chapter. FDA will disclose to a patient who requests a report, all the information in the report concerning that patient, as provided in Sec. 20.61 of this chapter; and

(3) Any names and other identifying information of a third party voluntarily submitting an adverse event report.

(c) FDA may not disclose the identity of a device user facility which makes a report under this part except in connection with:

(1) An action brought to enforce section 301(q) of the act, including the failure or refusal to furnish material or information required by section 519 of the act;

(2) A communication to a manufacturer of a device which is the subject of a report required by a user facility under Sec. 803.30; or (3) A disclosure to employees of the Department of Health and Human Services, to the Department of Justice, or to the duly authorized committees and subcommittees of the Congress.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4119, Jan. 26, 2000]

803.10 General description of reports required from user facilities, importers, and manufacturers.

(a) Device user facilities. User facilities must submit the following reports, which are described more fully in subpart C of this part.

(1) User facilities must submit MDR reports of individual adverse events within 10 days after the user facility becomes aware of an MDR reportable event as described in Secs. 803.30 and 803.32.

(i) User facilities must submit reports of device-related deaths to FDA and to the manufacturer, if known.

(ii) User facilities must submit reports of device-related serious injuries to manufacturers, or to FDA, if the manufacturer is unknown.

(2) User facilities must submit annual reports as described in Sec. 803.33.(b) Importers must submit MDR reports of individual adverse events within 30 days after the importer becomes aware of an MDR reportable event as described in Sec. 803.3. Importers must submit reports of device-related deaths or serious injuries to FDA and to the manufacturer and reports of malfunctions to the manufacturer.

(b) Device importers. Importers must submit the following reports, which are described more fully in subpart D of this part.

(1) Importers must submit MDR reports of individual adverse events within 30 days after the importer becomes aware of an MDR reportable event as described in Secs. 803.40 and 803.42.

(i) Importers must submit reports of device-related deaths or serious injuries to FDA and to the manufacturer.

(ii) Importers must submit reports of malfunctions to the manufacturer.

(2) [Reserved]

(c) Device manufacturers. Manufacturers must submit the following reports as described more fully in subpart E of this part:

(1) MDR reports of individual adverse events within 30 days after the manufacturer becomes aware of a reportable death, serious injury, or malfunction as described in Secs. 803.50 and 803.52.

(2) MDR reports of individual adverse events within 5 days of:

(i) Becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health or,

(ii) Becoming aware of an MDR reportable event for which FDA has made a written request, as described in Sec. 803.53.

(3) Annual baseline reports as described in Sec. 803.55.

(4) Supplemental reports if they obtain information that was not provided in an initial report as described in Sec. 803.56.

(5) Annual certification to FDA of the number of MDR reports filed during the preceding year as described in Sec. 803.57.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4119, Jan. 26, 2000; 66 FR 23157, May 8, 2001]

Sec. 803.11 Obtaining the forms.

User facilities and manufacturers must submit all reports of individual adverse events on FDA Form 3500A (MEDWATCH form) or in an electronic equivalent as approved under Sec. 803.14. This form and all other forms referenced in this section can also be obtained from the Consolidated Forms and Publications Office, Washington Commerce Center, 3222 Hubbard Rd., Landover, MD 20875; from the Food and Drug Administration, MEDWATCH (HF-2), 5600 Fishers Lane, Rockville, MD 20857, 301-827-7240; from the Division of Small Manufacturers Assistance, Office of Health and Industry Programs, Center for Devices and Radiological Health (HFZ-220), 1350 Piccard Dr. Rockville, MD 20850, FAX 301-443-8818; or from http://www.fda.gov/opacom/morechoices/fdaforms/cdrh.html on the Internet.

[65 FR 17136, Mar. 31, 2000]

Sec. 803.12 Where to submit reports.

(a) Any written report or additional information required under this part shall be submitted to: Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, MD 20847-3002.

(b) Each report and its envelope shall be specifically identified, e.g., “User Facility Report,” “Annual Report,” “Importer Report,” “Manufacturer Report,” “5-Day Report,” “Baseline Report,” etc. (c) If an entity is confronted with a public health emergency, this can be brought to FDA’s attention by contacting the FDA Emergency Operations Branch (HFC-162), Office of Regional Operations, at 301-443- 1240, and should be followed by the submission of a FAX report to 301- 443-3757.

(c) A voluntary telephone report may be submitted to, or information regarding voluntary reporting may be obtained from, the MEDWATCH hotline at 800-FDA-1088.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4119, Jan. 26, 2000]

803.13 English reporting requirement.

(a) All reports required in this part which are submitted in writing or electronic equivalent shall be submitted to FDA in English.

(b) All reports required in this part which are submitted on an electronic medium shall be submitted to FDA in a manner consistent with 803.14.

803.14 Electronic reporting.

(a) Any report required by this part may be submitted electronically with prior written consent from FDA. Such consent is revocable. Electronic report submissions include alternative reporting media (magnetic tape, disc, etc.) and computer-to-computer communication.

(b) Any electronic report meeting electronic reporting standards, guidance documents, or other procedures developed by the agency for MDR reporting will be deemed to have prior approval for use.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 56480, Sept. 19, 2000]

803.15 Requests for additional information.

(a) FDA may determine that protection of the public health requires additional or clarifying information for medical device reports submitted to FDA under this part. In these instances, and in cases when the additional information is beyond the scope of FDA reporting forms or is not readily accessible, the agency will notify the reporting entity in writing of the additional information that is required.

(b) Any request under this section shall state the reason or purpose for which the information is being requested, specify the date that the information is to be submitted and clearly relate the request to a reported event. All verbal requests will be confirmed in writing by the agency.

803.16 Disclaimers.

A report or other information submitted by a reporting entity under this part, and any release by FDA of that report or information, does not necessarily reflect a conclusion by the party submitting the report or by FDA that the report or information constitutes an admission that the device, or the reporting entity or its employees, caused or contributed to the reportable event. The reporting entity need not admit and may deny that the report or information submitted under this part constitutes an admission that the device, the party submitting the report, or employees thereof, caused or contributed to a reportable event.

803.17 Written MDR procedures.

User facilities, importers, and manufacturers shall devel-

op, maintain, and implement written MDR procedures for the following:

(a) Internal systems that provide for:

(1) Timely and effective identification, communication, and evaluation of events that may be subject to medical device reporting requirements;

(2) A standardized review process/procedure for determining when an event meets the criteria for reporting under this part; and

(3) Timely transmission of complete medical device reports to FDA and/or manufacturers;

(b) Documentation and recordkeeping requirements for:

(1) Information that was evaluated to determine if an event was reportable;

(2) All medical device reports and information submitted to FDA and manufacturers;

(3) Any information that was evaluated for the purpose of preparing the submission of semiannual reports or certification; and

(4) Systems that ensure access to information that facilitates timely followup and inspection by FDA.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4119, Jan. 26, 2000]

803.18 Files and distributor records.

(a) User facilities, importers, and manufacturers shall establish and maintain MDR event files. All MDR event files shall be prominently identified as such and filed to facilitate timely access.

