The following text is taken verbatim from the December 13, 1985, issue of the *Federal Register*, reporting the findings of an independent civilian advisory panel that considered the evidence for the safety and efficacy of vaccines available in the 1970s. The end of the document reports FDA's actions in response to the panel's recommendations. The entire report is 115 pages long (pages 51002 through 51117). All the sections that discuss anthrax vaccine are reprinted in their entirety below.

Department of Health and Human Services Food and Drug Administration

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[Excerpt from page 51002]

Under section 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 which was to:

1. Evaluate the safety and effectiveness of the biological products
2. Review labeling of the biological products
3. Identify the biological products under review that are safe, effective, and not misbranded. The advisory report includes recommendations classifying products into one of three categories.

Category I designates those biological products determined by the Panel to be safe, effective, and not misbranded. The Panel's statement may include any condition relating to active components, labeling, tests required prior to release of batches, product standards, or other conditions necessary or appropriate for their safety and effectiveness.

Category II designates those biological products determined by determined by the Panel to be unsafe, ineffective, or misbranded.

Category III designates those biological products determined by the Panel not to fall within either Category I or II on the basis of

the Panel's conclusion that the unavailable data are insufficient to classify such biological products, and for which further testing is therefore required. These biological products in Category III for which continued licensing, manufacturing, and marketing during the period of further testing are recommended are designated as Category IIIA. Those biological products in Category III for which suspension of the product licenses pending submission of additional data are recommended are designated as Category IIIB. The recommendation for either Category IIIA or IIIB is based on assessment of the present evidence of safety and effectiveness of the product and the potential benefits and risks likely to result from the continued use of the product for a limited period of time, while questions raised concerning the products are being resolved by further study.

[Excerpt from page 51003]

The Panel appointed by FDA to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of bacterial vaccines, toxoids, related antitoxins, and immune globulins included the following individuals:

Panel Chairman, Gene H. Stollerman, M.D., Professor and Chairman, Department of Medicine, University of Tennesee College Memphis, TN 38163 (now Professor of Medicine, Boston University Medical Center);

Geoffery Edsal, M.D. (deceased), Professor Emeritus of Microbiology (Harvard School of Public Health and London School of Hygiene and Tropical Medicine);

Theodore C. Eickhoff, M.D., Professor of Medicine, Head, Division of Infectious Diseases, University of Colorado Medical Center, Denver, CO 80262;

John C. Feeley, Ph.D., Chief, Bacterial Immuniology Branch (now Assistant Director for Laboratory Sciences, Bacterial Disease Division), Centers for Disease control, Atlanta, GA 30333;

Hjordis M. Foy, M.D., Ph.D. Associate Professor (since July 1, 1976, Professor) Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA 98195;

Edward A. Mortimer, Jr., M.D., Chairman of the Department of Pediatrics, School of Medicine, University of New Mexico, Albuquerque, NM 87131. (Since February 1, 1975, Professor and Chairman of the Department of Community Health and Professor of Pediatrics, School of Medicine, Case Western University, Cleveland, OH 44106.)

Jay P. Sanford, M.D., Professor, Department of Internal Medicine, University of Texas, Southwestern Medical School at Dallas, Dallas, TX 75235. (Since June 1, 1975, Dean, School of Medicine, Uniformed Services University, Bethesda, MD 20014.).

The Panel was convened on July 12, 1973, in an organizational meeting. Working meetings were held on: July 12, September

24-25, November 9-10, December 13-14, 1973; February 13-14, April 9-10, June 13-14, September 12-13, November 7-8 1974; January 13-14, February 24-25.

Two nonvoting liaison representatives served on the Panel. Ms. Laryl Lee Delker, nominated by the Consumer Federation of America, served as the representative. John Adams, Ph.D., of the Pharmaceutical Manufacturers Association, nominated by a number of producers with products under review by the Panel, served as the industry representative. Karl Bambach, Ph.D., substituted for Dr. Adams during his absences. Morris Schaefer, M.D., Ph.D., participated in the Panel meetings in his capacity as Director of the Office of Scientific Advisors and Consultants, FDA. Jack Gertzog, Deputy Director, Office of Scientific Advisors and Consultants, FDA, served as Executive Secretary of the Panel. Margaret Pittman, Ph.D., was selected by the panel as a consultant. Over 120 persons requested an opportunity or were otherwise invited to appear before the Panel and present their views on one or more of the vaccines and related matters. Every person who requested an opportunity was heard by the Panel. The names of these persons are on file with the Dockets Management Branch.

