§ 520.2456 [Removed]

■ 3. Remove § 520.2456.

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

■ 4. The authority citation for 21 CFR part 558 continues to read as follows:

Authority: 21 U.S.C. 360b, 371.

§ 558.600 [Amended]

■ 5. Amend § 558.600 in paragraph (b) and in the table in paragraphs (e)(1)(i) through (e)(1)(iv) in the ''Sponsor'' column by removing ''000010'' and by adding in its place ''058198''.

Dated: December 6, 2005.

Bernadette A. Dunham,

Deputy Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine.

[FR Doc. 05–24165 Filed 12–16–05; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. 1980N–0208]

Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule and final order.

SUMMARY: The Food and Drug Administration (FDA) proposed to amend the biologics regulations and proposed to classify the bacterial vaccines and toxoids on the basis of findings and recommendations of the Panel on Review of Bacterial Vaccines and Toxoids (the Panel) on December 13, 1985. The Panel reviewed the safety, efficacy, and labeling of bacterial vaccines and toxoids with standards of potency, bacterial antitoxins, and immune globulins. After the initial final rule and final order was vacated by the U.S. District Court for the District of Columbia on October 27, 2004, FDA published a new proposed rule and proposed order on December 29, 2004 (69 FR 78281). The purpose of this final rule and final order is to amend the biologics regulations, issue a final order in response to the report and recommendations of the Panel; and, respond to comments on the previously published proposed rule and proposed order submitted to the Division of Dockets Management. This final rule and final order does not address Anthrax Vaccine Adsorbed (AVA). The final order concerning AVA is published elsewhere in this issue of the **Federal Register**. FDA is classifying these products as Category I (safe, effective, and not misbranded), Category II (unsafe, ineffective, or misbranded), or Category IIIB (off the market pending completion of studies permitting a determination of effectiveness).

DATES: This rule is effective December 19, 2006. The final order on categorization of products is effective immediately.

FOR FURTHER INFORMATION CONTACT: Astrid Szeto, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

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I. Introduction

On December 13, 1985, FDA proposed to amend the biologics regulations and proposed to classify the bacterial vaccines and toxoids on the bases of findings and recommendations of the Panel. The Panel reviewed the safety, efficacy, and labeling of bacterial vaccines and toxoids with standards of potency, bacterial antitoxins, and immune globulins. After reviewing the Panel's report and comments on the proposal, FDA published a final rule and final order on January 5, 2004 (69 FR 255). On October 27, 2004, the U.S. District Court for the District of Columbia vacated the January 5, 2004, final rule and final order. On December 29, 2004, FDA published a withdrawal of the January 5, 2004, final rule and final order. Concurrently with the withdrawal of the final rule and final order, FDA published again a proposed rule and proposed order (69 FR 78281) to provide notice and to give interested persons an opportunity to comment.

The purpose of this document is to: (1) Categorize those bacterial vaccines

and toxoids licensed before July 1972 according to the evidence of their safety and effectiveness, thereby determining whether they may remain licensed and on the market;[1] (2) issue a final response to recommendations made in the Panel's report.[2] These recommendations concern conditions relating to active components, labeling, tests required before release of product lots, product standards, or other conditions considered by the Panel to be necessary or appropriate for assuring the safety and effectiveness of the reviewed products; and (3) revise the standard for potency of Tetanus Immune Globulin in § 610.21 (21 CFR 610.21).

II. Background

A. History of the Review

In the **Federal Register** of February 13, 1973 (38 FR 4319), FDA issued procedures for the review by independent advisory review panels of the safety, effectiveness, and labeling of biological products licensed before July 1, 1972. This process was eventually codified in § 601.25 (21 CFR 601.25) (38 FR 32048 at 32052, November 20, 1973). Under the panel assignments published in the **Federal Register** of June 19, 1974 (39 FR 21176), FDA assigned the biological product review to one of the following groups: (1) Bacterial vaccines and bacterial antigens with ''no U.S. standard of potency,'' (2) bacterial vaccines and toxoids with standards of potency, (3) viral vaccines and rickettsial vaccines, (4) allergenic extracts, (5) skin test antigens, and (6) blood and blood derivatives.

Under § 601.25, FDA assigned responsibility for the initial review of each of the biological product categories to a separate independent advisory panel consisting of qualified experts to ensure objectivity of the review and public confidence in the use of these products. Each panel was charged with preparing an advisory report to the Commissioner of Food and Drugs which was to: (1) Evaluate the safety and effectiveness of the biological products for which a license had been issued, (2) review their labeling, and (3) identify the biological products that are safe, effective, and not misbranded. Each advisory panel report was also to include recommendations classifying the products reviewed into one of three categories.

- Category I, designating those biological products determined by the panel to be safe, effective, and not misbranded.
- Category II, designating those biological products determined by the panel to be unsafe, ineffective, or misbranded.
- Category III, designating those biological products determined by the panel not to fall within either Category I or Category II on the basis of the panel's conclusion that the available data were insufficient to classify such biological products, and for which further testing was therefore required. Category III products were assigned to one of two subcategories. Category IIIA products were those that would be permitted to remain on the market pending the completion of further studies. Category IIIB products were those for which the panel recommended license revocation on the basis of the panel's assessment of potential risks and benefits.

In its report, the panel could also include recommendations concerning any condition relating to active components, labeling, tests appropriate before release of products, product standards, or other conditions necessary or appropriate for a biological product's safety and effectiveness.

In accordance with § 601.25, after reviewing the conclusions and recommendations of the review panels, FDA would publish in the **Federal Register** a proposed order containing: (1) A statement designating the biological products reviewed into Categories I, II, IIIA, or IIIB, (2) a description of the testing necessary for Category IIIA biological products, and (3) the complete panel report. Under the proposed order, FDA would propose to revoke the licenses of those products designated into Category II and Category IIIB. After reviewing public comments, FDA would publish a final order on the matters covered in the proposed order.

In the **Federal Register** of November 21, 1980 (45 FR 77134), FDA issued a notice of availability of the Panel's final report. In the **Federal Register** of December 13, 1985 (50 FR 51002), FDA issued a proposed rule that contained the full Panel report[3] and FDA's response to the recommendations of the Panel (the December 1985 proposal). In the December 1985 proposal, FDA proposed regulatory categories (Category I, Category II, or Category IIIB as defined previously in this document) for each bacterial vaccine and toxoid reviewed by the Panel, and responded to other recommendations made by the Panel. The public was offered 90 days to submit comments in response to the December 1985 proposal.