(b)(1) For purposes of this part, "MDR event files" are written or electronic files maintained by user facilities, importers, and manufacturers. MDR event files may incorporate references to other information, e.g., medical records, patient files, engineering reports, etc., in lieu of copying and maintaining duplicates in this file. MDR event files must contain:

(i) Information in the possession of the reporting entity or references to information related to the adverse event, including all documentation of the entity's deliberations and decision making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable under this part.

(ii) Copies of all MDR forms, as required by this part, and other information related to the event that was submitted to FDA and other entities (e.g., an importer, distributor, or manufacturer).

(2) User facilities, importers, and manufacturers shall permit any authorized FDA employee during all reasonable times to access, to copy, and to verify the records required by this part.

(c) User facilities shall retain an MDR event file relating to an adverse event for a period of 2 years from the date of the event. Manufacturers and importers shall retain an MDR event file relating to an adverse event for a period of 2 years from the date of the event or a period of time equivalent to the expected life of the device, whichever is greater. MDR event files must be maintained for the time periods described in this paragraph even if the device is no longer distributed.

(d)(1) A device distributor shall establish and maintain device complaint records containing any incident information, including any written, electronic, or oral communication, either received by or generated by the firm, that alleges deficiencies related to the identity (e.g., labeling), quality, durability, reliability, safety, effectiveness, or performance of a device. Information regarding the evaluation of the allegations, if any, shall also be maintained in the incident record. Device incident records shall be prominently identified as such and shall be filed by device, and may be maintained in written or electronic form. Files maintained in electronic form must be backed up.

(2) A device distributor shall retain copies of the records required to be maintained under this section for a period of 2 years from the date of inclusion of the record in the file or for a period of time equivalent to the expected life of the device, whichever is greater, even if the distributor has ceased to distribute the device that is the subject of the record.

(3) A device distributor shall maintain the device complaint files established under this section at the distributor's principal business establishment. A distributor that is also a manufacturer may maintain the file at the same location as the manufacturer maintains its complaint file under Secs. 820.180 and 820.198 of this chapter. A device distributor shall permit any authorized FDA employee, during all reasonable times, to have access to, and to copy and verify, the records required by this part.

(e) The manufacturer may maintain MDR event files as part of its complaint file, under Sec. 820.198 of this chapter, provided that such records are prominently identified as MDR reportable events. A report submitted under this subpart A shall not be considered to comply with this part unless the event has been evaluated in accordance with the requirements of Secs. 820.162 and 820.198 of this chapter. MDR files shall contain an explanation of why any information required by this part was not submitted or could not be obtained. The results of the evaluation of each event are to be documented and maintained in the manufacturer's MDR event file.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4119, Jan. 26, 2000]

803.19 Exemptions, variances, and alternative reporting requirements.

(a) The following persons are exempt from the reporting requirements under this part.

(1) An individual who is a licensed practitioner who prescribes or administers devices intended for use in humans and who manufactures or imports devices solely for use in diagnosing and treating persons with whom the practitioner has a "physician-patient" relationship.

(2) An individual who manufactures devices intended for use in humans solely for such person's use in research or teaching and not for sale, including any person who is subject to alternative reporting requirements under the investigational device exemption regulations, parts 812 and 813 of this chapter, which require reporting of all adverse device effects.

(3) Dental laboratories, or optical laboratories.

(b) Manufacturers, importers, or user facilities may request exemptions or variances from any or all of the reporting requirements in this part. The request shall be in writing and include information necessary to identify the firm and device, a complete statement of the request for exemption, variance, or alternative reporting, and an explanation why the request is justified.

(c) FDA may grant in writing, to a manufacturer, importer, or user facility, an exemption, variance, or alternative from, or to, any or all of the reporting requirements in this part and may change the frequency of reporting to quarterly, semi-annually, annually, or other appropriate time period. These modifications may be initiated by a request as specified in this section, or at the discretion of FDA. When granting such modifications, FDA may impose other reporting requirements to ensure the protection of public health.

(d) FDA may revoke or modify in writing an exemption, variance, or alternative reporting requirements if FDA determines that protection of the public health justifies the modification or a return to the requirements as stated in this part.

(e) Firms granted a reporting modification by FDA shall provide any reports or information required by that approval. The conditions of the approval will replace and supersede the reporting requirement specified in this part until such time that FDA revokes or modifies the alternative reporting requirements in accordance with paragraph (d) of this section.

[60 FR 63597, Dec. 11, 1995, as amended at 61 FR 44615, Aug. 28, 1996; 65 FR 4119, Jan. 26, 2000; 65 FR 17136, Mar. 31, 2000; 65 FR 23157, May 8, 2001]

Subpart B - Generally Applicable Requirements for Individual Adverse Event Reports

803.20 How to report.

(a) Description of form. There are two versions of the MEDWATCH form for individual reports of adverse events. FDA Form 3500 is available for use by health professionals and consumers for the submission of voluntary reports regarding FDA-regulated products. FDA Form 3500A is the mandatory reporting form to be used for submitting reports by user facilities and manufacturers of FDA-regulated products. The form has sections that must be completed by all reporters and other sections that must be completed only by the user facility, importer, or manufacturer.

(1) The front of FDA Form 3500A is to be filled out by all reporters. The front of the form requests information regarding the patient, the event, the device, and the "initial reporter" (i.e., the first person or entity that submitted the information to the user facility, manufacturer, or importer).

(2) The back part of the form contains sections to be completed by user facilities, importers, and manufacturers. User facilities must complete section F; device manufacturers must complete sections G and H. Manufacturers are not required to recopy information submitted to them on a Form 3500A unless the information is being copied onto an electronic medium. If the manufacturer corrects or supplies information missing from the other reporter's 3500A form, it should attach a copy of that form to the manufacturer's report form. If the information from the other reporter's 3500A form is complete and correct, the manufacturer can fill in the remaining information on the same form.

(b) Reporting standards.

(1) User facilities are required to submit MDR reports to:

(i) The device manufacturer and to FDA within 10 days of becoming aware of information that reasonably suggests that a device has or may have caused or contributed to a death; or

(ii) The manufacturer within 10 days of becoming aware of information that reasonably suggests that a device has or may have caused or contributed to a serious injury. Such reports shall be submitted to FDA if the device manufacturer is not known.

(2) Importers are required to submit death and serious injury reports to FDA and the device manufacturer and submit malfunction reports to the manufacturer only:

(i) Within 30 days of becoming aware of information that reasonably suggests that a device has or may have caused or contributed to a death or serious injury.

