Regulatory Procedures

Executive Order 12866

We have consulted with the Office of Management and Budget (OMB) and determined that these proposed rules meet the criteria for a significant regulatory action under Executive Order 12866. Thus, they were subject to OMB review. There are no program or administrative costs or savings associated with these proposed rules. Therefore, no assessment of costs and benefits is required.

Regulatory Flexibility Act

We certify that these proposed regulations will not have a significant economic impact on a substantial number of small entities because they affect only individuals. Therefore, a regulatory flexibility analysis, as provided in Public Law 96–354, the Regulatory Flexibility Act, is not required.

Paperwork Reduction Act

These proposed regulations will impose no new reporting or recordkeeping requirements requiring OMB clearance.

(Catalog of Federal Domestic Assistance Program Nos. 96.001, Social Security Disability Insurance; 96.006, Supplemental Security Income)

List of Subjects in 20 CFR Part 404

Administrative practice and procedure, Blind, Death benefits, Disability benefits, Old-Age, Survivors and Disability Insurance, Reporting and recordkeeping requirements, Social Security.

Dated: June 16, 1997.

John J. Callahan,

Acting Commissioner of Social Security.

For the reasons set out in the preamble, part 404, subpart P, Chapter III of Title 20, Code of Federal Regulations, is proposed to be amended as set forth below.

PART 404—FEDERAL OLD-AGE, SURVIVORS AND DISABILITY INSURANCE (1950–)

1. The authority citation for subpart P continues to read as follows:

Authority: Secs. 202, 205(a), (b), and (d)–(h), 216(i), 221(a) and (i), 222(c), 223, 225, and 702(a)(5) of the Social Security Act (42 U.S.C. 402, 405(a), (b), and (d)–(h), 416(i), 421(a) and (i), 422(c), 423, 425, and 902(a)(5)); sec. 211(b), Pub. L. 104–193, 110 Stat. 2105, 2189.

2. Section 201.00(h), appendix 2, subpart P, is revised to read as follows:

APPENDIX 2 TO SUBPART P—MEDICAL-VOCATIONAL GUIDELINES

* * * * *

201.00 Maximum sustained work capability limited to sedentary work as a result of severe medically determinable impairment(s).

* * * * *

(h) The term *younger individual* is used to denote an individual age 18 through 49. For individuals who are age 45–49, age is a less advantageous factor for making an adjustment to other work than for those who are age 18–44. Accordingly, for such individuals who: (1) are restricted to sedentary work, (2) are unskilled or have no transferable skills, (3) have no past relevant work or who can no longer perform past relevant work, and (4) are unable to communicate in English, or are able to speak and understand English but are illiterate in English, a finding of ''disabled'' is warranted. For individuals who are under age 45, age is a more advantageous factor for making an adjustment to other work and is usually not a significant factor in limiting such individuals' ability to make an adjustment to other work, even an adjustment to unskilled sedentary work, and even when the individuals are unable to communicate in English or are illiterate in English. A finding of ''disabled'' is not precluded for those individuals under age 45 (and those age 45–49 for whom rule 201.17 does not direct a decision of disabled) who do not meet all of the criteria of a specific rule and who do not have the ability to perform a full range of sedentary work. However, the inability to perform the full range of sedentary work does not necessarily equate with a finding of ''disabled.'' In deciding whether an individual who is limited to a partial range of sedentary work is able to make an adjustment to work other than any past relevant work, the adjudicator is required to make an individualized determination considering the individual's remaining occupational base, age, education, and work experience. Further, ''sedentary work'' represents a significantly restricted range of work, and individuals with a maximum sustained work capability limited to sedentary work have very serious functional limitations. Therefore, a finding that an individual is limited to less than the full range of sedentary work will be based on a careful consideration of the evidence of an individual's medical impairment(s) and the limitations and restrictions attributable thereto. Such evidence must support the finding that an individual's residual functional capacity is limited to less than the full range of sedentary work.

* * * * *

[FR Doc. 97–25125 Filed 9–22–97; 8:45 am]

BILLING CODE 4190–29–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 200

[Docket No. 96N–0048]

Sterility Requirements for Inhalation Solution Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations to require that all inhalation solutions for nebulization be sterile. Inhalation solutions for nebulization, as the term is used in this document, refers to inhalation solutions administered as a fine aqueous mist created by an atomizer or nebulizer. Currently, approximately half of these products are manufactured to be sterile. Based on reports of adverse drug experiences from contaminated nonsterile inhalation solutions for nebulization and recalls of these products, FDA is taking this action to ensure the safety and effectiveness of these solutions.

