DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 610

[Docket No. 2005N–0355]

RIN 0910–AF20

Revocation of Status of Specific Products; Group A Streptococcus

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is removing the regulation applicable to the status of specific products; Group A streptococcus. FDA is removing the regulation because the existing requirement for Group A streptococcus organisms and derivatives is both obsolete and a perceived impediment to the development of Group A streptococcus vaccines. The regulation was written to apply to a group of products that are no longer on the market. We are taking this action as part of our continuing effort to reduce the burden of unnecessary regulations on industry and to revise outdated regulations without diminishing public health protection. We are issuing the removal directly as a final rule because it is noncontroversial, and there is little likelihood that we will receive any significant adverse comments. Elsewhere in this issue of the **Federal Register**, we are publishing a companion proposed rule under our usual procedures for notice and comment in the event that we receive any significant adverse comments on the direct final rule. If we receive any significant adverse comments that warrant terminating the direct final rule, we will consider such comments on the proposed rule in developing the final rule.

DATES: This direct final rule is effective June 2, 2006. Submit written or electronic comments on or before February 15, 2006. If we receive no significant adverse comments during the specified comment period, we intend to publish a confirmation document on or before the effective date of this direct final rule confirming that the direct final rule will go into effect on June 2, 2006. If we receive any significant adverse comments during the comment period, we intend to withdraw this direct final rule before its effective date by publication in the **Federal Register**.

ADDRESSES: You may submit comments, identified by Docket No. 2005N–0355 and/or RIN number 0910–AF20, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: *http://www.regulations.gov*. Follow the instructions for submitting comments.
- Agency Web Site: *http://www.fda.gov/dockets/ecomments*. Follow the instructions for submitting comments on the agency Web site.

Written Submissions

Submit written submissions in the following ways:

- FAX: 301–827–6870.
- Mail/Hand delivery/Courier (for paper, disk, or CD–ROM submissions): Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

Instructions: All submissions received must include the agency name and docket number or regulatory information number (RIN) for this rulemaking. All comments received may be posted without change to *http://www.fda.gov/ohrms/dockets/default.htm*, including any personal information provided. For additional information on submitting comments, see the ''Comments'' heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to *http://www.fda.gov/ohrms/dockets/default.htm* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Valerie A. Butler, 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:

I. Background

Section 610.19 *Status of specific products; Group A streptococcus* (21 CFR 610.19), was published in the **Federal Register** of January 5, 1979 (44 FR 1544). FDA issued that regulation after reviewing and considering the findings of the independent advisory Panel on Review of Bacterial Vaccines and Bacterial Antigens with ''No U.S. Standard of Potency'' (the Panel). The preamble to the proposed rule for § 610.19, which was published in the **Federal Register** of November 8, 1977 (42 FR 58266), contained the findings of the Panel, including the Panel's specific findings about then-licensed products that contained Group A streptococcus (42 FR 58266 at 58277 through 58278). The regulation was a part of the Panel's review of the safety, effectiveness, and labeling of biological products licensed before July 1, 1972. In 1972, the regulatory authority of these biological products was transferred from the National Institutes of Health (NIH) to FDA. The Panel reviewed those licensed biological bacterial products that were labeled, ''No U.S. Standard of Potency.'' (There was a separate review for the ''Bacterial Vaccines and Toxoids with Standards of Potency.'') Products considered by the Panel included primarily mixtures of bacterial preparations, e.g., Mixed Vaccine Respiratory, which was described as containing chemically killed organisms consisting of *Streptococcus* (*pyrogenes*, *viridans*, and *nonhemolytic*), *Staphylococcus* (*aureus* and *albus*), *Diplococcus pneumoniae*, *Neiserria catarrhalis*, *Klebsiella pneumoniae*, and *Haemophilus influenzae* manufactured by Hollister-Stier, Division of Cutter Laboratories (42 FR 58266 at 58268). Many of the products considered by the Panel were indicated as treatments for diverse ailments such as colds, asthma, arthritis, and uveitis (42 FR 58266 at 58270).