(ii) Within 30 days of receiving information that a device marketed by the importer has malfunctioned and that such a device or a similar device marketed by the importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

(3) Manufacturers are required to submit MDR reports to FDA:

(i) Within 30 days of becoming aware of information that reasonably suggests that a device may have caused or contributed to a death or serious injury; or

(ii) Within 30 days of becoming aware of information that reasonably suggests a device has malfunctioned and that device or a similar device marketed by the manufacturer would be likely to cause a death or serious injury if the malfunction were to recur; or

(iii) Within 5 days if required by Sec. 803.53.

(c) Information that reasonably suggests a reportable event occurred.

(1) Information that reasonably suggests that a device has or may have caused or contributed to an MDR reportable event (i.e., death, serious injury, and, for manufacturers, a malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur) includes any information, such as professional, scientific or medical facts and observations or opinions, that would reasonably suggest that a device has caused or may have caused or contributed to a reportable event.

(2) Entities required to report under this part do not have to report adverse events for which there is information that would cause a person who is qualified to make a medical judgment (e.g., a physician, nurse, risk manager, or biomedical engineer) to reach a reasonable conclusion that a device did not cause or contribute to a death or serious injury, or that a malfunction would not be likely to cause or contribute to a death or serious injury if it were to recur. Information which leads the qualified person to determine that a device-related event is or is not reportable must be

contained in the MDR event files, as described in Sec. 803.18.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4119, Jan. 26, 2000; 66 FR 23157, May 8, 2001]

803.21 Reporting codes.

(a) FDA has developed a MEDWATCH Mandatory Reporting Form Coding Manual for use with medical device reports. This manual contains codes for hundreds of adverse events for use with FDA Form 3500A. The coding manual is available from the Division of Small Manufacturer Assistance, Center for Devices and Radiological Health, 1350 Piccard Dr., Rockville, MD 20850, FAX 301-443-8818.

(b) FDA may use additional coding of information on the reporting forms or modify the existing codes on an ad hoc or generic basis. In such cases, FDA will ensure that the new coding information is available to all reporters.

803.22 When not to file.

(a) Only one medical device report from the user facility, importer, or manufacturer is required under this part if the reporting entity becomes aware of information from multiple sources regarding the same patient and same event.

(b) A medical device report that would otherwise be required under this section is not required if:

(1) The user facility, importer, or manufacturer determines that the information received is erroneous in that a device-related adverse event did not occur. Documentation of such reports shall be retained in MDR files for time periods specified in Sec. 803.18.

(2) The manufacturer or importer determines that the device was manufactured or imported by another manufacturer or importer. Any reportable event information that is erroneously sent to a manufacturer or importer shall be forwarded to FDA, with a cover letter explaining that the device in question was not manufactured or imported by that firm.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4120, Jan. 26, 2000]

Subpart C -User Facility Reporting Requirements

803.30 Individual adverse event reports; user facilities.

(a) Reporting standard. A user facility shall submit the following reports to the manufacturer or to FDA, or both, as specified below:

(1) Reports of death. Whenever a user facility receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device has or may have caused or contributed to the death of a patient of the facility, the facility shall as soon as practicable, but not later than 10 work days after becoming aware of the information, report the information required by 803.32 to FDA, on FDA Form 3500A, or an electronic equivalent as approved under 803.14, and if the identity of the manufacturer is known, to the device manufacturer.

(2) Reports of serious injury. Whenever a user facility receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device has or may have caused or contributed to a serious injury to a patient of the facility, the facility shall, as soon as practicable but not later than 10 work days after becoming aware of the information, report the information required by 803.32, on FDA Form 3500A or electronic equivalent, as approved under 803.14, to the manufacturer of the device. If the identity of the manufacturer is not known, the report shall be submitted to FDA.

(b) Information that is reasonably known to user facilities. User facilities must provide all information required in this subpart C that is reasonably known to them. Such information includes information found in documents in the possession of the user facility and any information that becomes available as a result of reasonable followup within the facility. A user facility is not required to evaluate or investigate the event by obtaining or evaluating information that is not reasonably known to it.

803.32. Individual adverse event report data elements.

User facility reports shall contain the following information. reasonably known to them as described in 803.30(b), which corresponds to the format of FDA Form 3500A:

(a) Patient information (Block A) shall contain the following:

(1) Patient name or other identifier;

(2) Patient age at the time of event, or date of birth;

(3) Patient gender; and

(4) Patient weight.

(b) Adverse event or product problem (Block B) shall contain the following:

(1) Identification of adverse event or product problem;

(2) Outcomes attributed to the adverse event, e.g., death; or serious injury, that is:

(i) Life threatening injury or illness;

(ii) Disability resulting in permanent impairment of a body function or permanent damage to a body structure; or

(iii) Injury or illness that requires intervention to prevent permanent impairment of a body structure or function;

(3) Date of event;

(4) Date of report by the initial reporter;

(5) Description of event or problem, including a discussion of how the device was involved, nature of the problem, patient followup or required treatment, and any environmental conditions that may have influenced the event;

(6) Description of relevant tests including dates and laboratory data; and

(7) Description of other relevant history including preexisting medical conditions.

(c) Device information (Block D) shall contain the following:

(1) Brand name;

(2) Type of device;

(3) Manufacturer name and address;

(4) Operator of the device (health professional, patient, lay user, other);

(5) Expiration date;

(6) Model number, catalog number serial number, lot number, or other identifying number;

(7) Date of device implantation (month, day, year);

(8) Date of device explantation (month, day, year);

(9) Whether device was available for evaluation and whether device was returned to the manufacturer; if so, the date it was returned to the manufacturer; and

(10) Concomitant medical products and therapy dates. (Do not list products that were used to treat the event.)

(d) Initial reporter information (Block E) shall contain the following:

(1) Name, address, and telephone number of the reporter who initially provided information to the user facility, manufacturer, or distributor;

(2) Whether the initial reporter is a health professional;

(3) Occupation; and

(4) Whether initial reporter also sent a copy of the report to FDA, if known.

(e) User facility information (Block F) shall contain the following:

(1) Whether reporter is a user facility;

(2) User facility number;

(3) User facility address;

(4) Contact person;

(5) Contact person's telephone number;

(6) Date the user facility became aware of the event (month, day, year);

(7) Type of report (initial or followup; if followup, include report number of initial report);

(8) Date of the user facility report (month, day, year);

(9) Approximate age of device;

(10) Event problem codes"patient code and device code (refer to FDA "Coding Manual For Form 3500A");

(11) Whether a report was sent to FDA and the date it was sent (month, day, year);

(12) Location, where event occurred;

(13) Whether report was sent to the manufacturer and the date it was sent (month, day, year); and

(14) Manufacturer name and address; if available.