The definition of Category IIIA as described previously in this document was applied at the time of the Panel's review and served as the basis for the Panel's recommendations. In the **Federal Register** of October 5, 1982 (47 FR 44062), FDA revised § 601.25, and codified 21 CFR 601.26 which, established procedures to reclassify those products in Category IIIA into either Category I or Category II based on available evidence of effectiveness. The Panel recommended that a number of biological products be placed into Category IIIA. FDA assigned the review of those products previously classified into Category IIIA to the Vaccines and Related Biological Products Advisory Committee. FDA has addressed the review and reclassification of bacterial vaccines and toxoids classified into Category IIIA through a separate administrative procedure (see the **Federal Register** of May 15, 2000 (65 FR 31003), and May 29, 2001 (66 FR 29148)). Therefore, FDA does not further identify or discuss in this document any bacterial vaccines and toxoids classified into Category IIIA.

B. Comments on the December 1985 Proposal

FDA received four letters of comments in response to the December 1985 proposal. One letter from a licensed manufacturer of bacterial vaccine and toxoid products concerned the confidentiality of information it had submitted for the Panel's review. As provided in § 601.25(b)(2), FDA considered the extent to which the information fell within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), before placing the information in the public docket for the December 1985 proposal. Another comment from a member of the Panel provided an update of important scientific information related to bacterial vaccines and toxoids that had accrued since the time of the Panel's review. The letter did not comment on the December 1985 proposal nor did it contend that the newly available information should result in modification of the Panel's recommendations or FDA's proposed actions. FDA's responses to the comments contained in the remaining two letters follow.

[1] The final order concerning AVA is published elsewhere in this issue of the **Federal Register**.

[2] The Panel was convened on July 12, 1973, in an organizational meeting, followed by multiple working meetings until February 2, 1979. The Final Report of the Panel was completed in August 1979.

[3] In addition to publication in the **Federal Register** of December 13, 1985 (50 FR 51002), the full Panel report is available on FDA's Website at *http://www.fda.gov/ohrms/dockets/default.htm* (Docket No. 1980N–0208). A copy of the Panel report is also available at the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

(Comment 1) One comment from a licensed manufacturer of bacterial vaccines and toxoids objected to the proposed classification into Category IIIA of several of its products for use in primary immunization.

As described previously in this document, FDA has addressed those products proposed for Category IIIA in a separate rulemaking process.[4] This final rule and final order does not take any action regarding the further classification of those products proposed for Category IIIA, including those proposed for Category IIIA for primary immunization. All manufacturers and others in the general public have been offered additional opportunity to comment on the final categorization of specific Category IIIA products in the above-noted process.

(Comment 2) In response to FDA's proposal that Pertussis Immune Globulin (Human) be placed into Category IIIA because of insufficient evidence of efficacy, one comment stated that FDA should permit manufacture of Pertussis Immune Globulin (Human) for export only. The comment noted that medical practices in other countries may differ from those in the United States and that in some countries Pertussis Immune Globulin (Human) plays an important role in the augmentation of therapy with antibiotics in young, very ill infants with pertussis.

Since that time, FDA has revoked all licenses for Pertussis Immune Globulin (Human) at the requests of the individual manufacturers. The FDA Export Reform and Enhancement Act of 1996 (Public Law 104–134, as amended by Public Law 104–180) amended provisions of the Federal Food, Drug, and Cosmetic Act (the act) pertaining to the export of certain unapproved products. Section 802 of the act contains requirements for the export of products not approved in the United States. Under these provisions, products such as Pertussis Immune Globulin (Human) can be exported to other countries, if the requirements of section 802 of the act are met.

(Comment 3) One comment concerned the generic order and wording for product labeling recommended by the Panel and which FDA proposed to adopt in its response to the Panel recommendation. The comment recommended that a labeling section concerning ''Overdose'' be included only when circumstances dictate. The comment stated that because the biological products that would be subject to this labeling are prescription products administered by health care providers, the risk of overdose should be greatly reduced.

We agree that, in many cases, a labeling section in part 201 (21 CFR part 201) entitled ''Overdosage'' is not necessary. Section 201.56(d)(3) of the labeling regulations provides that the labeling may omit any section or subsection of the labeling format if clearly inapplicable. The ''Overdosage'' section, provided for in § 201.57(i) of the regulations, is omitted for many bacterial vaccine and toxoid products.

(Comment 4) One comment objected to several statements made by the Panel and provided in the Panel's written report, but did not object to or comment on FDA's proposed responses to the Panel's recommendations.

The Panel's recommendations represent the scientific opinions of a panel of experts and are not binding. We believe that the agency should not modify the statements and recommendations of the Panel as provided in its report, including through public comment. The purpose of the opportunity for comment is to allow comment on FDA's responses to the Panel report and not on the Panel report directly. In reaching our conclusion, we took into account the Panel report and comments on the Panel report.

In the December 1985 proposal, FDA provided the opportunity for comment on FDA's proposals in response to the Panel report. In the December 29, 2004 (69 FR 78281), proposed rule and proposed order (the December 2004 proposal), FDA again provided the opportunity for comment on FDA's proposals. The public was offered 90 days to submit comments in response to the December 2004 proposal.

In response to the December 2004 proposal, most of the comments received pertained to AVA. A response to comments about AVA is provided in a document published elsewhere in this issue of the **Federal Register**. A discussion of comments to the December 2004 proposal other than those pertaining to AVA is provided under section VI of this document.

III. Categorization of Products—Final Order

Category I. Licensed biological products determined to be safe and effective and not misbranded. Table 1 of this document is a list of those products proposed in December 2004 by FDA for Category I. Under the ''Comments'' column, FDA notes those products for which FDA's proposed category differs from that recommended by the Panel. Products for which the licenses were revoked before the December 1985 proposal and that were identified as such in the December 1985 proposal are not listed in the tables below. Products for which the licenses were revoked after the December 1985 proposal are identified in the ''Comments'' column. After review of the comments on the December 1985 and December 2004 proposals, and finding no additional scientific evidence to alter the proposed categorization, FDA adopts Category I as the final category for the listed products.