DATES: Written comments by December 22, 1997. Submit written comments on the information collection requirements by October 23, 1997. FDA proposes that any final rule that may issue based on this proposal become effective March 23, 1998.

ADDRESSES: Submit written comments on this proposed rule to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Carol E. Drew, Center for Drug Evaluation and Research (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–2041.

SUPPLEMENTARY INFORMATION:

I. Background

Inhalation solutions for nebulization are used to treat a variety of breathing disorders. Currently, approximately half of the marketed products are manufactured to be sterile. Those products not manufactured to be sterile are often manufactured under assigned

microbial count limits. For the reasons stated below, FDA has determined that current manufacturing methods and purported safeguards against contamination, including the microbial limits test, have not prevented dangerous microbial contamination of nonsterile inhalation solutions for nebulization. A sterility requirement is needed to prevent such microbial contamination.

Contaminated inhalation solutions for nebulization are likely to cause lung infections because the drug product is introduced directly into the lungs in a manner which at least partially bypasses the patient's natural defense mechanisms. Many patients using inhalation solution products for nebulization have chronic obstructive airway disease or cystic fibrosis, or are immunocompromised. Microbial contamination of these products may result in serious health consequences due to opportunistic pathogens entering the lungs or to the possible inactivation of the drug product by these microorganisms. Based on the significant health risk to users, FDA is proposing to require that all aqueous-based inhalation solutions for nebulization be manufactured as sterile.

Contamination problems with several different inhalation solution products and numerous adverse experience reports have led to FDA's determination that a sterility requirement is necessary for these products. In January 1994, a marketed albuterol sulfate inhalation solution product was found to be contaminated with a bacterium best identified as belonging to the *Pseudomonas fluorescens/putida* group. The manufacturer voluntarily recalled the product (class I recall to the consumer level) and issued a press release regarding the recall.

In June 1992, a manufacturer recalled its metaproterenol sulfate inhalation solution for nebulization when the product was found to contain excessive microbial growth identified as *P. gladioli/cepacia*. A press release was also issued concerning this recall.

In 1987, an FDA investigator identified at least two potential human fungal pathogens (*Aspergillus glaucus* and *Chrysosporium*) in another albuterol sulfate inhalation solution for nebulization before market distribution.

A sterility requirement for all inhalation solutions for nebulization will provide the necessary assurance that these solutions will not be contaminated. The sterility requirement is necessary for several reasons.

First, there is a high risk of contamination of inhalation solutions. Microbial contaminants identified in two of the recalls were *Pseudomonas* species (spp.), which are ubiquitous and are commonly found in pharmaceutical water supplies and nonsterile manufacturing environments.

Second, most species of *Pseudomonas* associated with the contamination of inhalation solutions have the potential to be human pathogens. Of special concern is the fact that many of the patients using these products have compromised pulmonary defense mechanisms and are therefore at a particularly high risk of serious infection.

Third, adherence to current good manufacturing practice (CGMP) regulations without appropriate sterilization procedures does not provide an adequate level of assurance that inhalation solutions for nebulization will not be contaminated. Even if antimicrobial preservatives are used in a product, they may not be effective because many bacteria, including *Pseudomonas* spp., may develop resistance to these preservatives. The albuterol sulfate product recalled in January 1994, for example, contained benzalkonium chloride, an antimicrobial preservative, yet the preservative failed to prevent microbial contamination of the product. Resistance to preservatives is not species specific; strains of many species are resistant. Furthermore, use of a single preservative in the manufacture of a nonsterile inhalation solution for an extended period may actually select for preservative-resistant strains of *Pseudomonas* spp. or other bacteria.

Also, the microbial limits test does not ensure against contamination. End-product microbial limits tests performed prior to distribution may not be capable of detecting sufficiently low levels of contamination; a product that initially passes the microbial limits test may support the growth of contaminating organisms, which could later grow to unacceptable levels.

FDA has therefore determined that all inhalation solutions for nebulization should be manufactured as sterile products. Any failure to comply with the sterility requirement would result in a finding that the drug product is adulterated under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351(a)(2)(B)), and misbranded under section 502(j) of the act (21 U.S.C. 352(j)). Failure to comply with the sterility requirement would also result in the agency's refusal to approve a new or abbreviated application for the product, pursuant to section 505(d)(1), (d)(2), (d)(3), and (j)(3)(A) of the act (21 U.S.C. 355(d)(1), (d)(2), (d)(3), and (j)(3)(A)).