803.33 Annual reports.

(a) Each user facility shall submit to FDA an annual report on FDA Form 3419, or electronic equivalent as approved by FDA under Sec. 803.14. Annual reports shall be submitted by January 1 of each year. The annual report and envelope shall be clearly identified and submitted to FDA with information that includes:

(1) User facility's HCFA provider number used for medical device reports, or number assigned by FDA for reporting purposes in accordance with Sec. 803.3(ee);

(2) Reporting year;

(3) Facility's name and complete address;

(4) Total number of reports attached or summarized;

(5) Date of the annual report and the lowest and highest user facility report number of medical device reports submitted during the report period, e.g., 1234567890-1995-0001 through 1000;

(6) Name, position title, and complete address of the individual designated as the facility contact person responsible for reporting to FDA and whether that person is a new contact for that facility; and

(7) Information for each reportable event that occurred during the annual reporting period including:

(i) User facility report number;

(ii) Name and address of the device manufacturer;

(iii) Device brand name and common name;

(iv) Product model, catalog, serial and lot number;

(v) A brief description of the event reported to the manufacturer and/or FDA; and

(vi) Where the report was submitted, i.e., to FDA, manufacturer, distributor, importer, etc.

(b) In lieu of submitting the information in paragraph (a)(7) of this section, a user facility may submit a copy of FDA Form 3500A, or an electronic equivalent as approved under section 803.14, for each medical device report submitted to FDA and/or manufacturers by that facility during the reporting period.

(c) If no reports are submitted to either FDA or manufacturers during these time periods, no annual report is required.

[60 FR 63597, Dec. 11, 1995, as amended at 65 FR 4120, Jan. 26, 2000]

Subpart D - Importer Reporting Requirements

Source: 65 FR 4120, Jan. 26, 2000, unless otherwise noted

803.40 Individual adverse event reporting requirements; importers.

(a) An importer shall submit to FDA a report, and a copy of such report to the manufacturer, containing the information required by Sec. 803.42 on FDA form 3500A as soon as practicable, but not later than 30 days after the importer receives or otherwise becomes aware of information from any source, including user facilities, individuals, or medical or scientific literature, whether published or unpublished, that reasonably suggests that one of its marketed devices may have caused or contributed to a death or serious injury.

(b) An importer shall submit to the manufacturer a report containing information required by Sec. 803.42 on FDA form 3500A, as soon as practicable, but not later than 30 days after the importer receives or otherwise becomes aware of information from any source, including user facilities, individuals, or through the importer's own research, testing, evaluation, servicing, or maintenance of one of its devices, that one of the devices marketed by the importer has malfunctioned and that such device or a similar device marketed by the importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

803.42 Individual adverse event report data elements.

Individual medical device importer reports shall contain the following information, in so far as the information is known or should be known to the importer, as described in Sec. 803.40, which corresponds to the format of FDA Form 3500A:

(a) Patient information (Block A) shall contain the following:

(1) Patient name or other identifier;
(2) Patient age at the time of event, or date of birth;
(3) Patient gender; and
(4) Patient weight.
(b) Adverse event or product problem (Block B) shall contain the following:
(1) Adverse event or product problem;
(2) Outcomes attributed to the adverse event, that is:
(i) Death;
(ii) Life threatening injury or illness;
(iii) Disability resulting in permanent impairment of a body function or permanent damage to a body structure; or
(iv) Injury or illness that requires intervention to prevent permanent impairment of a body structure or function;
(3) Date of event;
(4) Date of report by the initial reporter;
(5) Description of the event or problem to include a discussion of how the device was involved, nature of the problem, patient followup or required treatment, and any environmental conditions that may have influenced the event;
(6) Description of relevant tests, including dates and laboratory data; and
(7) Other relevant patient history including preexisting medical conditions.
(c) Device information (Block D) shall contain the following:
(1) Brand name;
(2) Type of device;
(3) Manufacturer name and address;
(4) Operator of the device (health professional, patient, lay user, other);
(5) Expiration date;
(6) Model number, catalog number, serial number, lot number or other identifying number;
(7) Date of device implantation (month, day, year);
(8) Date of device explantation (month, day, year);
(9) Whether the device was available for evaluation, and whether the device was returned to the manufacturer, and if so, the date it was returned to the manufacturer; and
(10) Concomitant medical products and therapy dates. (Do not list products that were used to treat the event.)
(d) Initial reporter information (Block E) shall contain the following:
(1) Name, address, and phone number of the reporter who initially provided information to the user facility, manufacturer, or distributor;
(2) Whether the initial reporter is a health professional;
(3) Occupation; and
(4) Whether the initial reporter also sent a copy of the report to FDA, if known.
(e) Importer information (Block F) shall contain the following:
(1) Whether reporter is an importer;
(2) Importer report number;
(3) Importer address;
(4) Contact person;
(5) Contact person's telephone number;
(6) Date the importer became aware of the event (month, day, year);
(7) Type of report (initial or followup (if followup, include report number of initial report));
(8) Date of the importer report (month, day, year);
(9) Approximate age of device;
(10) Event problem codes—patient code and device code (refer to FDA "Coding Manual For Form 3500A");
(11) Whether a report was sent to FDA and the date it was sent (month, day, year);
(12) Location, where event occurred;
(13) Whether a report was sent to the manufacturer and the date it was sent (month, day, year); and
(14) Manufacturer name and address; if available.

Subpart E - Manufacturer Reporting Requirements

803.50 Individual adverse event reports; manufacturers

(a) Reporting standards. Device manufacturers are required to report within 30 days whenever the manufacturer receives or otherwise becomes aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer:
(1) May have caused or contributed to a death or serious injury; or
(2) Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.
(b) Information that is reasonably known to manufacturers.
(1) Manufacturers must provide all information required in this subpart E that is reasonably known to them. FDA considers the following information to be reasonably known to the manufacturer:
(i) Any information that can be obtained by contacting a user facility, distributor and/or other initial reporter;
(ii) Any information in a manufacturer's possession; or
(iii) Any information that can be obtained by analysis, testing or other evaluation of the device.
(2) Manufacturers are responsible for obtaining and providing FDA with information that is incomplete or missing from reports submitted by user facilities, distributors, and other initial reporters. Manufacturers are also responsible for conducting an investigation of each event, and evaluating the cause of the event. If a manufacturer cannot provide complete information on an MDR report, it must provide a statement explaining why such information was incomplete and the steps taken to obtain the information. Any required information not available at the time of the report, which is obtained after the initial filing, must be provided by the manufacturer in a supplemental report under 803.56.