TABLE 1.—CATEGORY I

Manufacturer/License No.	Products*	Comments
Alpha Therapeutic Corp., License No. 744	Tetanus Immune Globulin (Human)	Although the Panel recommended that Tetanus Immune Globulin (Human), manufactured by Alpha Therapeutic Corp., be placed in Category IIIB, FDA proposed that it be placed in Category I. Alpha Therapeutic Corp. no longer exists. The new owner is Grifols Biologicals, Inc. On August 15, 2003, FDA revoked the license for Tetanus Immune Globulin (Human)
Advance Biofactures Corp., License No. 383	Collagenase	

[4] See the **Federal Register** of May 15, 2000 (65 FR 31003) and May 29, 2001 (66 FR 29148), containing the proposed order to reclassify Category IIIA products into Category I and Category II based on the review and recommendation of the Vaccines and Related Biological Products Advisory Committee.

TABLE 1.—CATEGORY I—Continued

Manufacturer/License No.	Products*	Comments
Armour Pharmaceutical Co., License No. 149	Tetanus Immune Globulin (Human)	The manufacturer's licensed name is now ZLB Behring AG. On July 26, 1999, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
Aventis Pasteur, Ltd., License No. 1280	BCG Vaccine, Botulism Antitoxin (Types A, B, and E), Botulism Antitoxin (Type E), Tetanus Toxoid	On February 24, 2000, a name change to Aventis Pasteur, Ltd. with an accompanying license number change to 1280 was granted. On December 21, 2000, FDA revoked the license for Tetanus Toxoid at the request of the manufacturer
Connaught Laboratories, Inc., License No. 711	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, and Diphtheria Antitoxin	On December 9, 1999, a name change to Aventis Pasteur, Inc. with an accompanying license number change to 1277 was granted to Connaught Laboratories, Inc. FDA revoked the licenses for these products at the request of the manufacturer on July 6, 2001, and August 2, 2001, respectively
Cutter Laboratories, Inc., License No. 8	Plague Vaccine, Tetanus Immune Globulin (Human)	On October 5, 1994, the manufacturing facilities and process for Plague Vaccine were transferred to Greer Laboratories, Inc., License No. 308. On May 24, 1995, FDA revoked Cutter's license for Plague Vaccine at the request of Cutter, the previous manufacturer; the license for Greer Laboratories, Inc. remains in effect. Bayer Corp. now holds the license for Tetanus Immune Globulin (Human) under License No. 8. The Bayer Corp. subsidiary that holds the license for Tetanus Immune Globulin (Human) is Talecris Biopharmaceutics, Inc. under License No. 1716
Eli Lilly & Co., License No. 56	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	On December 2, 1985, FDA revoked the license for Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed at the request of the manufacturer
Glaxo Laboratories, Ltd., License No. 337	BCG Vaccine	On July 17, 1990, FDA revoked the license for BCG Vaccine at the request of the manufacturer
Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238	Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed	On July 17, 1990, FDA revoked the license for Diphtheria Antitoxin at the request of the manufacturer. On July 27, 1993, FDA revoked the licenses for Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed at the request of the manufacturer
Lederle Laboratories, Division American Cyanamid Co., License No. 17	Cholera Vaccine, Tetanus Immune Globulin (Human)	On December 23, 1992, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer. On October 23, 1996, FDA revoked the license for Cholera Vaccine at the request of the manufacturer
Massachusetts Public Health Biologic Laboratories, License No. 64	Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Antitoxin, Tetanus Immune Globulin (Human), Tetanus Toxoid Adsorbed, Typhoid Vaccine	Although the Panel recommended that Tetanus Antitoxin be placed in Category IIIB, FDA proposed in the December 1985 proposal that it be placed in Category I. On October 26, 1988, FDA revoked the license for Typhoid Vaccine at the request of the manufacturer. On January 10, 1994, FDA revoked the license for Tetanus Antitoxin at the request of the manufacturer. On December 22, 1998, FDA revoked the license for Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed at the request of the manufacturer. On August 3, 2000, FDA revoked the license for Diphtheria and Tetanus Toxoids Adsorbed at the request of the manufacturer. On July 1, 2004, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer. On August 23, 2004, FDA revoked the license for Tetanus Toxoid Adsorbed at the request of the manufacturer
Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2	Tetanus Immune Globulin (Human)	The manufacturer is now known as Merck & Co., Inc. On January 31, 1986, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
Michigan Department of Public Health, License No. 99	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Typhoid Vaccine*	On November 11, 1998, a name change to BioPort Corp. (BioPort) with an accompanying license number change to 1260 was granted. The license for Typhoid Vaccine was revoked on June 25, 1985, at the request of the manufacturer. The license for Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed was revoked at the request of the manufacturer (BioPort) on November 20, 2000. The license for Pertussis Vaccine Adsorbed was revoked at the request of the manufacturer (BioPort) on April 22, 2003

TABLE 1.—CATEGORY I—Continued

Manufacturer/License No.	Products*	Comments
Parke-Davis, Division of Warner-Lambert Co., License No. 1	Tetanus Immune Globulin (Human)	On November 19, 1983, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
Swiss Serum and Vaccine Institute Berne, License No. 21	Tetanus Antitoxin	Although the Panel recommended that Tetanus Antitoxin be placed in Category IIIB, FDA proposed that it be placed in Category I. On March 13, 1980, FDA revoked the license for Tetanus Antitoxin at the request of the manufacturer
Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140	Tetanus Immune Globulin (Human)	The manufacturer is now known as Baxter Healthcare Corp. On July 27, 1995, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer
University of Illinois, License No. 188	BCG Vaccine	On May 29, 1987, FDA revoked the license for BCG Vaccine at the request of the manufacturer
Wyeth Laboratories, Inc., License No. 3	Cholera Vaccine, Tetanus Immune Globulin (Human), Typhoid Vaccine (acetone inactivated), Typhoid Vaccine (heat-phenol inactivated)	On December 23, 1992, FDA revoked the license for Tetanus Immune Globulin (Human) at the request of the manufacturer. On September 11, 2001, FDA revoked the licenses for Cholera Vaccine and Typhoid Vaccine (both forms) at the request of the manufacturer

*The final order for Anthrax Vaccine Adsorbed is published elsewhere in this issue of the **Federal Register**.

Category II. Licensed biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce. FDA did not propose that any products be placed in Category II and in this final rule and final order does not categorize any products in Category II.