[Excerpt from page 51058]

Anthrax Vaccine, Adsorbed

Anthrax is an acute bacterial disease caused by *Bacillus anthracis*. The reservoir is any of several species (cattle, sheep, goats, horses, pigs) and the organism produces extremely resistant spores which may persist in soil and contaminate animals or their products. The disease is primarily an occupational hazard for industrial workers who process hides, hair (especially goat), bone meal, and wool, as well as veterinarians and agricultural workers who may contact infected animals.

Most infections are cutaneous; if untreated they may spread to regional lymph nodes and may cause a fatal septicemia. Primary inhalation and gastrointestinal infections do occur, but with low frequency, and are highly fatal.

Description of Product

Anthrax vaccine is an aluminum hydroxide adsorbed, protective, proteinaceous, antigenic fraction prepared from a nonencapsulated mutant of the Vollum strain of *Bacillus anthracis*. It contains no more than 0.83 mg aluminum per 0.5 mL dose, 0.0025 percent benzethonium chloride as a preservative, and 0.0037 percent formaldehyde, which is believed to act as a stabilizer.

The product is tested according to the Public Health Service regulations for biological products and specific additional standards for anthrax vaccine. In addition to tests for general safety and sterility, the product is subjected to a potency assay of its protective antigen in guinea pigs, which are challenged with virulent *Bacillus anthracis*.

Indications and Contraindications

Immunization with this vaccine is indicated only for certain occupational groups with risk of uncontrollable or unavoidable exposure to the organism. It is recommended for individuals in industrial settings who come in contact with imported animal hides, furs, wool hair (especially goat hair), bristles, and bone meal, as well as in laboratory workers involved in ongoing studies on the organism.

Contraindications to its use include:

1. A history of clinical anthrax infection which may enhance the risk of severe reactions.
2. Severe systemic reactions with marked chills and fever following a prior injection - in this case further attempts at immunization should be abandoned.
3. The presence of acute respiratory disease or other febrile illnesses in order not to confuse the cause of further fever.
4. Therapy with corticosteroids or other immunosuppressive agents - in this case immunization should be deferred until such therapy has been completed. If on a long-term therapy, a more intensive immunization schedule should be considered.

Safety

In general, safety of this product is not a major concern, especially considering its very limited distribution and the benefit-to-risk aspects of occupational exposure in those individuals for whom it is indicated. Local reactions are typically mild, with erythema and slight local tenderness for 24 to 48 hours. Some individuals may have more severe local reactions, with edema, erythema greater than 5 x 5 cm, induration, local warmth, tenderness, and pruritus. Only a few systemic reactions with marked chills and fever have been recorded. All reactions reported have been self-limited.

Efficacy

The best evidence for the efficacy of anthrax vaccine comes from a placebo-controlled field trial conducted by Brachman (Ref. 1) covering four mills processing raw imported goathair into garment underlinings. The study involved approximately 1,200 mill employees of whom about 40 percent received the vaccine and the remainder received the placebo or nothing. The average yearly incidence of clinical anthrax in this population was 1 percent. During the evaluation period, 26 cases of anthrax occurred. Twenty-one had received no vaccine, four had incomplete immunization and one had complete immunization. Based upon analysis of attack rates per 1000 person-months, the vaccine was calculated to give 93 percent (lower 95 percent confidence limit=65 percent) protection against cutaneous anthrax based upon comparison with the control group. Inhalation anthrax occurred too infrequently to assess the protective effect of the vaccine against this form of the disease.

The Center for Disease Control has continued to collect data on the occurrence of anthrax in at-risk industrial settings. These data were summarized for the period 1962 to 1974. Twenty-seven cases were identified. Three cases were not mill employees, but worked in or near mills; none of these cases were vaccinated. Twenty-four cases were mill employees; three were partially

immunized (one with 1 dose, two with 2 doses); the remainder (89 percent) being unvaccinated. Therefore, no cases have occurred in fully vaccinated subjects while the risk of infection has continued. These observations lend further support to the effectiveness of the product.