803.52 Individual adverse event report data elements.

Individual medical device manufacturer reports shall contain the following information, known or reasonably known to them as described in 803.50(b), which corresponds to the format of FDA Form 3500A:
(a) Patient information (Block A) shall contain the following:
(1) Patient name or other identifier

(2) Patient age at the time of event, or date of birth;
(3) Patient gender; and
(4) Patient weight.
(b) Adverse event or product problem (Block B) shall contain the following:
(1) Adverse event or product problem
(2) Outcomes attributed to the adverse event, e.g., death; or serious injury, that is:
(i) Life threatening injury or illness;
(ii) Disability resulting in permanent impairment of a body function or permanent damage to a body structure, or
(iii) Injury or illness that requires intervention to prevent permanent impairment of a body structure or function;
(3) Date of event;
(4) Date of report by the initial reporter;
(5) Description of the event or problem to include a discussion of how the device was involved, nature of the problem, patient followup or required treatment, and any environmental conditions that may have influenced the event;
(6) Description of relevant tests, including dates and laboratory data, and
(7) Other relevant patient history including pre-existing medical conditions.
(c) Device information (Block D) shall contain the following:
(1) Brand name;
(2) Type of device
(3) Manufacturer name and address
(4) Operator of the device (health professional, patient, lay user, other);
(5) Expiration date;
(6) Model number, catalog number serial number, lot number or other identifying number;
(7) Date of device implantation (month, day, year);
(8) Date of device explantation (month, day, year);
(9) Whether the device was available for evaluation, and whether the device was returned to the manufacturer, and if so, the date it was returned to the manufacturer; and
(10) Concomitant medical products and therapy dates. (Do not list products that were used to treat the event.)
(d) Initial reporter information (Block E) shall contain the following:
(1) Name, address, and phone number of the reporter who initially provided information to the user facility, manufacturer, or distributor;
(2) Whether the initial reporter is a health professional;
(3) Occupation, and
(4) Whether the initial reporter also sent a copy of the report to FDA, if known.
(e) All manufacturers (Block G) shall contain the following:
(1) Contact office name and address and device manufacturing site;
(2) Telephone number;
(3) Report sources;
(4) Date received by manufacturer (month, day, year);
(5) Type of report being submitted (e.g., 5-day, initial, supplemental); and
(6) Manufacturer report number.
(f) Device manufacturers (Block H) shall contain the following:
(1) Type of reportable event (death serious injury, malfunction, etc.)
(2) Type of followup report, if applicable (e.g., correction, response to FDA request, etc.);
(3) If the device was returned to the manufacturer and evaluated by the manufacturer, a summary of the evaluation. If no evaluation was performed, provide an explanation why no evaluation was performed
(4) Device manufacture date (month, day, year);
(5) Was device labeled for single use;
(6) Evaluation codes (including event codes, method of evaluation, result and conclusion codes) (refer to FDA "Coding Manual for Form 3500A")
(7) Whether remedial action was taken and type
(8) Whether use of device was initial reuse, or unknown;
(9) Whether remedial action was reported as a removal or correction under section 519(f) of the act (list the correction/removal report number); and
(10) Additional manufacturer narrative; and/or
(11) Corrected data, including:
(i) Any information missing on the user facility report or distributor report, including missing event codes, or information corrected on such forms after manufacturer verification;
(ii) For each event code provided by the user facility under 803.32(d)(10) or a distributor, a statement of whether the type of the event represented by the code is addressed in the device labeling; and
(iii) If any required information was not provided, an explanation of why such information was not provided and the steps taken to obtain such information.

803.53 Five-day reports.

A manufacturer shall submit a 5-day report to FDA, on Form 3500A or electronic equivalent as approved by FDA under 803.14 within 5 workdays of:
(a) Becoming aware that a reportable MDR event or events, from any information, including any trend analysis, necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health; or
(b) Becoming aware of an MDR reportable event for which FDA has made a written request for the submission of a 5-day report. When such a request is made, the manufacturer shall submit, without further requests, a 5-day report for all subsequent events of the same nature that involve substantially similar devices for the time period specified in the written request. The time period stated in the original written request can be extended by FDA if it is in the interest of the public health.

803.55 Baseline report.

(a) A manufacturer shall submit a baseline report on FDA Form 3417, or electronic equivalent as approved by FDA under 803.14 for a device when the device model is first reported under 803.50.
(b) Each baseline report shall be updated annually, on the anniversary month of the initial submission, after the initial baseline report is submitted. Changes to baseline information shall be reported in the manner described in 803.56 (i.e., include only the new, changed, or corrected informa-

tion in the appropriate portion(s) of the report form). Baseline reports shall contain the following:

(1) Name, complete address, and registration number of the manufacturer's reporting site. If the reporting site is not registered, FDA will assign a temporary registration number until the reporting site officially registers. The manufacturer will be informed of the temporary registration number;

(2) FDA registration number of each site where the device is manufactured;

(3) Name, complete address, and telephone number of the individual who has been designated by the manufacturer as its MDR contact and date of the report. For foreign manufacturers, a confirmation that the individual submitting the report is the agent of the manufacturer designated under 803.58(a) is required;

(4) Product identification, including device family, brand name, generic name, model number, catalog number, product code and any other product identification number or designation;

(5) Identification of any device previously reported in a baseline report that is substantially similar (e.g., same device with a different model number, or same device except for cosmetic differences in color or shape) to the device being reported, including the identification of the previously reported device by model number, catalog number or other product identification, and the date of the baseline report for the previously reported device;

(6) Basis for marketing, including 510(k) premarket notification number or PMA number, if applicable, and whether the device is currently the subject of an approved post-market study under section 522 of the act;

(7) Date the device was initially marketed and, if applicable, the date on which the manufacturer ceased marketing the device;

(8) Shelf life, if applicable, and expected life of the device;

(9) The number of devices manufactured and distributed in the last 12 months and, an estimate of the number of devices in current use; and

(10) Brief description of any methods used to estimate the number of devices distributed and the method used to estimate the number of devices in current use. If this information was provided in a previous baseline report, in lieu of resubmitting the information, it may be referenced by providing the date and product identification for the previous baseline report.

EFFECTIVE DATE NOTE: At 61 FR 39869, July 31, 1996, in 803.55, paragraphs (b)(9) and (10) were stayed indefinitely.

803.56 Supplemental reports.

When a manufacturer obtains information required under this part that was not provided because it was not known or was not available when the initial report was submitted, the manufacturer shall submit to FDA the supplemental information within 1 month following receipt of such information. In supplemental reports, the manufacturer shall:

(a) Indicate on the form and the envelope, that the reporting form being submitted is a supplemental report. If the report being supplemented is an FDA Form 3500A report, the manufacturer must select, in Item H-2, the appropriate code for the type of supplemental information being submitted

(b) Provide the appropriate identification numbers of the report that will be updated with the supplemental information, e.g., original manufacturer report number and user facility report number, if applicable;

(c) For reports that cross reference previous reports, include only the new, changed, or corrected information in the appropriate portion(s) of the respective form(s).

803.58 Foreign Manufacturers

(a) Every foreign manufacturer whose devices are distributed in the United States shall designate a U.S. agent to be responsible for reporting in accordance with 807.40 of this chapter. The U.S. designated agent accepts responsibility for the duties that Such designation entails. Upon the effective date of this regulation, foreign manufacturers shall inform FDA, by letter, of the name and address of the U.S. agent designated under this section and 807.40 of this chapter, and shall update this information as necessary. Such updated information shall be submitted to FDA, within 5 days of a change in the designated agent information.