Category IIIB. Biological products for which available data are insufficient to classify their safety and effectiveness and should not continue in interstate commerce. Table 2 of this document is a list of those products proposed by FDA for Category IIIB. We have not listed in this document products for which FDA revoked the licenses before the December 1985 proposal but we identified them in the December 1985 proposal. Products for which FDA revoked the licenses after the December 1985 proposal are identified in the ''Comments'' column.

FDA has revoked the licenses of all products proposed by FDA for Category IIIB. After review of the comments on the December 1985 and December 2004 proposals, and finding no additional scientific evidence to alter the proposed categorization, FDA adopts Category IIIB as the final category for the listed products.

TABLE 2.—CATEGORY IIIB

Manufacturer/License No.	Products	Comments
Connaught Laboratories, Inc., License No. 711	Diphtheria Toxoid, Pertussis Vaccine	On June 21, 1994, FDA revoked the license for Diphtheria Toxoid and on December 19, 1997, FDA revoked the license for Pertussis Vaccine, in both cases at the request of the manufacturer
Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238	Diphtheria Toxoid	On July 27, 1993, FDA revoked the license for Diphtheria Toxoid at the request of the manufacturer
Massachusetts Public Health Biologic Laboratories, License No. 64	Tetanus Toxoid	On October 11, 1989, FDA revoked the license for Tetanus Toxoid at the request of the manufacturer
Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2	Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Typhoid Vaccine	The manufacturer is now known as Merck & Co., Inc. On January 31, 1986, FDA revoked the licenses for all the listed products at the request of the manufacturer
Michigan Department of Public Health, License No. 99	Diphtheria Toxoid Adsorbed	On November 11, 1998, the name of the manufacturer was changed to BioPort, and the license number was changed to 1260. On November 20, 2000, FDA revoked the license for Diphtheria Toxoid Adsorbed at the request of the manufacturer
Wyeth Laboratories, Inc., License No. 3	Diphtheria Toxoid, Diphtheria Toxoid Adsorbed, Pertussis Vaccine	On May 19, 1987, FDA revoked the licenses for all listed products at the request of the manufacturer

IV. FDA's Responses to Additional Panel Recommendations

In the December 1985 proposal, FDA responded to the Panel's general recommendations regarding the products under review and to the procedures involved in their manufacture and regulation. In this section of the document, FDA responds in final to the general recommendations.

A. Generic Order and Wording of Labeling

The Panel recommended changes to the labeling of the biological products under review. The Panel also recommended a generic order and wording for information in the labeling of bacterial vaccines. In the December 1985 proposal, FDA agreed with the labeling changes recommended by the Panel.

In the December 1985 proposal, FDA proposed that 6 months after publication of a final rule, manufacturers of products subject to this Panel review submit, for FDA's review and approval, draft labeling revised in conformance with the Panel's report and with the regulations. FDA proposed to require that the revised labeling accompany all products initially introduced or initially delivered for introduction into interstate commerce 30 months after the date of publication of the final rule. The proposed labeling review schedule was consistent with the scheduling provided in § 201.59 of the regulations. Although proposed, we are not making this change because it does not appear to be necessary at this time.

Since the time of the Panel's recommendation, FDA has made a number of changes to the labeling regulations and related regulatory policies. FDA has added or revised the requirements in § 201.57 for including in the labeling, in standardized language, the information concerning use during pregnancy, pediatric use, and geriatric use. Section 201.57 requires a specific order and content for drug product labeling. A number of labeling sections included in § 201.57 were not included in the Panel's recommended ordering and wording of the labeling but are now required to help ensure clarity in the labeling. FDA has also provided guidance regarding the wording of sections in which the agency believes complete and consistent language is important. Because FDA regularly monitors labeling for the products subject to this Panel review to determine if the labeling is consistent with applicable labeling requirements, we do not believe that a labeling review is necessary at this time.

Section 314 of the National Childhood Vaccine Injury Act (NCVIA) of 1986 required FDA to review the warnings, use instructions, and precautionary information that are distributed with each vaccine listed in section 2114 of the Public Health Service Act and to determine whether this information was adequate to warn health care providers of the nature and extent of the dangers posed by such vaccine. Since the December 1985 proposal, FDA has completed this review and labeling has been revised accordingly.

B. Periodic Review of Product Labeling

In its report, the Panel noted a number of labeling deficiencies. To improve the labeling, the Panel recommended that labeling be reviewed and revised as necessary at intervals of no more than every 2 years.

As discussed in the December 1985 proposal and December 2004 proposal, we believe the current system of labeling review will adequately assure accurate labeling. Periodic review of labeling on a set schedule is unnecessary. Section 601.12(f) (21 CFR 601.12(f)) prescribes when revised labeling must be submitted, either as a supplement or, if changes are minor, in an annual report. In addition, FDA may request revision of labeling when indicated by current scientific knowledge. We believe that, by these mechanisms, product labeling is kept up to date, and a scheduled, routine review of labeling is unnecessary and burdensome for both the agency and manufacturers.

C. Improvement in the Reporting of Adverse Reactions

The Panel recommended that actions be taken to improve the reporting and documentation of adverse reactions to biological products. The Panel particularly noted the need to improve the surveillance systems to identify adverse reactions to pertussis vaccine.

Since publication of the Panel's report, the Vaccine Adverse Event Reporting System (VAERS) was created as an outgrowth of NCVIA and is administered by FDA and the Centers for Disease Control and Prevention (CDC). VAERS accepts from health care providers, manufacturers, and the public, reports of adverse events that may be associated with U.S.-licensed vaccines. Health care providers must report certain adverse events included in a Reportable Events Table (Ref. 1) and any event listed in the vaccine's package insert as a contraindication to subsequent doses of the vaccine. Health care providers also may report other clinically significant adverse events. FDA and CDC receive about 1,000 reports each month under the VAERS program. A guidance document is available which explains how to complete the VAERS form (Ref. 2).

D. Periodic Review of Product Licenses

The Panel recommended that all licensed vaccines be periodically reviewed to assure that data concerning the safety and effectiveness of these products are kept current and that licenses be revoked for products which have not been marketed for years or which have never been marketed in the licensed form. The Panel noted that, by limiting the period for which specific vaccines may be licensed, older products would be assured periodic review, and new products for which additional efficacy data are required could be provisionally licensed for a limited time period during which additional data can be generated.