II. Description of the Proposed Regulation

This proposal would amend the regulations governing requirements for specific classes of drugs to include new § 200.51 for inhalation solutions for nebulization. Proposed § 200.51(a) would require that all prescription and over-the-counter (OTC) inhalation solutions for nebulization be sterile. Manufacturers may use any appropriate process to achieve sterility of their inhalation solution products, as long as the method is in compliance with current FDA regulations. In the **Federal Register** of October 11, 1991 (56 FR 51354), FDA proposed to require that manufacturers use a terminal sterilization process when preparing a sterile drug unless the process adversely affects the drug product. The October 11, 1991, proposed rule would require that manufacturers include in their applications a written justification for not using terminal sterilization if such process is not appropriate. Should that proposed rule become final, manufacturers of inhalation solution products would be subject to its requirements.

Under this proposal, all manufacturers of nonsterile inhalation solutions for nebulization have until 1 year after the date of publication of the final rule to comply with the sterility requirement. This effective date reflects the time that FDA believes applicants may need to establish the sterility of their products.

Persons holding an approved application for a nonsterile inhalation solution product should submit to FDA a supplemental application establishing the sterility of the product. If they intend to sterilize their product by terminal sterilization or make other changes listed under § 314.70(b)(2) (21 CFR 314.70(b)(2)), they must obtain FDA approval of a supplement under that section before making the change(s). If they intend to manufacture the sterile product by aseptic processing, to retain the same container and closure system, and make no changes other than those listed under § 314.70(c)(1), they may submit a supplemental application under that section.

The following information should be included in the supplements: Complete qualification data for the aseptic process, executed batch record for a production batch of the product using the approved formulation, in-process and release control data, updated release specifications that include sterility, 3 months' accelerated stability data, updated stability protocol to

include either sterility or container/closure integrity testing initially and at expiry, and commitment to place the first three commercial batches into the routine stability program and submit the data in annual reports.

Proposed § 200.51(b) states that manufacturers must comply with the recordkeeping requirements of 21 CFR 211.113(b) of FDA's CGMP regulations. This section requires that manufacturers establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures must include validation of any sterilization process.

III. Proposed Effective Date

The agency's proposal would prohibit all manufacturers of nonsterile inhalation solution products for nebulization, including those products currently approved, from introducing or delivering for introduction into interstate commerce any such products that are nonsterile from 1 year after the date of publication in the **Federal Register** of any final rule based on this proposal.

Holders of approved new drug applications (NDA's) and abbreviated new drug applications (ANDA's) must submit data to FDA to establish sterility of these products within 1 year after the publication in the **Federal Register** of any final rule based on this proposal. This effective date reflects the time that FDA believes applicants may need to establish the sterility of their products.

Any NDA or ANDA for a nonsterile inhalation solution for nebulization under review by FDA on or after the date of publication of the final rule but before the effective date of the final rule may be approved if the application is otherwise approvable and the applicant agrees to establish the sterility of its product by the effective date. On or after the effective date of the final rule, FDA will refuse to approve an NDA or ANDA for a nonsterile inhalation solution for nebulization if the applicant has not established the sterility of the product.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires an analysis of regulatory options that would minimize any significant impact of a rule on small entities. The Unfunded Mandates Reform Act requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 (adjusted annually for inflation).

The expected aggregate costs of this proposed rule, and the anticipated impact of the rule on small entities, are described in the analysis below. The agency believes that the proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. This rule is not a significant regulatory action as defined by the Executive Order, does not impose any mandates on State, local, or tribal governments, and is not a significant regulatory action under the Unfunded Mandates Reform Act. Based on the following analysis, FDA estimates that this rule will have significant adverse effects on about four to five small firms that currently manufacture nonsterile inhalation solutions for nebulization. However, since the exact number of firms manufacturing nonsterile inhalation solutions is not certain, FDA invites comments from firms that believe they would be affected by the proposed rule. The statutory basis for FDA's authority to issue the rule is presented previously in this preamble. FDA has not identified any other Federal rules that duplicate, overlap, or conflict with the proposed rule.

As described in section I of this document, the objective of the proposed rule is to ensure that all inhalation solutions for nebulization are manufactured as sterile products and are thus safe and effective for use. Nonsterile inhalation solutions have been found to result in serious health consequences to users. By ensuring sterilization, the proposed rule is expected to yield benefits from the elimination of extended patient suffering and hospitalization associated with contaminated nonsterile inhalation solution products. In addition, the industry would benefit by avoiding liability claims from persons harmed due to the contamination of nonsterile inhalation solution products.