(b) U.S.-designated agents of foreign manufacturers are required to:

(1) Report to FDA in accordance with 803.50, 803.52, 803.53, 803.55, and 803.56;

(2) Conduct, or obtain from the foreign manufacturer the necessary information regarding, the investigation and evaluation of the event to comport with the requirements of 803.50;

(3) Certify in accordance with 803.57;

(4) Forward MDR complaints to the foreign manufacturer and maintain documentation of this requirement;

(5) Maintain complaint files in accordance with 803.18;

EFFECTIVE DATE NOTE: At 61 FR 38347, July 23,1996, 803.58 was stayed indefinitely.

PART 820 - QUALITY SYSTEM REGULATION

AUTHORITY: 21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360j, 360l, 371, 374, 381, 383.
SOURCE: 61 FR 52654, Oct 7, 1996, unless otherwise noted.

Subpart A - General Provisions

820.1 Scope.

(a) Applicability.

(1) Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (the act). This part establishes basic requirements applica-

ble to manufacturers of finished medical devices. If a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged. With respect to class I devices, design controls apply only to those devices listed in Sec. 820.30(a)(2). This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance. Manufacturers of human blood and blood components are not subject to this part, but are subject to part 606 of this chapter.

(2) The provisions of this part shall be applicable to any finished device as defined in this part, intended for human use, that is manufactured, imported, or offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(3) In this regulation the term "where appropriate" is used several times. When a requirement is qualified by "where appropriate," it is deemed to be "appropriate" unless the manufacturer can document justification otherwise. A requirement is "appropriate" if nonimplementation could reasonably be expected to result in the product not meeting its specified requirements or the manufacturer not being able to carry out any necessary corrective action.

(b) Limitations. The quality system regulation in this part supplements regulations in other parts of this chapter except where explicitly stated otherwise. In the event that it is impossible to comply with all applicable regulations, both in this part and in other parts of this chapter, the regulations specifically applicable to the device in question shall supersede any other generally applicable requirements.

(c) Authority. Part 820 is established and issued under authority of sections 501, 502, 510, 513, 514, 515, 518, 519, 520, 522, 701, 704, 801, 803 of the act (21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 360l, 371, 374, 381, 383). The failure to comply with any applicable provision in this part renders a device adulterated under section 501(h) of the act. Such a device, as well as any person responsible for the failure to comply, is subject to regulatory action.

(d) Foreign manufacturers. If a manufacturer who offers devices for import into the United States refuses to permit or allow the completion of a Food and Drug Administration (FDA) inspection of the foreign facility for the purpose of determining compliance with this part, it shall appear for purposes of section 801(a) of the act, that the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, or servicing of any devices produced at such facility that are offered for import into the United States do not conform to the requirements of section 520(f) of the act and this part and that the devices manufactured at that facility are adulterated under section 501(h) of the act.

(e) Exemptions or variances.

(1) Any person who wishes to petition for an exemption or variance from any device quality system requirement is subject to the requirements of section 520(f)(2) of the act. Petitions for an exemption or variance shall be submitted according to the procedures set forth in Sec. 10.30 of this chapter, the FDA's administrative procedures. Guidance is available from the Center for Devices and Radiological Health, Division of Small Manufacturers Assistance (HFZ-220), 1350 Piccard Dr., Rockville, MD 20850, U.S.A., telephone 1-800-638-2041 or 1-301-443-6597, FAX 301-443-8818.

(2) FDA may initiate and grant a variance from any device quality system requirement when the agency determines that such variance is in the best interest of the public health. Such variance will remain in effect only so long as there remains a public health need for the device and the device would not likely be made sufficiently available without the variance.

[61 FR 52654, Oct. 7, 1996, as amended at 65 FR 17136, Mar. 31, 2000; 65 FR 66636, Nov. 7, 2000]

820.3 Definitions.

(a) Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-903, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-394)). All definitions in section 201 of the act shall apply to the regulations in this part.

(b) Complaint means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

(c) Component means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

(d) Control number means any distinctive symbols, such as a distinctive combination of letters or numbers, or both, from which the history of the manufacturing, packaging, labeling, and distribution of a unit, lot, or batch of finished devices can be determined.

(e) Design history file (DHF) means a compilation of records which describes the design history of a finished device.

(f) Design input means the physical and performance requirements of a device that are used as a basis for device design.

(g) Design output means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.

(h) Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

(i) Device history record (DHR) means a compilation of records containing the production history of a finished device.

(j) Device master record (DMR) means a compilation of records containing the procedures and specifications for a finished device.

(k) Establish means define, document (in writing or electronically), and implement.

(l) Finished device means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.

(m) Lot or batch means one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits.

(n) Management with executive responsibility means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system.

(o) Manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and U.S. designated agents of foreign entities performing these functions.

(p) Manufacturing material means any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produce during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer.

(q) Nonconformity means the nonfulfillment of a specified requirement.

(r) Product means components, manufacturing materials, in-process devices, finished devices, and returned devices.

(s) Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.

(t) Quality audit means a systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

(u) Quality policy means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.

(v) Quality system means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

(w) Remanufacturer means any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use.

(x) Rework means action taken on a nonconforming product so that it will fulfill the specified DMR requirements before it is released for distribution.

(y) Specification means any requirement with which a product, process, service, or other activity must conform.

(z) Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

(1) Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

(2) Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

(aa) Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

Subpart B - Quality System Requirements

820.5 Quality system.

Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part.

820.20 Management responsibility.

(a) Quality policy. Management with executive responsibility shall establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

(b) Organization . Each manufacturer shall establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the requirements of this part.

(1) Responsibility and authority. Each manufacturer shall establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks.

(2) Resources. Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities, including internal quality audits, to meet the requirements of this part.

(3) Management representative. Management with executive responsibility shall appoint, and document such appointment of, a member of management who, irrespective of other responsibilities, shall have established authority over and responsibility for:

(i) Ensuring that quality system requirements are effectively established and effectively maintained in accordance with this part; and

(ii) Reporting on the performance of the quality system to management with executive responsibility for review.

(c) Management review. Management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of this part and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews shall be documented.

(d) Quality planning. Each manufacturer shall establish a quality plan which defines the quality practices, resources , and activities relevant to devices that are designed and

manufactured. The manufacturer shall establish how the requirements for quality will be met.

(e) Quality system procedures . Each manufacturer shall establish quality system procedures and instructions. An outline of the structure of the documentation used in the quality system shall be established where appropriate.

820.22 Quality audit.

Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. Quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited. Corrective action(s), including a reaudit of deficient matters, shall be taken when necessary. A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and reaudits shall be documented.

820.25 Personnel.

(a) General. Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed.

(b) Training. Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented.

(1) As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs.

(2) Personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.