In the December 1985 proposal (50 FR 51002 at 51109), FDA noted that licensing policies in effect at the time of the review resulted in licenses being held for some products which were never intended to be marketed as individual products or which were no longer being marketed as individual products. FDA had required that manufacturers licensed for a combination vaccine also hold a license for each individual vaccine contained in the combination. For example, a manufacturer of diphtheria and tetanus toxoids and pertussis (DTP) vaccine would also be required to have separate licenses for Diphtheria Toxoid, Tetanus Toxoid, and Pertussis Vaccines. Because this policy is no longer in effect, most licenses are for currently marketed products. In a few cases, there may be no current demand for a product but, for public health reasons, a license continues to be held for the product. There are some vaccines for which there is little current demand but continued licensure could expedite the manufacture and availability of the product in the event an outbreak of the targeted disease should occur. We believe that the routine inspection of licensed facilities adequately assures that the information held in product licenses is current and that a routine review of safety and efficacy data is unnecessary and burdensome. The Panel's recommendation that some new vaccines be provisionally licensed for only limited periods of time while additional data are generated is inconsistent with the law that requires a determination that a biologic product

is safe, pure, and potent before it is licensed.

E. Compensation for Individuals Suffering Injury From Vaccination

The Panel recommended that compensation from public funds be provided to individuals suffering injury from vaccinations that were recommended by competent authorities, carried out with approved vaccines, and where the injury was not a consequence of defective or inappropriate manufacture or administration of the vaccines.

A compensation program has been implemented consistent with the Panel's recommendation. The NCVIA established the National Vaccine Injury Compensation Program (NVICP) designed to compensate individuals, or families of individuals, who have been injured by childhood vaccines, whether administered in the private or public sector. The NVICP, administered by the Health Resources and Services Administration, Department of Health and Human Services (HHS), is a no-fault alternative to the tort system for resolving claims resulting from adverse reactions to routinely recommended childhood vaccines. The specific vaccines and injuries covered by NVICP are identified in a Vaccine Injury Table that may periodically be revised as new vaccines come into use or new types of potential injuries are identified. The NVICP has resulted in a reduction in the amount of litigation related to injury from childhood vaccines while assuring adequate liability coverage and protection. The NVICP applies only to vaccines routinely recommended for infants and children. Vaccines recommended for adults are not covered unless they are routinely recommended for children as well, e.g., Hepatitis B Vaccine.

F. Public Support for Immunization Programs

The Panel recommended that both FDA and the public support widespread immunization programs for tetanus, diphtheria, and pertussis.

The National Immunization Program is part of CDC and was established to provide leadership to health agencies in planning and implementing immunization programs, to identify unvaccinated populations in the United States, to assess vaccination levels in State and local areas, and to generally promote immunization programs for children, including vaccination against diphtheria, tetanus, and pertussis. A recent survey shows that nearly 95 percent of children 19 to 35 months of age have received three or more doses of any vaccine that contained diphtheria and tetanus toxoids (i.e., diphtheria and tetanus toxoids and pertussis (DTP), diphtheria and tetanus toxoids and acellular pertussis (DTaP) or diphtheria and tetanus toxoids vaccines (DT)) (Ref. 3).

G. Assuring Adequate Supplies of Bacterial Vaccines and Toxoids; Establishment of a National Vaccine Commission

The Panel recommended that FDA work closely with CDC and other groups to assure that adequate supplies of vaccines and passive immunization products continue to be available. The Panel recommended establishment of a national vaccine commission to address such issues.

Since the publication of the December 1985 proposal, the National Vaccine Program was created by Congress (Public Law 99–660) with the National Vaccine Program Office (NVPO) within HHS designated to provide leadership and coordination among Federal agencies as they work together to carry out the goals of the National Vaccine Plan. The National Vaccine Plan provides a framework, including goals, objectives, and strategies, for pursuing the prevention of infectious diseases through immunizations. The National Vaccine Program brings together all of the groups that have key roles in immunizations, and coordinates the vaccine-related activities, including addressing adequate production and supply issues. Despite efforts to assure vaccine availability, shortages may occur (Ref. 4) for a variety of reasons. FDA will continue to work with the NVPO, the National Institutes of Health, CDC, and vaccine manufacturers to help facilitate continued vaccine availability making the establishment of a national vaccine commission unnecessary.

H. Consistency of Efficacy Protocols

The Panel recommended that the protocols for efficacy studies be reasonably consistent throughout the industry for any generic product. To achieve this goal, the Panel recommended the development of industry guidelines that provide standardized methodology for adducing required information.

We believe that the standardization of clinical testing methodology for a group of vaccines is often not practical or useful. Because of the variety of possible vaccine types, e.g., live vaccines, killed vaccines, toxoids, bioengineered vaccines, acellular vaccines, and the diversity of populations in which the vaccine may be studied, it is difficult to develop guidance that would apply to more than one or two studies. We routinely meet with manufacturers before the initiation of clinical studies to discuss the study and will comment on proposed protocols for efficacy studies. We intend to continue to allow flexibility in selecting appropriate tests, procedures, and study populations for a clinical study while assuring that the necessary data are generated to fulfill the intended objectives of the study.

I. The Effect of Regulations Protecting and Informing Human Study Subjects on the Ability to Conduct Clinical Trials

The Panel expressed concern that the regulations governing informed consent and the protection of human subjects involved in clinical investigations should not establish unnecessary impediments to the goal of obtaining adequate evidence for the safety and effectiveness of a product.

We believe that the regulations and policies applying to informed consent and the protection of human subjects do not inhibit the adequate clinical study of a product. We note that whenever the regulations or guidance documents related to these subjects are modified or amended, FDA offers an opportunity for public comment on the revisions. We particularly welcome comments on how appropriate informed consent and protection of human subjects can be maintained while assuring that the development and study of useful products are not inhibited.

J. Standards for Determining the Purity of Diphtheria and Tetanus Toxoids

The Panel recommended that standards should be established for purity of both diphtheria and tetanus toxoids in terms of limits of flocculation (Lf) content per milligram (mg) of nitrogen.

In the December 1985 proposal, we agreed that standards should be set. We have since determined that this approach is overly restrictive and does not allow FDA to keep pace with advances in manufacturing and technology. The Center for Biologics Evaluation and Research (CBER) approves the release specifications for the purity of diphtheria and tetanus toxoids during the review of a Biologics License Application (BLA). The purity of diphtheria toxoids in vaccines currently licensed in the United States is usually at least 1,500 Lf/mg nondialyzable nitrogen and the purity of tetanus toxoids in vaccines currently licensed in the United States is usually at least 1,000 Lf/mg of nondialyzable nitrogen. However, because the purity of tetanus and diphtheria toxoids in different vaccines is established during

the BLA review, the purity may vary between products.