A. Affected Entities

This proposed rule would affect only those manufacturers of inhalation solutions for nebulization that do not already manufacture the products to be sterile. Based on its compliance data base, FDA believes that all innovator prescription products are currently manufactured as sterile. Of the approximately 28 generic and OTC firms that manufacture inhalation solutions, FDA estimates that up to five firms may still use nonsterile manufacturing processes and will be affected by this proposed rule. (The remainder are believed to have either implemented sterile processes themselves or to have contracted out the manufacturing of their inhalation products to firms that use a sterile process.) All of these affected firms may be small entities as defined by the Regulatory Flexibility Act.

B. Compliance Requirements and Costs

To comply with this rule, the affected firms must implement a sterile process for manufacturing their inhalation products, either by converting their in-house manufacturing operations to ensure that the products are sterile, or by arranging to have these products manufactured under contract by a firm that can do so under sterile conditions. In addition, affected firms must: (1) Develop appropriate written procedures designed to prevent contamination of the products, including validation of the new inhalation solution processes; and (2) submit to FDA a supplemental application establishing the sterility of the product.

Firms choosing to convert in-house manufacturing operations would need to set up an in-plant sterilization process by constructing a clean room especially designated for the inhalation solution product. FDA finds that the cost of building a new clean room may amount to almost $600 per square foot. The size of pharmaceutical clean rooms is reported to vary widely, from 200 to 2,500 square feet. Thus, the estimated cost of installing a clean room in a manufacturing facility may range from $120,000 to $1,500,000 per firm. Since affected firms would presumably contract out their manufacturing process if to do so would lower their costs of

complying with this proposed rule, this figure is an upper bound.

Firms would also need to validate the new inhalation solution processes at an estimated cost of $75,000 to $100,000 per product. The firms that would need to complete these validation procedures produce an average of approximately two inhalation products each, leading to validation costs per firm of approximately $150,000 to $200,000. Each firm would also be required to incur the paperwork costs associated with filing a supplemental application for each product with FDA.

Thus, overall costs for implementing and validating a sterile manufacturing process for inhalation products would total approximately $270,000 to $1,700,000 per affected firm. Assuming that five firms are affected, the costs of complying with this rule would range from approximately $1,350,000 to $8,500,000. Amortized over 10 years at a 7 percent interest rate implies total annualized costs of $192,000 to $1,210,000. In addition, affected firms will incur any costs associated with preparing and submitting a supplemental application.

Affected firms will need to acquire some new professional skills, since this rule deals with a new manufacturing process that will require technicians to have a knowledge of sterility procedures, specifically the asceptic sterilization process. Any other skills necessary for implementation of this proposal (e.g., skills associated with preparing the application) should already exist within the firms and should not need to be newly acquired.

C. Minimizing the Impact on Small Entities

FDA initially considered requiring conversion to sterile procedures to take place within 6 months of the publication of a final rule, due to the health hazards associated with existing unsterilized inhalation products. However, the agency is concerned that this short timeframe would give affected firms an inadequate opportunity to implement aseptic manufacturing processes and might force some small firms to temporarily suspend production. Thus, this proposed rule allows 1 year for the manufacturing conversion to take place.

Exempting small businesses from the rule is not a feasible alternative, since all of the firms believed to still be using nonsterile manufacturing for these products are small. A size-based exemption would thus defeat the purpose of this proposed rule.

VI. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Therefore, in accordance with 44 U.S.C. 3506(c)(2)(B) and 5 CFR part 1320, FDA is providing the following title, description, and respondent description of the information collection contained in this proposal, along with an estimate of the resulting annual collection of information burden. This estimate includes the time needed for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Sterility requirements for inhalation solution products.

Description: The proposal would require that all inhalation solution products, including those currently approved, be manufactured as sterile. Applicants will have 1 year after the date of publication of the final rule to comply with the sterility requirement.

Description of Respondents: Drug manufacturers.

As indicated in the accompanying chart, the proposed one-time reporting requirement would require that most firms commit about 160 additional hours per product to report the sterility information in a supplement to a drug application (20 hours for certain manufacturers of sterile products) and about 2 additional hours per product to document sterility of their inhalation products.

The expected burden under the proposed rule is as follows:

ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.97	5	1	5	160	800[1]
314.70	2	1	2	20	40[2]

[1] Reporting burden for manufacturers of nonsterile products.
[2] Reporting burden for manufacturers of sterile products.