The Panel report listed a number of major concerns with this group of products (''No U.S. Standard of Potency'') (42 FR 58266 at 58269). One of the major concerns was that no defined standards of potency existed for any of the products, so it was not possible to establish that the microbial factors manufacturers claimed to be present in the products were indeed there or in what concentration (42 FR 58266 at 58270). Many of these products were developed years before specific etiologic agents were associated with the cause of specific diseases. Moreover, the labeled indications for these products were for diseases of obscure etiology (Id.). Manufacturers could provide to the Panel neither clinical data to support the safety or efficacy of the products, nor any justification for

using the products as described other than uncontrolled and unconfirmed clinical impressions (Id.). Additional safety questions arose from the fact that the products were administered repeatedly over extended periods of time with no evidence of systematic followup for the types of adverse effects that might be associated with repeated inoculations (Id.). The Panel stated in their report, that in view of what was known from laboratory studies about potential risks associated with repeated inoculations of foreign substances, they had reservations about the long-term safety of this group of products (42 FR 58266 at 58270 through 58271). In fact, the Panel did not classify any of these products into category I (those biological products determined to be safe, effective, and not misbranded) (42 FR 58266 at 58315).

In the Panel report, the section specifically concerning Group A streptococcal vaccines describes the history, dating back to the 1930s, of major attempts to immunize humans with hemolytic streptococci (42 FR 58266 at 58277). These early studies demonstrated severe systemic toxicities (Id.). One study (Ref. 1) described the occurrence of acute rheumatic fever in siblings of rheumatic fever patients following vaccination with a partially purified preparation (Id.). In addition, immunological cross-reactivity between streptococcal cell wall protein and mammalian myocardium was demonstrated in vitro (Id.) (Ref. 2). However, the Panel report differentiated between the licensed products under review and highly purified preparations, which were at the research stage. The Panel report stated that the safety profile for a highly purified preparation was quite different, noting that no anti-heart reactive antibody has been observed in the post immunization sera of infants or adults receiving the purified preparation (Id.) (Ref. 3). The Panel concluded, based on demonstrated safety concerns, that the uncontrolled use of the Group A streptococcal antigens in bacterial vaccines with ''No U.S. Standard of Potency'' represented unacceptable risks (42 FR 58266 at 58278). In fact, the Panel stated:

> In view of the carefully conducted controlled studies currently under way with purified chemically defined antigenic preparations, one finds it difficult to justify the use of uncontrolled, poorly defined preparations presumed to contain antigens that have been demonstrated in earlier studies to produce local and systemic reactions. The hypothetical and theoretical objections stemming from laboratory studies linking mammalian and streptococcal antigens have been given serious consideration in the design and conduct of present studies treating humans with the newer purified streptococcal antigens. (42 FR 58266 at 58277). In contrast to the uncontrolled, poorly defined preparations, the Panel made clear at the time that they were not condemning the use of purified or characterized streptococcal antigens (Id.). Further, FDA reviews each biological product and determines whether the risk-benefit relationship is acceptable for the stage of investigation and for licensure (see 21 CFR parts 312 and 601). This review is performed under the authority of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act (see 21 U.S.C. 355(i); 42 U.S.C. 262(a)(3) and (a)(2)(A)). FDA's review is adequate to assess the safety, purity, and potency of products that companies seek to license, and to ensure that human subjects in clinical trials of investigational products are not exposed to unreasonable and significant risk of illness or injury.

Therefore, FDA concludes that § 610.19, which was codified following the Panel report, was meant to apply only to those bacterial vaccines which the Panel had under their review—licensed but poorly characterized products labeled ''No U.S. Standard of Potency''—and not to more characterized preparations under investigation then or now. Because there are no bacterial mixtures with ''No U.S. Standard of Potency'' containing Group A streptococcal antigens licensed at this time, and current manufacturing technology allows for characterization and purification of Group A streptococcal products, this regulation is obsolete. Although it was never intended to apply to the development of Group A streptococcal vaccines that had adequate testing, FDA has determined that it has been perceived to cover these products as well, and therefore should be removed in a direct final rule.