K. Immunogenic Superiority of Adsorbed Toxoids Over Fluid Toxoids

The Panel recommended that the immunogenic superiority of the adsorbed diphtheria and tetanus toxoids over the fluid (plain) preparations be strongly emphasized in product labeling, especially with regard to the duration of protection.

Tetanus Toxoid fluid, manufactured by Aventis Pasteur, Inc., is the only fluid toxoid product that remains licensed in the United States in 2005. This product is licensed for booster use only in persons over 7 years of age. The current package insert for this product states that, although the rates of seroconversion are essentially equivalent with either type of tetanus toxoid, the adsorbed toxoids induce more persistent antitoxin titers than fluid products.

L. Laboratory Testing Systems for Determining Potency of Tetanus and Diphtheria Toxoids

The Panel noted a need for further studies with tetanus toxoids in a World Health Organization (WHO) sponsored quantitative potency test in animals to establish the conditions under which the test results are reproducible, and to relate these results more closely to those obtained in the immunization of humans. The Panel also recommended the development of an animal or laboratory testing system for diphtheria toxoid that correlates consistently, and with acceptable precision, with primary immunogenicity in humans.

Diphtheria and tetanus toxoids containing vaccines are tested during the licensing process for their ability to induce acceptable levels of protective antibodies in clinical trials in the target populations. Properties of vaccines used in these clinical trials, including potency, also are determined during licensing. The acceptance criteria for commercial lots of these vaccines are set at licensing on the basis of the properties of the vaccines that induced acceptable quantitative/qualitative levels of antibodies.

The animal potency tests currently required by WHO, the European Pharmacopoeia (EP), and FDA differ. Despite these differences, the potency tests have been adequate to ensure sufficient immunogenic activity of the vaccines to induce protective immunity in target populations. However, international efforts to harmonize the diphtheria and tetanus potency tests under development are based on immunogenicity in animals. CBER is currently participating in these international harmonization efforts.

M. Potency Testing of Diphtheria and Tetanus Toxoids for Pediatric Use

The Panel recommended FDA require potency testing after combination of the individual diphtheria and tetanus toxoid components in Diphtheria and Tetanus Toxoid vaccines for pediatric use.

We agree with the recommendation. All manufacturers and the FDA testing laboratory follow this procedure on products submitted to the agency for release.

N. Potency Requirements for Pertussis Vaccine

The Panel recommended that the regulations concerning the maximum pertussis vaccine dose should be updated to reflect current recommendations and practices. At the time of the Panel review, whole cell pertussis vaccines were in use. Specifically, the Panel recommended that pertussis vaccine have a potency of four protective units per single human dose with the upper estimate of a single human dose not to exceed eight protective units. The Panel also recommended that the total immunizing dose be defined as four doses of four units each, compared to the three doses of four units each defined at the time of the recommendation in the regulations.

We have removed the additional standard regulations applicable to pertussis vaccine (Ref. 5). As whole cell pertussis vaccines are no longer licensed for human use in the United States, this recommendation no longer applies to products available in the United States.

O. Weight-Gain Test in Mice for Pertussis Vaccine

The Panel recommended that the weight-gain test in mice used to determine toxicity of pertussis vaccines be revised to include a reference standard and specifications regarding mouse strains to be used.

At the time of the Panel's deliberations, only DTP vaccines containing a whole-cell pertussis component were licensed in the United States. The mouse weight-gain test was a toxicity test used for whole-cell pertussis vaccines. Whole-cell pertussis vaccines are no longer licensed in the United States for human use, thus the mouse weight-gain test is no longer in use. Currently, only DTP vaccines containing an acellular pertussis component (DTaP) vaccines are licensed in the United States.

Although not currently licensed in the United States, vaccines containing a whole-cell pertussis component are still in use in other countries. CBER continues to participate in international efforts to improve the tests used to assess toxicity of whole-cell pertussis vaccines, including the mouse weight-gain test. CBER is represented on WHO committees and working groups with the goal of improving regulation and testing of whole-cell pertussis vaccines.

P. Agglutination Test to Determine Pertussis Vaccine Response in Humans

The Panel recommended that the agglutination test used to determine pertussis vaccine response in humans be standardized and that a reference serum be used for comparison. It also recommended that a reference laboratory be available at FDA.

As stated previously in this document, at the time of the Panel's deliberations, only whole-cell pertussis vaccines were licensed in the United States. The agglutination test was used for the clinical evaluation of DTP vaccines. Under the Panel's recommendations, FDA (CBER) developed and distributed reference materials for the agglutination assay and served as a reference laboratory. Currently, only DTaP or DTaP combination vaccines are licensed in the United States. For the clinical evaluation of DTaP vaccines, the agglutination test was replaced by antigen-specific immunoassays, specifically enzyme-linked immunosorbent assays (ELISAs). As had been done with the agglutination assay, CBER took an active role in standardization of the ELISAs used to measure the specific antibody to the pertussis components of DTaP vaccines. Specifically, CBER distributes reference and control materials for the antigen-specific pertussis ELISA and has served as a reference laboratory.

Q. Warnings in Labeling for Pertussis Vaccine

The Panel recommended that the pertussis vaccine label warn that if shock, encephalopathic symptoms, convulsions, or thrombocytopenia follow a vaccine injection, no additional injections with pertussis vaccine should be given. The Panel also recommended that the label include a cautionary statement about fever, excessive screaming, and somnolence.

We agree with the recommendation except that such information should be included in product labeling as described in § 201.100(d), i.e., the package insert, rather than the product label. Labeling applicable to whole-cell

pertussis vaccines was revised to include much of the information recommended by the Panel; whole-cell pertussis vaccines are no longer licensed in the United States. Because the acellular forms of pertussis vaccine have a different profile of potential adverse events and contraindications, the product labeling for these products is worded consistent with available data.

R. Field Testing of Fractionated Pertussis Vaccines

The Panel recommended that any fractionated pertussis vaccine that differs from the original whole cell vaccine be field tested until better laboratory methods for evaluating immunogenicity are developed. The Panel recommended that the field-testing include agglutination testing and, if possible, evaluation of clinical effectiveness.