ESTIMATED ANNUAL RECORDKEEPING BURDEN

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
211.113(b)	7	1	1	2	14

There are no capital costs or operating and maintenance costs associated with this proposed rule.

The agency has submitted a copy of this proposed rule to OMB for its review and approval of this information collection. Interested persons are requested to send comments regarding this collection of information to the Office of Information and Regulatory Affairs (address above).

VII. Request for Comments

Interested persons may, on or before December 22, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 200

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 200 be amended as follows:

PART 200—GENERAL

1. The authority citation for 21 CFR part 200 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 515, 701, 704, 705 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360e, 371, 374, 375).

2. New § 200.51 is added to subpart C to read as follows:

§ 200.51 Sterility requirements for inhalation solution drug products.

(a) All inhalation solutions for nebulization shall be manufactured to be sterile.

(b) Manufacturers shall also comply with the recordkeeping requirements in § 211.113(b) of this chapter.

Dated: September 12, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 97–25130 Filed 9–22–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 600 and 606

[Docket No. 97N–0242]

Biological Products; Reporting of Errors and Accidents in Manufacturing

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the regulations requiring licensed manufacturers of biological products to report errors and accidents in manufacturing that may affect the safety, purity, or potency of a product. FDA is proposing to establish a reporting period for licensed biological products; require that error and accident reports be submitted for products that have been made available for distribution, and amend the current good manufacturing practice (CGMP) regulations for blood and blood components to require error and accident reporting by unlicensed registered blood establishments and transfusion services which are currently reporting on a voluntary basis. The proposed reporting requirements are intended to expedite reporting of errors and accidents in manufacturing of biological products; provide FDA with a more accurate surveillance of the nation's blood supply, thereby enabling FDA to monitor actions taken in response to the errors and accidents detected for all establishments involved in manufacturing of blood and blood components; and facilitate a rapid response where the public health may be at risk.

DATES: Submit written comments on the proposed rule by December 22, 1997. Submit written comments on the information collection provisions by October 23, 1997. The agency is proposing that any final rule that may issue based upon this proposed rule become effective March 23, 1998.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503. ATTN: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION:

I. Introduction

Establishments that engage in the manufacture, preparation, propagation, compounding, or processing of drug and device products, including biological products, must register with the FDA under section 510 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360), unless specifically exempted by regulation.

Establishments propagating or manufacturing and preparing biological products for interstate commerce are subject to licensing under the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)). These licenses are issued by FDA only upon a showing that the establishment and the product for which a license is desired meet applicable standards designed to ensure the continued safety, purity, and potency of such products prescribed in the regulations (42 U.S.C. 262(d)(1)).

Blood and blood products are regulated as drugs under section 201(g) of the act (21 U.S.C. 321(g)) and biologicals are regulated under 42 U.S.C. 262 of the PHS Act. Establishments manufacturing blood and blood components are required to register with FDA and to comply with the CGMP (parts 211 and 606 (21 CFR parts 211 and 606)). Transfusion services which do not routinely collect or process blood and blood components are exempted from registering as blood establishments (§ 607.65(f) (21 CFR 607.65(f))), but are required under 42 CFR 493.1273(a) to comply with parts 606 and 640 (21 CFR part 640) as they pertain to the performance of manufacturing activities, such as compatibility testing, storage, labeling, and recordkeeping, or any other process involving manufacturing.

A product is considered adulterated under the act when the methods used in its manufacture, processing, packing, or holding do not conform to the CGMP (section 501(a)(1) of the act (21 U.S.C. 351(a)(1))). By applying the CGMP, firms assure that the products meet the requirements for safety, have the identity and strength, and meet the quality and purity characteristics which they purport or are represented to possess (section 501(a)(2)(B) of the act). A product is also adulterated if its strength differs from, or purity or quality falls below what it is purported or represented to possess (section 501(c) of the act). A product is considered misbranded if its labeling is false or misleading in any particular (section 502(a) of the act (21 U.S.C. 352(a))) or if the product is dangerous to health when used as labeled under section 502(j) of the act. The introduction or delivery for introduction of adulterated and/or misbranded biological products into interstate commerce is prohibited under section 301(a) of the act (21 U.S.C. 331(a)). It is also a prohibited act to adulterate and/or misbrand biological products while held for sale after receipt of shipment in interstate commerce (section 301(k) of the act). These prohibited acts are punishable by prescribed penalties under the act.