Special Problems

Anthrax vaccine poses no serious special problems other than the fact that its efficacy against inhalation anthrax is not well documented. This question is not amenable to study due to the low incidence and sporadic occurrence of the disease. In fact, the industrial setting in which the studies above were conducted is vanishing, precluding any further clinical studies.

In any event, further studies on this vaccine would receive low priority for available funding.

Recommendations

The Panel believes that [page 51059] there is sufficient evidence to conclude that anthrax vaccine is safe and effective under the limited circumstances for which this vaccine is employed.

Reference

1. Brachman, P.S., H. Gold, S.A. Plotkin, R. Fekety, M. Werrin, and N.R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," American Journal of Public Health, 52:632-645, 1962.

SPECIFIC PRODUCT REVIEW

Anthrax Vaccine Adsorbed Manufactured by Bureau of Laboratories, Michigan Department of Public Health

1. *Description*. Anthrax vaccine adsorbed is an aluminum hydroxide adsorbed preparation of protective antigen of *Bacillus anthracis*. The product is prepared from a microaerophilic culture of an avirulent, nonproteolytic, nonencapsulated strain. The product contains 0.83 mg of aluminum per single human dose (0.5 mL) and is preserved with 0.0025 percent benzethonium chloride. Not more than 0.0037 percent formaldehyde is added as a stabilizer.
2. *Labeling*.
   A. *Recommended use / indications*. This product is intended solely for immunization of high risk of exposure industrial populations such as individuals who contact imported animal hides, furs, bone meal, wool, hair (especially goat hair), and bristles. It is also recommended for laboratory investigators handling the organism. Primary immunization consists of 6 subcutaneous 0.5 mL injections at 0, 2, and 4 weeks and 6, 12, and 18 months. Subsequent boosters at yearly intervals are recommended.

B. *Contraindications*. Prior anthrax infection is an absolute contraindication. Immunization should be avoided in acute respiratory disease or other active infections. Corticosteroid therapy should be avoided in acute respiratory disease or other active infections. Corticosteroid therapy may suppress response. Further immunization should be discontinued in those rare individuals who suffer severe systemic reactions.

3. *Analysis* -
   A. Efficacy
      i. *Animal*. This product meets Federal requirements<.
      ii. *Human.*The vaccine manufactured by the Michigan Department of Public Health has not been employed in a controlled field trial. A similar vaccine prepared by Merck Sharp & Dohme for Fort Detrick was employed by Brachman (Ref. 1) in a placebo-controlled field trial in mills processing imported goat hair. This vaccine appeared 93 percent protective (lower 95 percent confidence level = 65 percent protective) against cutaneous anthrax. No meaningful assessment of its value against inhalational anthrax is possible due to its low incidence. The Michigan Department of Public Health vaccine is patterned after that of the Merck Sharp & Dohme with various minor production changes. It has been distributed by the Center for Disease Control since 1966, first as an investigational new drug and since 1972 as a licensed product. A review of the Center for Disease Control data pertinent to this product for the period 1962 to 1974 in at risk industrial settings indicates that no cases have occurred in fully immunized workers (see Generic Statement).
4. *Safety*.
   A. *Animal*. This product meets Federal requirements.
   B. *Human.*Accumulated data for the Center for Disease Control suggests that this product is fairly well tolerated with the majority of reactions consisting of local erythema and edema. Severe local reactions and systemic reactions are relatively rare.
5. *Benefit / risk ratio*. This vaccine is recommended for a limited high-risk of exposure population along with other industrial safety measures designed to minimize contact with potentially contaminated material. The benefit-to-risk assessment is satisfactory under the prevailing circumstances of use.
6. *Labeling.*The labeling seems generally adequate. There is a conflict, however, with additional standards for anthrax vaccine. Section 620.24(a) (21 CFR 620.24(a)) defines a total primary immunizing dose a 3 single doses of 0.5 mL. The labeling defines primary immunization as 6 doses (0, 2, and 4 weeks plus 6, 12, and 18 months).
7. *Critique.*This product appears to offer significant protection against cutaneous anthrax in fully immunized subjects. This is adequately established by the controlled field trial of the very similar Merck Sharp & Dohme experimental vaccine and by the Center for Disease Control surveillance data conducted on industrial high-risk settings.
8. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product. Labeling revisions in accordance with this Report are recommended.