The currently approved vaccines containing an acellular pertussis component were studied in the United States and abroad in human populations with the antibody response being measured and clinical effectiveness evaluated.

S. Use of Same Seed Lot Strain in Manufacturing Bacillus Calmette-Guerin (BCG) Vaccine

The Panel recommended that all BCG vaccines be prepared from the same seed lot strain with demonstrated efficacy, if available data justify such action.

BCG vaccines are not recommended for routine immunization in the United States. The two currently U.S.-licensed BCG vaccines are produced using different seed strains. Most BCG vaccines produced globally are manufactured using seed strains with a unique history. Recent evidence suggests that these different BCG strains do differ genetically and have slightly varying phenotypes. However, a meta analysis of the current human BCG vaccination data performed in 1994 by Harvard University concluded that no strain-to-strain differences in protection could be detected. Although there have been differences in immunogencity among strains demonstrated in animal models, no significant differences have been seen in human clinical trials (Ref. 6). Thus, FDA does not find that available human data justify requirement of a single BCG vaccine strain.

T. Development of an Improved Cholera Vaccine

The Panel recommended public support for development of an improved cholera vaccine because unsatisfactory sanitary conditions in many countries make it clear that control of the disease by sanitation alone cannot be realized in the foreseeable future.

Cholera is not an endemic disease in the United States. However, there is risk to U.S. travelers to certain countries where the disease is endemic. We continue to cooperate with international health agencies in efforts to evaluate new types of vaccines and to study the pathogenesis of the disease. CBER personnel have chaired and participated in the WHO Cholera Vaccine Standardization Committee and have participated in drafting new WHO guidelines for immune measurement of protection from cholera.

U. Plague Vaccine Immunization Schedule

The Panel recommended that the following plague vaccine immunization schedule be considered:

1. A primary series of three intramuscular (IM) injections (1 milliliter (mL), 0.2 mL, and 0.2 mL), 1 and 6 months apart, respectively;
2. Booster IM injections of 0.2 mL at 12, 18, and 24 months; and
3. For persons achieving a titer of 1:128 after the third and fifth inoculations, booster doses when the passive agglutination titer falls below 1:32 and empirically every 2 years when the patient cannot be tested serologically.

We agree with the recommendation, and the currently licensed vaccine is labeled consistent with the recommendation. However, this vaccine is not currently in production or distribution.

V. FDA's Response to General Research Recommendations

In its report, the Panel identified many areas in which there should be further investigation to improve existing products, develop new products, develop new testing methodologies, and monitor the population for its immune status against bacterial disease. In the December 1985 proposal, we responded to these recommendations in the responses identified as items 11, 17 (in part), 21, 25, and 27. As discussed in the December 1985 proposal, we considered the Panel's recommendations in defining its research priorities at the time the recommendations were made. Because a considerable amount of time has elapsed since these recommendations were made and FDA initially responded to the recommendations, we are not providing specific responses to each recommendation. As in any area of scientific research, new discoveries and new concerns require a continual reevaluation of research priorities and objectives to assure their relevance to current concerns.

We recognize the Panel's desire to have FDA's research program evolve with the significant issues and findings of medical science. In order to assure the continued relevance of its research program, CBER's research program for vaccines, including bacterial vaccines and related biological products, is subject to peer review by the Panel's successor, the Vaccines and Related Biological Products Advisory Committee (see, for example, the transcripts from the meetings of February 17, 2005 (Ref. 7), May 6, 2004 (Ref. 8), and May 8, 2003 (Ref. 9). In addition, CBER has defined as part of its strategic plan its goal of a high quality research program that contributes directly to its regulatory mission. This goal includes a plan to assure that CBER's research program continues to support the regulatory review of products and timely development of regulatory policy, and to have a significant impact on the evaluation of biological products for safety and efficacy.

Because of limited resources, we also support the leveraging of resources to create effective collaborations in the advancement of science. We have issued a *Guidance for FDA Staff: The Leveraging Handbook, an Agency Resource for Effective Collaborations* (Ref. 10). Through cooperation with international, other Federal, and State health care agencies and the industry and academia, the agency intends that its research resources will reap the benefits of a wide range of experience, expertise, and energy from the greater scientific community while the agency maintains its legal and regulatory obligations. We invite comment at any time on ways we may improve our research program and set our objectives.

VI. What Comments Did We Receive?

We received about 350 comments on the December 2004 proposal. Most of the comments related to AVA. A response to comments about AVA is provided in a document published elsewhere in this issue of the **Federal Register**. Comments on the December 2004 proposal not relating to AVA are discussed in this section of this document.

A. FDA's Consideration of Comments on the Panel's Report

(Comment 1) Some comments criticized FDA for stating in the December 2004 proposal that we were

not considering comments on the Panel report.

(Response) We wish to clarify our review of comments. We are not considering comments on the Panel report because the Panel's recommendations are not binding on the public or FDA. The Panel is comprised of experts offering scientific opinions for our consideration. We should not modify the statements and recommendations of the Panel as provided in their report, including through public comment. The purpose of the opportunity for public comment allows comment on FDA's responses to the Panel report and not on the Panel report directly. We can take action with regard to public comments on FDA's responses to the Panel report and therefore, we directed comments to our responses rather than to the report itself.

B. Biological Products Review Process

(Comment 2) One comment submitted by the former Chief Counsel for FDA during the time that the proposed and final regulations on the Biological Products Review were issued discussed the historical development of the Biological Products Review. The commenter did not comment on the December 2004 proposal nor did he request modification of FDA's proposed actions.

(Response) We offer no response to this informative general comment.

C. Plague Vaccine

(Comment 3) One comment noted that the plague vaccine was licensed and once recommended by the CDC's Advisory Committee on Immunization Practices, but is no longer produced.

(Response) As mentioned earlier in this document and consistent with the comment, the plague vaccine remains licensed but is not currently in production or distribution.

D. Miscellaneous Comments

(Comment 4) Numerous miscellaneous comments on the December 2004 proposal were received. Many of the comments expressed an opinion about the conduct of vaccination administration programs or activities associated with the Department of Defense. Other miscellaneous comments provided links to Internet sites, but did not provide a comment on the December 2004 proposal. Other submissions to the Docket were electronic mailings to other parties that copied the Docket.