Subpart C - Design Controls

820.30 Design controls.

(a) General.

(1) Each manufacturer of any class III or class II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.

(2) The following class I devices are subject to design controls:

(i) Devices automated with computer software; and

(ii) The devices listed in the following chart:

Section	Device
868.6810	Catheter, Tracheobronchial Suction
878.4460	Glove, Surgeon's
880.6760	Restraint, Protective
892.5650	System, Applicator, Radionuclide, Manual
892.5740	Source, Radionuclide Teletherapy

(b) Design and development planning. Each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process. The plans shall be reviewed, updated, and approved as design and development evolves.

(c) Design input. Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

(c) Design output. Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning of the device are identified. Design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented.

(e) Design review. Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file (the DHF).

(f) Design verification. Each manufacturer shall establish and maintain procedures for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

(g) Design validation. Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification

of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.

(h) Design transfer. Each manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications.

(i) Design changes. Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.

(j) Design history file. Each manufacturer shall establish and maintain a DHF for each type of device. The DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part.

Subpart D - Document Controls

820.40 Document controls.

Each manufacturer shall establish and maintain procedures to control all documents that are required by this part. The procedures shall provide for the following:

(a) Document approval and distribution. Each manufacturer shall designate an individual(s) to review for adequacy and approve prior to issuance all documents established to meet the requirements of this part. The approval, including the date and signature of the individual(s) approving the document, shall be documented. Documents established to meet the requirements of this part shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use.

(b) Document changes. Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective.

Subpart E - Purchasing Controls

820.50 Purchasing controls.

Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.

(a) Evaluation of suppliers, contractors, and consultants. Each manufacturer shall establish and maintain the requirements, including quality requirements, that must be met by suppliers, contractors, and consultants. Each manufacturer shall:

(1) Evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements. The evaluation shall be documented.

(2) Define the type and extent of control to be exercised over the product, services, suppliers, contractors, and consultants, based on the evaluation results.

(3) Establish and maintain records of acceptable suppliers, contractors, and consultants.

(b) Purchasing data. Each manufacturer shall establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services. Purchasing documents shall include, where possible, an agreement that the suppliers, contractors, and consultants agree to notify the manufacturer of changes in the product or service so that manufacturers may determine whether the changes may affect the quality of a finished device. Purchasing data shall be approved in accordance with 820.40.

Subpart F - Identification and Traceability

820.60 Identification.

Each manufacturer shall establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and installation to prevent mixups.

820.65 Traceability.

Each manufacturer of a device that is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user shall establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and where appropriate components. The procedures shall facilitate corrective action. Such identification shall be documented in the DHR.

Subpart G - Production and Process Controls

820.70 Production and process controls.

(a) General. Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications. Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications. Where process controls are needed they shall include:

(1) Documented instructions, standard operating procedures (SOP's), and methods that define and control the manner of production;

(2) Monitoring and control of process parameters and component and device characteristics during production;

(3) Compliance with specified reference standards or codes;

(4) The approval of processes and process equipment; and

(5) Criteria for workmanship which shall be expressed in

documented standards or by means of identified and approved representative samples.

(b) Production and process changes. Each manufacturer shall establish and maintain procedures for changes to a specification, method, process, or procedure. Such changes shall be verified or where appropriate validated according to 820.75, before implementation and these activities shall be documented. Changes shall be approved in accordance with 820.40.

(c) Environmental control. Where environmental conditions could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures to adequately control these environmental conditions. Environmental control system(s) shall be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. These activities shall be documented and reviewed.

(d) Personnel. Each manufacturer shall establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and product or environment could reasonably be expected to have an adverse effect on product quality. The manufacturer shall ensure that maintenance and other personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual.

(e) Contamination control. Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.

(f) Buildings. Buildings shall be of suitable design and contain sufficient space to perform necessary operations, prevent mixups, and assure orderly handling.

(g) Equipment. Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use.

(1) Maintenance schedule. Each manufacturer shall establish and maintain schedules for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities, including the date and individual(s) performing the maintenance activities, shall be documented.

(2) Inspection. Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual(s) conducting the inspections, shall be documented.

(3) Adjustment. Each manufacturer shall ensure that any inherent limitations or allowable tolerances are visibly posted on or near equipment requiring periodic adjustments or are readily available to personnel performing these adjustments.

(h) Manufacturing material. Where a manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. The removal or reduction of such manufacturing material shall be documented.

(i) Automated processes. When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.

820.72 Inspection, measuring, and test equipment.

(a) Control of inspection, measuring, and test equipment. Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.

(b) Calibration. Calibration procedures shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented.

(1) Calibration standards. Calibration standards used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.

(2) Calibration records. The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date shall be documented. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.

820.75 Process validation.

(a) Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

(b) Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

(1) Each manufacturer shall ensure that validated processes are performed by qualified individual(s).

(2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented.

(c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

Subpart H - Acceptance Activities

820.80 Receiving, in-process, and finished device acceptance.

(a) General. Each manufacturer shall establish and maintain procedures for acceptance activities. Acceptance activities include inspections, tests, or other verification activities.

(b) Receiving acceptance activities. Each manufacturer shall establish and maintain procedures for acceptance of incoming product. Incoming product shall be inspected, tested, or otherwise verified as conforming to specified requirements. Acceptance or rejection shall be documented.

(c) In-process acceptance activities . Each manufacturer shall establish and maintain acceptance procedures, where appropriate, to ensure that specified requirements for in-process product are met. Such procedures shall ensure that in-process product is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received, and are documented.

(d) Final acceptance activities. Each manufacturer shall establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. Finished devices shall be held in quarantine or otherwise adequately controlled until released. Finished devices shall not be released for distribution until:

(1) The activities required in the DMR are completed;

(2) The associated data and documentation is reviewed;

(3) the release is authorized by the signature of a designated individual(s); and

(4) the authorization is dated.

(e) Acceptance records. Each manufacturer shall document acceptance activities required by this part. These records shall include:

(1) The acceptance activities performed;

(2) the dates acceptance activities are performed;

(3) the results;

(4) the signature of the individual(s) conducting the acceptance activities; and

(5) where appropriate the equipment used. These records shall be part of the DHR.

820.86 Acceptance status.

Each manufacturer shall identify by suitable means the acceptance status of product, to indicate the conformance or nonconformance of product with acceptance criteria. The identification of acceptance status shall be maintained throughout manufacturing, packaging, labeling, installation, and servicing of the product to ensure that only product which has passed the required acceptance activities is distributed, used, or installed.

Subpart I - Nonconforming Product

820.90 Nonconforming product.

(a) Control of nonconforming product. Each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented.

(b) Nonconformity review and disposition.

(1) Each manufacturer shall establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product. The procedures shall set forth the review and disposition process. Disposition of nonconforming product shall be documented. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.

(2) Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications. Rework and reevaluation activities, including a determination of any adverse effect from the rework upon the product, shall be documented in the DHR.