Reference

(1) Brachman, P.S., H. Gold, S.A. Plotkin, R. Fekety, M. Werrin, and N.R. Ingraham, "Field Evaluation of a Human Anthrax Vaccine," American Journal of Public Health, 52:632-645, 1962.

[Excerpt from page 51104]

A. Regulatory Categories

1. The Panel recommended that bacterial vaccines and toxoids be grouped into regulatory categories as follows:

    a. Category I

    1. Licensed biological products determined to be safe and effective and not misbranded [and may continue in interstate commerce]: Collagenase, Advance Biofactures Corp., License No. 383; Tetanus Immune Globulin (Human), Armour Pharmaceutical Co., License No. 149; BCG Vaccine, Botulism Antitoxin (Types A, B, and E), Botulism Antitoxin (Type E), Tetanus Toxoid, Connaught Laboratories, Ltd., License No. 73; Plague Vaccine, Tetanus Immune Globulin (Human), Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Eli Lilly & Co., License No. 56; BCG Vaccine, Glaxo Laboratories, Ltd., License No. 337; Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No.238; Cholera Vaccine, Tetanus Immune Globulin (Human), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus and Pertussis Toxoids Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Immune Globulin (Human), Tetanus Toxoid Adsorbe, Typhoid Vaccine, Massachusetts Public Health Biologic Laboratories, License No. 64; Tetanus Immune Globulin (Human), Merck Sharp and Dohme, Division of Merck & Co., Inc., License No. 2; Anthrax Vaccine Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Typhoid Vaccine, Michigan Department of Public Health, License No. 99; Tetanus Immune Globulin (Human), Parke-Davis, Division of Warner-Lambert Co., License No. 1: Tetanus Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140; BCG Vaccine, University of Illinois, License No. 188; and Cholera Vaccine, Tetanus Immune Globulin (Human), Typhoid Vaccine (acerone inactivated), Typhoid Vaccine (heat-phenol inactivated), Wyeth Laboratories, Inc.., License No.3.
    2. Biological products also recommended for category I but for which product license has been revoked at the manufacturers request subsequent to the Panel's review. Diphtheria Toxoid, Connaught Laboratories, Ltd., License No. 73; Tetanus Toxoid, Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (with aluminum phosphate), Tetanus Immune Globulin (Human), Dow Chemical Co., License No. 110; Cholera Vaccine, Pertussis Vaccine, Typhoid Vaccine, Eli Lilly & Co., License No. 56; Streptokinase-Streptodornase (Varidase, Topical), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Diphtheria Antitoxin, Merril-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Tetanus Immune Globulin (Human), Michigan

Department of Public Health, License No., 99; Tetanus Immune Globulin (Human), Oesterrichisches Institut fuer Haemoderivate GmbH, License No. 258; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Parke-Davis, Division of Warner-Lambert Co., License No. 1; and Pertussis Vaccine, Typhoid Vaccine, Texas Department of Health Resources, License No. 121.

A list of all voluntarily revoked products reviewed by the Panel, with the date of the license revocation, is on file with FDA's Dockets Management Branch (address above). No further regulatory or administrative action is necessary for these products.

Merrell-National Laboratoriers, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, and Diphtheria Antitoxin to Connaught Laboratories, Inc. Connaught Laboratories was issued License No. 711 on January 3, 1978, FDA advises that all comments and recommendations directed to the Merrell-National products apply equally to the products now manufactured by Connaught Laboratories, Inc.

FDA agrees with the Panel's findings and recommendations for these products, and hereby proposes to adopt its conclusions, including proposed labeling revisions concerning the intended use of the products. Comments or additional data on this classification are invited.

a. *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce:*

Streptokinase-Streptodornase Varidase-buccal tablet, intramuscular, and oral tablet dosage forms), Lederle Laboratories, Division American Cyanamid Co., License No. 17.

Lederle Laboratories was licensed for the manufacture and sale of five forms of Streptokinase-Streptodornase: topical, topical jelly, buccal tablet, intramuscular, and oral tablet. The topical form was recommended for Category I, the topical jelly for Category IIIA, and the buccal tablet, intramuscular, and oral tablet for Category IIIB. At the request of the manufacturer, the product license for the[page 51105] manufacture and sale of all forms of Streptokinase-Streptodornase has been revoked. Accordingly, no further FDA action is necessary.