(Response) These miscellaneous comments noted above are not relevant or responsive to the December 2004 proposed order and accordingly, we are not providing any response to them.

VII. Amendment to the Regulations

In the December 1985 proposal and December 2004 proposal, we proposed to amend § 610.21, limits of potency, by revising the potency requirements for Tetanus Immune Globulin (Human) (TIG). We proposed to amend the regulations to require a minimum potency of 250 units of tetanus antitoxin per container for TIG.

The current regulation requires that the minimum potency of TIG must not be less than 50 units of tetanus antitoxin per mL of fluid. All currently licensed TIG meets this minimum potency standard, and is marketed with a labeled potency of 250 units per container. However the number of units per mL has varied (the current standard provides only a minimum potency per mL of fluid) and thus, the volume per 250 unit container has varied. Because the volume of the final products has varied without any apparent effect on performance of the product, FDA has determined that it is not appropriate to regulate the potency of TIG on a per mL basis. We advise that in this discussion and in the regulation, ''per container'' means that amount of the contents of the container (vial or syringe) deliverable to the patient in normal use. FDA believes that TIG should continue to be marketed at a potency of no less than 250 units per container, which is the dose routinely recommended for prophylaxis against tetanus. All current manufacturers of TIG are already conforming to the proposed requirement by labeling their products with a potency of 250 units per container, while also complying with the existing regulation. Thus, the FDA believes this change will better reflect modern labeling practices.

We received no comments opposing the proposed revision to § 610.21 and therefore, we are amending the regulations to require a minimum potency of 250 units of tetanus antitoxin per container for TIG.

VIII. Analysis of Impacts

A. Review Under Executive Order 12866, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act of 1995

FDA has examined the impacts of this final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 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). The agency believes that this final rule is not a significant regulatory action under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, this final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. Because this final rule does not impose new requirements on any entity and has no associated compliance costs, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

B. Environmental Impact

The agency has determined under 21 CFR 25.31(h) 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.

C. Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

D. Federalism

FDA has analyzed this final rule in accordance with the principles set forth

in Executive Order 13132. FDA has determined that the final rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the final rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web sites after this document publishes in the **Federal Register**).

1. ''Table of Reportable Events Following Vaccination,'' *http://www.vaers.hhs.gov/reportable.htm*.

2. ''Guidance for Industry: How to Complete the Vaccine Adverse Event Reporting System Form (VAERS–1)'', September 1998, *http://www.fda.gov/cber/gdlns/vaers-1.pdf*.

3. ''Estimated Vaccination Coverage With 3+DTP Among Children 19–35 Months of Age by Race/Ethnicity, and by State and Immunization Action Plan Area—U.S., National Immunization Survey, Q3/2000–Q2/2001'', *http://www.cdc.gov/nip/coverage/NIS/00-01/tab19-3dpt_race_iap.htm*.

4. Protecting Our Kids: What Is Causing the Current Shortage in Childhood Vaccines?—Testimony Before the Committee on Governmental Affairs, United States Senate, June 12, 2002, *http://www.cdc.gov/nip/news/testimonies/vac-shortages-walt-6-12-2002.htm*.

5. 61 FR 40153, August 1, 1996.

6. Colditz, et al., ''Efficacy of BCG Vaccine in the Prevention of Tuberculosis: Meta Analysis of the Published Literature,'' *Journal of the American Medical Association*, 271:698–702, 1994.

7. *http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4087T2.htm*

8. *http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4038t1.htm*

9. *http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3948t1.txt*

10. *http://www.fda.gov/cber/gdlns/leverhnbk.pdf*

List of Subjects

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 610 is amended as follows:

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

■ 1. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

■ 2. Section 610.21 is amended by revising the entry ''Tetanus Immune Globulin (Human), 50 units of tetanus antitoxin per milliliter'' under the heading ''ANTIBODIES'' to read as follows:

§ 610.21 Limits of potency.

* * * * *

ANTIBODIES

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Tetanus Immune Globulin (Human), 250 units of tetanus antitoxin per container.

* * * * *

Dated: December 12, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05–24224 Filed 12–15–05; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[TD 9234]

RIN 1545–AU98

Obligations of States and Political Subdivisions

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Final regulations.

SUMMARY: This document contains final regulations on the definition of private activity bond applicable to tax-exempt bonds issued by State and local governments. These regulations affect issuers of tax-exempt bonds and provide needed guidance for applying the private activity bond restrictions to refunding issues.

DATES: Effective Date: These regulations are effective February 17, 2006.

Applicability Date: For dates of applicability, see § 1.141–15(j) of these regulations.

FOR FURTHER INFORMATION CONTACT: Johanna Som de Cerff, (202) 622–3980 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

This document amends the Income Tax Regulations (26 CFR part 1) under section 141 of the Internal Revenue Code (Code) by providing rules on the application of the private activity bond tests to refunding issues. This document also amends the Income Tax Regulations under sections 145, 149 and 150 by providing rules on certain related matters.

On May 14, 2003, the IRS published in the **Federal Register** a notice of proposed rulemaking (REG–113007–99) (68 FR 25845) (the proposed regulations) relating to the matters addressed in this Treasury decision. A public hearing on the proposed regulations was scheduled for September 9, 2003. However, the public hearing was cancelled because no requests to speak were received. Written comments on the proposed regulations were received. After consideration of all the written comments, the proposed regulations are adopted as revised by this Treasury decision (the final regulations). The revisions are discussed below.

Explanation of Provisions

A. Introduction

In general, under section 103, gross income does not include the interest on any State or local bond. However, this exclusion does not apply to private activity bonds (other than certain qualified bonds). Section 141(a) defines a private activity bond as any bond issued as part of an issue that meets either (1) the private business use test in section 141(b)(1) and the private security or payment test in section 141(b)(2) (the private business tests) or (2) the private loan financing test in section 141(c) (the private business tests and the private loan financing test are referred to collectively as the ''private activity bond tests'').

The private business use test is met if more than 10 percent of the proceeds of an issue are to be used for any private business use. Section 141(b)(6) defines private business use as use directly or indirectly in a trade or business that is carried on by any person other than a governmental unit.

The private security or payment test is met if the payment of the principal of, or the interest on, more than 10 percent of the proceeds of an issue is directly or indirectly (1) secured by an interest in property used or to be used for a private business use, (2) secured by an interest in payments in respect of such property, or (3) to be derived from payments,