Subpart J - Corrective and Preventive Action

820.100 Corrective and preventive action.

(a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:

(1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;

(2) Investigating the cause of nonconformities relating to product, processes, and the quality system;

(3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

(4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

(5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;

(6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly

responsible for assuring the quality of such product or the prevention of such problems; and

(7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

(b) All activities required under this section, and their results, shall be documented.

Subpart K- Labeling and Packaging Control

820.120 Device labeling.

Each manufacturer shall establish and maintain procedures to control labeling activities.

(a) Label integrity. Labels shall be printed and applied so as to remain legible and affixed during the customary conditions of processing, storage, handling, distribution, and where appropriate use.

(b) Labeling inspection. Labeling shall not be released for storage or use until a designated individual(s) has examined the labeling for accuracy including, where applicable, the correct expiration date, control number, storage instructions, handling instructions, and any additional processing instructions. The release, including the date and signature of the individual(s) performing the examination, shall be documented in the DHR.

(c) Labeling storage. Each manufacturer shall store labeling in a manner that provides proper identification and is designed to prevent mixups.

(d) Labeling operations. Each manufacturer shall control labeling and packaging operations to prevent labeling mixups. The label and labeling used for each production unit, lot, or batch shall be documented in the DHR.

(e) Control number. Where a control number is required by 820.65, that control number shall be on or shall accompany the device through distribution.

820.130 Device packaging.

Each manufacturer shall ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution.

Subpart L - Handling, Storage, Distribution, and Installation

820.140 Handling.

Each manufacturer shall establish and maintain procedures to ensure that mixups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling.

820.150 Storage.

(a) Each manufacturer shall establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, and its condition shall be assessed as appropriate.

(b) Each manufacturer shall establish and maintain procedures that describe the methods for authorizing receipt from and dispatch to storage areas and stock rooms.

820.160 Distribution.

(a) Each manufacturer shall establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed and that purchase orders are reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution. Where a device's fitness for use or quality deteriorates over time, the procedures shall ensure that expired devices or devices deteriorated beyond acceptable fitness for use are not distributed.

(b) Each manufacturer shall maintain distribution records which include or refer to the location of:

(1) The name and address of the initial consignee;

(2) The identification and quantity of devices shipped;

(3) The date shipped; and

(4) Any control number(s) used.

820.170 Installation.

(a) Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection instructions, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device.

(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall document the inspection and any test results to demonstrate proper installation.

Subpart M - Records

820.180 General requirements

All records required by this part shall be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to employees of FDA designated to perform inspections. Such records, including those not stored at the inspected establishment, shall be made readily available for review and copying by FDA employee(s). Such records shall be legible and shall be stored to minimize deterioration and to prevent loss. Those records stored in automated data processing systems shall be backed up.

(a) Confidentiality. Records deemed confidential by the manufacturer may be marked to aid FDA in determining whether information may be disclosed under the public information regulation in part 20 of this chapter.

(b) Record retention period. All records required by this part shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer.

(c) Exceptions. This section does not apply to the reports required by 820.20(c) Management review, 820.22 Quality audits, and supplier audit reports used to meet the requirements of 820.50(a) Evaluation of suppliers, contractors, and consultants, but does apply to procedures established under these provisions. Upon request of a designated employee of FDA, an employee in management with executive responsibility shall certify in writing that the management reviews and quality audits required under this part, and supplier audits where applicable, have been performed and documented, the dates on which they were performed, and that any required corrective action has been undertaken.

820.181 Device master record.

Each manufacturer shall maintain device master records (DMR's). Each manufacturer shall ensure that each DMR is prepared and approved in accordance with 820.40. The DMR for each type of device shall include, or refer to the location of, the following information:

(a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications;

(b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications;

(c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used;

(d) Packaging and labeling specifications, including methods and processes used; and

(e) Installation, maintenance, and servicing procedures and methods.

820.184 Device history record.

Each manufacturer shall maintain device history records (DHR's). Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part. The DHR shall include or refer to the location of, the following information:

(a) The dates of manufacture;

(b) The quantity manufactured;

(c) The quantity released for distribution;

(d) The acceptance records which demonstrate the device is manufactured in accordance with the DMR;

(e) The primary identification label and labeling used for each production unit; and

(f) Any device identification(s) and control number(s) used.

820.186 Quality system record.

Each manufacturer shall maintain a quality system record (QSR). The QSR shall include, or refer to the location of, procedures and the documentation of activities required by this part that are not specific to a particular type of device(s), including, but not limited to, the records required by 820.20. Each manufacturer shall ensure that the QSR is prepared and approved in accordance with 820.40.

820.198 Complaint files.

(a) Each manufacturer shall maintain complaint files. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that:

(1) All complaints are processed in a uniform and timely manner;

(2) Oral complaints are documented upon receipt; and

(3) Complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803 or 804 of this chapter, Medical Device Reporting.

(b) Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary. When no investigation is made, the manufacturer shall maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate.

(c) Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

(d) Any complaint that represents an event which must be reported to FDA under part 803 or 804 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint flies or otherwise clearly identified. In addition to the information required by 820.198(e), records of investigation under this paragraph shall include a determination of:

(1) Whether the device failed to meet specifications;

(2) Whether the device was being used for treatment or diagnosis; and

(3) The relationship, if any, of the device to the reported incident or adverse event.

(e) When an investigation is made under this section, a record of the investigation shall be maintained by the formally designated unit identified in paragraph (a) of this section. The record of investigation shall include:

(1) The name of the device;

(2) The date the complaint was received;

(3) Any device identification(s) and control number(s) used

(4) The name, address, and phone number of the complainant;

(5) The nature and details of the complaint;

(6) The dates and results of the investigation;

(7) Any corrective action taken; and

(8) Any reply to the complainant.

(f) When the manufacturer's formally designated complaint unit is located at a site separate from the manufacturing establishment, the investigated complaint(s) and the record(s) of investigation shall be reasonably accessible to the manufacturing establishment.

(g) If a manufacturer's formally designated complaint unit is located outside of the United States, records required by this section shall be reasonably accessible in the United States at either:

(1) A location in the United States where the manufacturer's records are regularly kept; or

(2) The location of the initial distributor.

Subpart N - Servicing

820.200 Servicing.

(a) Where servicing is a specified requirement, each manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.

(b) Each manufacturer shall analyze service reports with appropriate statistical methodology in accordance with 820.100.

(c) Each manufacturer who receives a service report that represents an event which must be reported to FDA under part 803 or 804 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.

(d) Service reports shall be documented and shall include:

(1) The name of the device serviced;

(2) Any device identification(s) and control number(s) used;

(3) The date of service;

(4) The individual(s) servicing the device;

(5) The service performed; and

(6) The test and inspection data.

Subpart O - Statistical Techniques

820.250 Statistical techniques.

(a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.