II. Highlights of the Direct Final Rule

We are removing § 610.19 because the existing requirement is obsolete and perceived to be impeding the development of Group A streptococcal vaccines using purified or characterized streptococcal antigens. The regulation is obsolete because it was written to apply to a group of products that are no longer on the market. Certain parties interested in developing new Group A streptococcal vaccines perceive the regulation as an impediment, voiced during public meetings and workshops, e.g., the Group A streptococcus workshop sponsored by the National Institute of Allergy and Infectious Diseases, NIH, held in Bethesda, MD on March 29 and 30, 2004. Group A streptococci are responsible for significant morbidity and mortality worldwide, including rheumatic fever and glomerulonephritis, as well as pharyngitis, impetigo, and other clinical manifestations. Therefore, a vaccine to prevent diseases caused by this organism would have a public health benefit. We are taking this action as part of our continuing effort to reduce the burden of unnecessary regulations on industry and to revise outdated regulations without diminishing public health protection.

III. Rulemaking Action

In the **Federal Register** of November 21, 1997 (62 FR 62466), FDA described its procedures on when and how the agency will employ direct final rulemaking. We have determined that this rule is appropriate for direct final rulemaking because we believe that it is noncontroversial and we anticipate no significant adverse comments. Consistent with our procedures on direct final rulemaking, FDA is publishing elsewhere in this issue of the **Federal Register** a companion proposed rule to remove § 610.19. FDA is removing the regulation because it is both obsolete and a perceived impediment to the development of Group A streptococcus vaccines. The companion proposed rule provides a procedural framework within which the rule may be finalized in the event that the direct final rule is withdrawn because of any significant adverse comment. The comment period for the direct final rule runs concurrently with the companion proposed rule. Any comments received in response to the companion proposed rule will be considered as comments regarding the direct final rule.

We are providing a comment period on the direct final rule of 75 days after the date of publication in the **Federal Register**. If we receive any significant adverse comments, we intend to withdraw this direct final rule before its effective date by publication of a notice in the **Federal Register**. A significant adverse comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. In determining whether an adverse comment is significant and warrants terminating a direct final rulemaking, we will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process in accordance with section 553 of the Administrative Procedure Act (5 U.S.C. 553). Comments that are

frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. A comment recommending a regulation change in addition to those in the rule would not be considered a significant adverse comment unless the comment states why the rule would be ineffective without the additional change. In addition, if a significant adverse comment applies to an amendment, paragraph, or section of this rule and that provision can be severed from the remainder of the rule, we may adopt as final those provisions of the rule that are not the subjects of a significant adverse comment.

If any significant adverse comments are received during the comment period, FDA will publish, before the effective date of this direct final rule, a document withdrawing the direct final rule. If we withdraw the direct final rule, any comments received will be applied to the proposed rule and will be considered in developing a final rule using the usual notice-and-comment procedures.

If FDA receives no significant adverse comments during the specified comment period, FDA intends to publish a document, before the effective date of the direct final rule, confirming the effective date.

IV. Analysis of Impacts

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

FDA has examined the impacts of the direct 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 direct 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. Because the direct final rule is removing a regulation, it would not result in any increased burden or costs on small entities. Therefore, the agency certifies that the direct 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 direct 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. Federalism

FDA has analyzed this direct final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the direct 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 direct 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.

V. Paperwork Reduction Act of 1995

This direct final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520) is not required.

VI. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper 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 Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

VII. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**), and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Massell, B.F., L.H. Honikman, and J. Amezcua, ''Rheumatic Fever Following Streptococcal Vaccination. Report of Three Cases,'' *Journal of the American Medical Association*, 207(6): 1115–1119, 1969.

2. Kaplan, M.H. and M. Meyeserian, ''An Immunological Cross-Reaction Between Group A Streptococcal Cells and Human Heart Tissue,'' *Lancet*, 1:706–710, 1962.

3. Fox, E.N., L.M. Pachman, M.K. Wittner, and A. Dorfman, ''Primary Immunization of Infants and Children with Group A Streptococcal M Protein,'' *Journal of Infectious Diseases*, 120:598–604, 1969.

List of Subjects in 21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated by 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.

§ 610.19 [Removed]

■ 2. Remove § 610.19.

Dated: November 21, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05–23546 Filed 12–1–05; 8:45 am]

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DEPARTMENT OF JUSTICE

Federal Bureau of Investigation

28 CFR Part 16

[AAG/A Order No. 010–2005]

Privacy Act of 1974; Implementation

AGENCY: Federal Bureau of Investigation, DOJ.

ACTION: Final rule.